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Physiological effects of noninvasive respiratory support strategies in adults with acute hypoxemic respiratory failure: a systematic review and network meta-analysis

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Abstract

Background In hypoxemic patients, the respective effects of noninvasive respiratory support strategies on lung injury determinants remain unclear, primarily due to the difficulty of obtaining standardized measurements for all interventions within the same study. We conducted a systematic review and network meta-analysis to assess the effects of noninvasive strategies on transpulmonary driving pressure and inspiratory effort in patients with acute hypoxemic respiratory failure.

Methods We conducted a systematic search (Ovid MEDLINE, Embase, Scopus, and PubMed) and performed a network meta-analysis of physiological studies involving hypoxemic adults published up to February 16th, 2025. We included studies that assessed inspiratory effort with esophageal manometry under at least two noninvasive respiratory support strategies [standard oxygen, high-flow nasal oxygen (HFNO), noninvasive ventilation (NIV), and continuous positive airway pressure (CPAP)]. Outcomes included transpulmonary driving pressure, inspiratory effort per breath and per minute, respiratory rate, and gas exchange. Treatment effects are displayed as mean differences [95% confidence intervals].

Results Among 5876 citations, thirteen studies (n = