***Review Article***

**Systematic Review of Nebulized Furosemide for the Management of Dyspnea: Efficacy and Safety in Clinical Practice**

**Abstract**

**Background**: Nebulized furosemide, a non-opioid option for dyspnea, shows promise in alleviating breathlessness by reducing pulmonary edema and modulating airway receptors. While studies indicate improvements in symptoms and quality of life, optimal dosage and long-term safety require further investigation. This review evaluates the efficacy and safety of nebulized furosemide to inform its potential role in dyspnea management.

**Methods**: This systematic review focused on randomized controlled trials and literature reviews involving participants who experienced dyspnea and received nebulized furosemide as part of their treatment.

**Results**: Searches measured across three databases and additional sources using key terms yielded 150 unduplicated papers. Finally, seven studies—two of which were literature reviews—met inclusion criteria, assessing the short-term effects of nebulized furosemide on dyspnea and pulmonary function tests. Four studies reported a statistically significant improvement in patient-reported symptoms.

**Conclusion**: Although preliminary research suggests potential benefits of nebulized furosemide in symptom relief and pulmonary function improvement, the available data remains insufficient to confirm the therapy’s effectiveness definitively.

***Keywords:*** *Dyspnea, Chronic Obstructive Pulmonary Disease, Asthma, Furosemide*

**1. Background**

Nebulized furosemide has recently gained attention as a non-opioid option for managing dyspnea, a distressing symptom often associated with conditions such as chronic obstructive pulmonary disease (COPD), heart failure, asthma, cancers, and interstitial lung disease (ILD) [1-4]. Traditionally known for its diuretic properties, furosemide administered via nebulization is thought to alleviate breathlessness through mechanisms beyond its systemic effects on fluid balance. Studies suggest that it reduces pulmonary edema and influences airway sensory receptors, decreasing the sensation of dyspnea without significantly altering lung volumes or ventilation mechanics [5, 6].

Research into nebulized furosemide has demonstrated its potential in a variety of patient populations, including those suffering from refractory dyspnea unresponsive to standard therapies [2]. Clinical trials have shown that nebulized furosemide improves subjective measures of breathlessness, exercise tolerance, and overall quality of life in patients with chronic respiratory diseases [7]. In COPD patients, for instance, adding nebulized furosemide to conventional therapy resulted in improved forced vital capacity (FVC) and peak expiratory flow (PEF), suggesting enhanced bronchodilation and airway function [5, 8]. Furthermore, nebulized furosemide has been explored in acute settings, such as palliative care for cancer patients with refractory dyspnea, where it demonstrated rapid symptomatic relief [2].

Despite encouraging findings, the pharmacologic mechanisms by which nebulized furosemide relieves dyspnea are not fully understood [9]. It is hypothesized that it reduces afferent nerve stimulation in the airways, modulating the neural pathways involved in the perception of breathlessness [10, 11]. Additionally, it may exert local anti-inflammatory and vasodilatory effects, reducing airway resistance and promoting more effective gas exchange [12].

However, data on the optimal dosage, frequency of administration, and long-term safety of nebulized furosemide are limited. Small-scale trials have reported no significant adverse effects, but larger, randomized controlled trials are necessary to establish its clinical utility more definitively [13, 14]. Questions remain regarding its efficacy compared to existing treatments, including bronchodilators, opioids, and non-pharmacologic interventions like pulmonary rehabilitation [2, 15, 16].

This systematic review aims to evaluate the efficacy and safety of nebulized furosemide in the management of dyspnea. By synthesizing evidence from recent clinical trials and systematic review studies, it seeks to provide a comprehensive assessment of its therapeutic potential, addressing gaps in current knowledge and offering recommendations for its integration into clinical practice.

**2. Methods**

**2.1 Identification of studies**

A pre-established protocol for this review was registered in the international prospective register of systematic reviews (PROSPERO) . The review includes five randomized controlled trials (RCTs) and two literature reviews focused on assessing the efficacy and safety of nebulized furosemide in managing dyspnea and pulmonary function outcomes. Studies that did not address nebulized furosemide's efficacy and safety in patients with dyspnea were excluded.

**2.2 Outcome measures**

In this systematic review on nebulized furosemide for dyspnea management, the primary outcome measures focus on assessing efficacy through dyspnea score reduction (e.g. Visual Analog Scale (VAS) for dyspnea), respiratory rate improvement, and the duration of symptom relief. Secondary efficacy outcomes include enhancements in quality of life and a potential reduction in healthcare utilization, such as emergency visits.

Safety outcomes track adverse events and the long-term safety profile of nebulized furosemide, with an emphasis on respiratory and electrolyte-related side effects. Exploratory outcomes also include patient satisfaction and potential changes in pulmonary function (changes in forced expiratory volume in 1 second (FEV1) and other relevant pulmonary metrics), offering a comprehensive assessment of both the efficacy and safety of nebulized furosemide in clinical practice.

**2.3 Information sources**

This literature review involved searches in three databases—PubMed, Cochrane Library, and Scopus—for studies published between 2014 and 2024, to ensure relevance to current healthcare practice. Citation tracking was conducted for all identified documents. Additionally, Google Scholar, Google, and ClinicalTrials.gov were searched using “furosemide” and “dyspnea” as keywords. Authors of promising abstracts were contacted to request full-text versions, but no responses were received. The most recent search took place on October 26, 2024.

**2.4 Search strategy and assessment of studies**

To achieve the most effective and precise searches in PubMed, the following MeSH terms were utilized: vapor\* OR Nebuli\* AND Furosemide OR lasix OR Frusemide OR Fusid OR Errolon OR Furanth\* AND Dyspnea OR Breathlessness (see Table 1).

To enhance the search, filters were applied to include only studies from the past 10 years, conducted in humans, and published in English. Priority was given to high-evidence sources such as meta-analyses, systematic reviews, randomized controlled trials, and practice guidelines to assess the effects of nebulized furosemide on dyspnea and pulmonary function. Titles, abstracts, and keywords were screened, and articles were filtered for relevance and quality using the Cochrane risk-of-bias tool. Articles selected for full-text review were assessed by study title, date, design, sample size, participants, interventions, controls, outcomes, and conflicts of interest. Only studies with control groups receiving adequate standard care were included.

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with the Consolidated Standards of Reporting Trials checklist and Cochrane Collaboration guidelines used to assess bias in the included RCTs.

**3. Results**

**3.1 Study selection**

Using key terms and specific search parameters, the search yielded three results from PubMed, 20 from the Cochrane Library, 143 from Scopus, and 23 from Google Scholar, Google, and clinical trial databases. In total, 150 unique results were identified (see Figure 1). Of these, 41 articles met the initial screening criteria and were evaluated for eligibility. Thirty-four were excluded, comprising descriptive articles (4), abstracts only (20), and studies not discussing nebulized furosemide’s efficacy or safety (10). All included studies, published within the past decade, examined nebulized furosemide’s use in patients experiencing dyspnea.

**3.2 Characteristics of studies**

This literature review includes seven studies, encompassing five randomized controlled trials (RCTs) with a combined total of 261 participants, all of whom experienced dyspnea, either due to underlying conditions or exercise. One RCT grouped chronic obstructive pulmonary disease (COPD) with asthma, while another focused on COVID-19-related dyspnea and respiratory failure. Two literature reviews analyzed COPD independently, and two RCTs examined dyspnea in healthy individuals. Each study evaluated the effects of nebulized furosemide on dyspnea and pulmonary function, using FEV1, FVC, and/or PEFR, though specific metrics varied. Despite some differences in measuring dyspnea perception, subjective assessments were predominantly used.

**3.3 Critical analysis**

The risk of bias in the RCTs was evaluated using the Cochrane Risk of Bias Assessment Tool following the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions [17]. The included RCTs ranged in quality, with most showing low risk of bias, while some had an unclear risk due to limited details (see Table 2). For assessing the literature review quality, the PRISMA criteria were applied, indicating a high-quality review that used the GRADE system to rate the strength of evidence in the studies included.

**3.4 Effect of intervention**

All studies evaluated the effect of nebulized furosemide on short-term relief of dyspnea and its immediate impact on pulmonary function in individuals experiencing breathlessness. Table 3 provides a summary of these studies, including their key findings.

Most of the studies reported a statistically significant improvement in perceived dyspnea with nebulized furosemide as the intervention. For example, Ragab et al. demonstrated that, in COPD patients, adding furosemide to standard treatment significantly lowered CAT and Borg scores, indicating a reduction in dyspnea symptoms [8].

Pulmonary function values (FEV1, FVC, and PEFR) were assessed in four of the publications separately. In a randomized, double-blind clinical trial, Masoumi et al. found that the addition of nebulized furosemide to salbutamol in patients with reactive airways disease (RAD) significantly increased peak expiratory flow rate (PEFR) compared to salbutamol alone [18]. Ragab et al. found that nebulized furosemide was superior to saline as adjunctive therapy compared to salbutamol-ipratropium in improving the first second to forced vital capacity ratio (FEV1/FVC) in COPD patients with heart failure [8].

In a literature review, Atwi et al. reported significant improvements in forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) after treatment with nebulized furosemide in patients with COPD. A significant improvement of about 7% in FEV1 with nebulized furosemide was reported in this paper. Besides, a significant improvement in mean FEV1 and FVC was reported after treatment with nebulized furosemide [5].

In a systematic review, Ghaysouri et al. reported that nebulized furosemide had a significant positive effect on breathing rate and heart rate. Compared to the control group, blood pressure and heart rate were closer to the normal range in patients who were treated with nebulized furosemide. FEV1 and PEFR in COPD patients who received furosemide were closer to the reference range than patients in the placebo group. However, no significant difference in the levels of PaCO2, SaO2, HCO3 and PaO2 was observed between furosemide and placebo groups [19].

In a phase 2, randomized, controlled double-blind study, Muscedere et al. found no significant difference in the primary outcome of Pao2/Fio2 ratio changes during the first 5 days of treatment between the groups (nebulized furosemide or placebo). There were no significant differences in secondary outcomes, including mortality, duration of mechanical ventilation, ventilator-free days, oxygen-free days, and length of hospital stay between groups. No side effects were reported and this supports evidence on the safety of nebulized furosemide [11].

In a randomized, double blind, placebo-controlled crossover trial, Grogono1 et al. found that compared with nebulized saline, nebulized furosemide significantly improved air hunger sensation scores on the visual analog scale (VAS). However, nebulized furosemide did not make any significant improvement in scores on perceived effort/labored breathing on the visual analog scale. There were no adverse events reported during the study [20].

In a single-center, randomized, double-blind, crossover study, Waskiw-Ford et al. did not find significant differences in ratings of perceived dyspnea severity during exercise or in cardiometabolic responses, ventilation, breathing pattern, or dynamic lung volume during exercise between the furosemide and saline groups. Significant increases in urine production rate, percentage of participants reporting "need to urinate," and perceived intensity of "need to urinate" after inhalation of furosemide 120 mg solution compared with 0.9% saline and furosemide 40 mg was observed. No other systemic or adverse side effects were reported after inhalation of furosemide 40 and 120 mg solutions [21].

**4. Discussion**

**4.1 Summary of main findings**

The articles included in this literature review suggest that nebulized furosemide may have a significant impact on alleviating dyspnea and improving pulmonary function in affected individuals. While one study identified dyspnea as a primary outcome, others focused on various pulmonary function metrics. All publications concentrated on the short-term effects of nebulized furosemide, without addressing any long-term outcomes. This limitation raises important considerations for clinical practice, as the systemic effects of nebulized furosemide remain unverified based on the current studies.

Future investigations should examine the long-term effects of nebulized furosemide on both dyspnea and pulmonary function values. Additionally, more research is necessary to determine its viability as a treatment option for patients experiencing dyspnea. In the interim, given that nebulized furosemide has demonstrated clinically significant improvements in dyspnea, it may be beneficial for researchers and clinicians to explore its use alongside established interventions to help manage symptoms effectively.

**4.2 Quality of the evidence**

The quality of evidence from the RCTs was evaluated using the Cochrane risk-of-bias tool, assessing factors such as random sequence generation (selection bias), allocation concealment, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential biases. The risk-of-bias assessment across the RCTs showed variability, with studies exhibiting a range from low to unclear and high risk of bias in different areas, as presented in Table 2.

**4.3 Potential biases in the review process**

There were no identified sources of bias in the review process. However, a general limitation of this literature review is that only articles from 2014 up until 2024 were included.

**5. Conclusion**

To date, nebulized furosemide is not a widely adopted treatment for dyspnea relief or for improving pulmonary function in patients suffering dyspnea. Rigorous, evidence-based studies are needed to establish the role of nebulized furosemide within existing therapeutic protocols. Although preliminary research suggests potential benefits in symptom relief and pulmonary function improvement, the available data remains insufficient to confirm the therapy’s effectiveness definitively.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

**References**

1. Abdallah SJ, Jensen D, Lewthwaite H. Updates in opioid and nonopioid treatment for chronic breathlessness. Current opinion in supportive and palliative care. 2019;13(3):167-73.

2. Awan S, Wilcock A. Nonopioid medication for the relief of refractory breathlessness. Current Opinion in Supportive and Palliative Care. 2015;9(3):227-31.

3. Gök Metin Z, Arikan Dönmez A. Dyspnea management in patients with cancer. Turk Onkoloji Dergisi. 2016;31(2):61-7.

4. Mahshidfar B, Mosaddegh R, Rezaee M, Alimardani A. The Effect of Nebulized Furosemide in Patients with Acute Cardiogenic Pulmonary Edema: A Randomized Clinical Trial. Qom University of Medical Sciences Journal. 2018;12(10):1-8.

5. Atwi Z. Effects of inhaled furosemide on dyspnea and pulmonary function in people with COPD: A literature review. Canadian Journal of Respiratory Therapy. 2022;58:170-4.

6. Jeba J, George R, Pease N. Nebulised furosemide in the palliation of dyspnoea in cancer: a systematic review. BMJ Supportive & Palliative Care. 2014;4(2):132-9.

7. Waskiw-Ford M. Effect of inhaled nebulized furosemide on breathlessness during exercise in the setting of abnormal restrictive constraints on tidal colume expansion: a randomized, double blind, placebo contolled, crossover, dose-response study: McGill University (Canada); 2017.

8. Ragab R, Zaki A, Abdallah AE, Shehata GM, Elsayed M, Hameed AA. Enhancing Lung Function in COPD Patients using Nebulized Furosemide as an Adjunct therapy: A Triple-Blinded, Cross-Over RCT. 2024.

9. Boyden JY, Connor SR, Otolorin L, Nathan SD, Fine PG, Davis MS, et al. Nebulized medications for the treatment of dyspnea: A literature review. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2015;28(1):1-19.

10. Carone L, Oxberry SG, Twycross R, Charlesworth S, Mihalyo M, Wilcock A. Furosemide. Journal of Pain and Symptom Management. 2016;52(1):144-50.

11. Muscedere J, Maslove DM, Barden CJ, Weaver DF, Boyd JG, Sibley S, et al. Nebulized Furosemide for Pulmonary Inflammation in Intubated Patients With COVID-19: A Phase 2 Randomized Controlled Double-Blind Study. Critical Care Explorations. 2024;6(2):e1045.

12. Brennecke A, Villar L, Wang Z, Doyle LM, Meek A, Reed M, et al. Is Inhaled Furosemide a Potential Therapeutic for COVID-19? American Journal of the Medical Sciences. 2020;360(3):216-21.

13. Vozoris NT, Wang X, Austin PC, O'Donnell DE, Aaron SD, To TM, et al. Incident diuretic drug use and adverse respiratory events among older adults with chronic obstructive pulmonary disease. British Journal of Clinical Pharmacology. 2018;84(3):579-89.

14. Takagi K, Miró O, Gayat E, Llorens P, Wussler DN, Čerlinskaitė K, et al. Safety of diuretic administration during the early management of dyspnea patients who are not finally diagnosed with acute heart failure. European Journal of Emergency Medicine. 2020;27(6):422-8.

15. Consider opioid therapy for chronic refractory breathlessness. Drugs and Therapy Perspectives. 2014;30(8):294-7.

16. Barbetta C, Currow DC, Johnson MJ. Non-opioid medications for the relief of chronic breathlessness: current evidence. Expert Review of Respiratory Medicine. 2017;11(4):333-41.

17. Chandler J, Cumpston M, Li T, Page MJ, Welch V. Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley. 2019.

18. Masoumi K, Forouzan A, Haddadzadeh Shoushtari M, Porozan S, Feli M, Fallah Bagher Sheidaee M, et al. The efficacy of nebulized furosemide and salbutamol compared with salbutamol alone in reactive airway disease: a double blind randomized, clinical trial. Emergency medicine international. 2014;2014(1):638102.

19. Ghaysouri A, Basati G, Shams M, Tavan H. Efficiency of nebulizing furosemide in the treatment of chronic pulmonary obstructive disease: A systematic review and meta-analysis of clinical trials. Tanaffos. 2020;19(4):340-9.

20. Grogono JC, Butler C, Izadi H, Moosavi SH. Inhaled furosemide for relief of air hunger versus sense of breathing effort: A randomized controlled trial. Respiratory Research. 2018;19(1).

21. Waskiw-Ford M, Wu A, Mainra A, Marchand N, Alhuzaim A, Bourbeau J, et al. Effect of inhaled nebulized furosemide (40 and 120 mg) on breathlessness during exercise in the presence of external thoracic restriction in healthy men. Frontiers in Physiology. 2018;9(FEB).

**FIGURE 1.** PRISMA flowsheet.

**Identification of studies via databases and registers**

Records identified from:

Databases (PubMed, Scopus, Cochrane Library)

(n = 166)

Other sources (Google scholar, clinical trials registry, and hand searches)

 (n = 23)

**Identification**

Records after removing duplicates

(n = 150)

Reports screened by title and abstract

(n = 150)

Records excluded

 (n = 109)

**Screening**

Full-text papers excluded:

Abstracts (n = 20)

Descriptive papers (n = 4)

Studies not mentioning efficacy and safety of inhaled furosemide (n = 10)

Full-text papers assessed for eligibility

(n = 41)

Studies included in review

(n = 7)

**Included**

**Table 1.** Resource search strategy in scientific databases

|  |
| --- |
| Time |
| From 2014 to 2024 |
| **Language** |
| English |
| **PubMed** | (("Furosemide"[MeSH Terms] OR ("Furosemide"[MeSH Terms] OR "Furosemide"[All Fields] OR "frusemide"[All Fields] OR "furosemid"[All Fields] OR "lasix"[All Fields]) OR ("Furosemide"[MeSH Terms] OR "Furosemide"[All Fields] OR "frusemide"[All Fields] OR "furosemid"[All Fields]) OR ("Furosemide"[MeSH Terms] OR "Furosemide"[All Fields] OR "fusid"[All Fields]) OR ("Furosemide"[MeSH Terms] OR "Furosemide"[All Fields] OR "errolon"[All Fields]) OR "furanth\*"[All Fields]) AND ("nebuli\*"[All Fields] OR "vapor\*"[All Fields]) AND ("Dyspnea"[MeSH Terms] OR ("Dyspnea"[MeSH Terms] OR "Dyspnea"[All Fields] OR "breathless"[All Fields] OR "breathlessness"[All Fields]))) AND ((y\_10[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (humans[Filter])) |
| **Scopus** | (Furosemide OR lasix OR Frusemide OR Fusid OR Errolon OR Furanth\*) AND (Dyspnea OR Breathlessness) AND (Nebuli\* OR vapor\*) AND PUBYEAR > 2013 AND PUBYEAR < 2025 AND ( LIMIT-TO ( SRCTYPE,"j" ) ) AND ( LIMIT-TO ( DOCTYPE,"ar" ) OR LIMIT-TO ( DOCTYPE,"re" ) ) AND ( LIMIT-TO ( LANGUAGE,"English" ) ) AND ( LIMIT-TO ( EXACTKEYWORD,"Human" ) OR LIMIT-TO ( EXACTKEYWORD,"Humans" ) OR LIMIT-TO ( EXACTKEYWORD,"Furosemide" ) ) |
| Google scholar | (Furosemide OR lasix OR Frusemide OR Fusid OR Errolon OR Furanth\*) AND (Nebuli\* OR vapor\*) AND (Dyspnea OR Breathlessness) |

**Table 2.** Cochrane risk of bias assessment tool for included randomized control trials

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Random sequence generation | Allocation concealment | Blinding participants and personnel | Blinding outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
| Ragab et. al (2024) [8] | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |
| Muscedere et. al (2024) [11] | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | High Risk |
| Waskiw-Ford et. al (2018) [21] | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |
| Grogono et. al (2018) [20] | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Unclear risk | Unclear risk |
| Masoumi et. al (2014) [18] | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Unclear risk | Unclear risk |

**Table 3.** Summary of included articles

| Study | Participants | Intervention/Outcomes | Results |
| --- | --- | --- | --- |
| Ragab et. al (2024) [8]triple-blinded, crossover,randomized controlled trial | n = 92 patientswith COPD with the average age 60.43 ± 8.7 years. 14% of the study participants were female | Participants were divided into two groups:* Group” A” received nebulized conventional therapy (nebulized ipratropium, with or without salbutamol according to presence of Heart failure disease), then nebulized furosemide (intervention group) (n = 47).
* Group “B” received nebulized conventional therapy (nebulized ipratropium, with or without salbutamol according to presence of Heart failure disease), then nebulized saline (control group) (n = 45).
 | Compared to baseline, both saline and furosemide groups significantly improved FVC%, FEV1%, FEV1/FVC, PEF%, FEV25-75%, CAT score, and Borg score (all p < 0.001). Furthermore, furosemide resulted in significantly greater improvements in FVC%, FEV1%, FEV1/FVC, PEF%, FEV25-75%, CAT score, and Borg score compared to saline (all p < 0.001). No significant differences were observed in oxygen saturation between the two groups. |
| Muscedere et. al (2024) [11]A double-blind, randomized, placebo-controlled trial | n = 39 patients with respiratory failure requiring invasive mechanical ventilation secondary to COVID-19 with duration of invasive mechanical ventilation less than 48 hours. The average age was 70.5 ± 10.8 years. | Patients were randomized within 48 hours of intubation to receive inhaled furosemide (n = 21) or placebo (n = 18) until day 28, death, or liberation from mechanical ventilation.The primary outcome was improvement in oxygenation as determined by change in a standardized Pao2/Fio2 ratio determination between randomization and study day 6.Secondary outcomes included all-cause mortality (ICU, hospital, and day 60), duration of mechanical ventilation, ventilator-free days (VFDs) (25), oxygen-free days (26,27), and length of stay (ICU and hospital). Safety was measured as the occurrence of serious adverse events in accordance with guidelines for academic ICU drug trials (29) and the occurrence of allergic reactions. | For the primary outcome of the difference in Pao2/Fio2 ratio between day 1 and day 6, the change in Pao2/Fio2 ratio was +31.4 ± 83.5 in the furosemide arm versus +20.1 ± 92.8 in the control. The difference in change in Pao2/Fio2 ratio between the arms after controlling for baseline Pao2/Fio2 ratio and sex via ANCOVA was found to be 14.7 (95% CI, –36.8, 66.2, p = 0.56).For the secondary outcomes; ICU, hospital, and 60-day mortality, duration of mechanical ventilation, VFDs, oxygen-free days, and length of stay were not significantly different between the groups. The average value across the 28 days in Pao2/Fio2 ratio was not significantly different between arms (p = 0.58). |
| Waskiw-Ford et. al (2018) [21]single-center, randomized, double-blind, crossover study | n = 24 healthy, non-obese (body mass index, 23.9 ± 0.6 kg/m2) men aged 25.3 ± 1.2 years with normal spirometry (FEV1, 99 ± 3% predicted, z-score −0.13 ± 0.22; FEV1/FVC, 79.7 ± 1.3%, z-score −0.78 ± 0.19) and a symptom-limited PPO and peak rate of oxygen uptake (VO2peak) on incremental CPET with CWS of 205 ± 10 W and 41.9 ± 1.9 ml/kg/min, respectively. | Visit 1 included: screening for eligibility criteria; routine clinical assessment of heart rate and rhythm by 12-lead electrocardiography, blood pressure by automated sphygmomanometer, and oxyhemoglobin saturation by finger pulse oximeter; pulmonary function testing, including spirometry and slow vital capacity (SVC) maneuvers; external thoracic restriction by chest wall strapping (CWS) to reduce SVC by ~20% of its baseline (unrestricted) value at rest; spirometry and SVC maneuvers after ~5-min of acclimatization to the CWS; and a symptom-limited incremental cardiopulmonary cycle exercise test (CPET) in the presence of CWS to determine peak power output (PPO) as well as to familiarize participants to CPET with CWS.Patients were randomized within visits 2-4 to receive 12 mL of inhaled solution in 0.9% saline of 40 mg of furosemide (n = 12) or 120 mg of furosemide (n = 12). | Under the experimental conditions of this study, inhalation of nebulized furosemide at doses of 40 and 120 mg did not alleviate breathlessness during exercise in healthy men.Urine production rate, the percentage of participants reporting an “urge to urinate” and the intensity of perceived “urge to urinate” were all significantly greater after inhaling the 120 mg furosemide solution compared with both 0.9% saline and 40 mg furosemide solutions. No other systemic or adverse effects were reported following inhalation of the 40 and 120 mg furosemide solutions. |
| Grogono et. al (2018) [20]randomised, double blind, placebo-controlled crossover trial | n = 16 healthy volunteers (9 male) attended the Oxford Brookes Cardiorespiratory Research Laboratory on 4 occasions. Inclusion criteria included; age above 18 years, no regular prescription medication in the previous 2 weeks and if female, not pregnant or planning pregnancy. | Each participant visited the laboratory on 4 occasions; two practice sessions to familiarise themselves with the equipment and to become accustomed to rating the sensation of dyspnoea and; two ‘test’ sessions where participants inhaled the mists, with different dyspnoea stimuli (AH or WE) on different days in random order. On these days the participants were randomised to either inhale aerosolized mist (nebuliser) in the order of furosemide (40 mg, 10 mg/ml), saline (4 ml), furosemide (FSF) or saline, furosemide, saline (SFS) for both study days. Prior to each mist inhalation they gargled with a menthol mouthwash. The nebulisation duration of the furosemide mist was approximately 10-15 min and the saline mist 5-10 min. Each mist inhalation started after 6–11 min of the steady state test level of each pre-mist AH or WE test. The post mist steady state test level was between 9 and 14 min after the end of the mist inhalations. Each AH or WE test lasted 10 min, with a total visit duration of around 3 h (7 AH or WE tests, and 3 mist inhalations.) | The FSF mist order group and the SFS mist order group were well matched apart from by chance a higher proportion of participants who were Caucasian in the FSF compared to the SFS groups (p = 0.031). It is notable that 2 of the 3 (S9, S12) individuals who had an increase in AH (rather than a relief) following inhaled furosemide had a history of asthma. These two and S15 who also had a history of asthma were in the SFS group. No other notable differences were observed for individuals with a history of asthma. |
| Masoumi et. al (2014) [18]randomised, double blind, placebo-controlled crossover trial | n = 90 Patients who were 18–55 years old with dyspnea, cough, and wheezing or history of using the inhaler.Recorded formal diagnosis of asthma or COPD, noncardiac pulmonary edema, symptoms related to inhalation of irritant gas, aerosol or smoke, long duration of symptom onset (>10 hour), smoking more than 10 packs/year, comorbid acute medical problems, pregnancy, and administration of nebulized beta-agonist in the previous 6 hours were considered as exclusion criteria. | Eligible patients were randomly divided into intervention and control groups:in the intervention group, 5 mg of salbutamol (2.5 mg/2 cc) and 40 mg of furosemide vial (20 mg/2 cc) were nebulized for the patients during 15 minutes and, in the control group, 5 mg of salbutamol alone was nebulized for the patients during 15 minutes. The PEFR was measured in every patient before nebulization and in the 15, 30, and 45 minutes after it.Patients of both groups received 100 mg of methylprednisolone (500 mg/vial as sodium succinate) intravenously stat. If any patient did not respond to the treatment and their general condition was aggravated, other lines of treatment (MgSO4 IV, epinephrine IM) were tried or the treatment was repeated. Such subjects were excluded from the trial. | Adding furosemide to salbutamol in patients suffering from acute RAD considerably improve PEFR but there is not sufficient proof to confirm it as a routine standard treatment of acute asthma or acute RAD or miscellaneous dyspnea. |
| Atwi et. al (2022) [5]Systematic review | n = 4 publications. Search of Medline/ PubMed, CINAHL, Cochrane, Google Scholar, and the clinical trials registry (2010-2020). Inclusion criteria included: investigating the effect of inhaled furosemide on dyspnea and pulmonary function values in patients with COPD. Exclusion criteria included: if the outcomes were studied in general with no relation to COPD or if inhaled furosemide was not explicitly studied in relation to dyspnea and pulmonary function. | The studies in this review specifically looked at inhaled furosemide use with COPD participants. The dose used was between 20 mg – 40 mg depending on the study with one study using up to 160 mg. | A potential benefit was suggested for nebulized furosemide.Included studies indicated significant improvements in FEV1, FVC, and dyspnea relief with inhaled furosemide. |
| Ghaysouri et. al (2020) [19]Systematic Review and Meta-Analysis of Clinical Trials | n = 8 publications. Search of Magiran, Iran Medex, PubMed, Cochrane, Web of Science, Scopus, and Google scholar (2002-2018). Inclusion criteria included: The clinical trials comparing the therapeutic effects of nebulizing furosemide and placebo in patients with COPD. Exclusion criteria included: Low-quality studies, irrelevant articles, studies with inadequate data, reviews, case reports, letters to editors, qualitative studies, and abstracts of congress papers that contained incomplete information. | The studies in this review specifically looked at inhaled furosemide use with COPD participants.The outcomes included changes in the vital signs (i.e. respiratory rate, blood pressure, and heart rate) and respiratory parameters (i.e. PaCo2, Pao2, Hco3, pH, forced expiratory volume in the first second (FEV1), peak expiratory flow rate (PEFR), and SaO2). | Comparison of the vital signs between the two study groups showed that patients treated with nebulizing furosemide had values closer to normal.The results showed that patients who had received nebulizing furosemide had respiratory values closer to the normal levels indicating good therapeutic efficacy for this agent. |

COPD: Chronic Obstructive Pulmonary Disease; RAD: reactive airway disease; FEV1: forced expiratory volume in 1-s; FVC: forced vital capacity; PPO: peak power output; PEFR: peak expiratory flow rate; CPET: cardiopulmonary cycle exercise test; CWS: chest wall strapping.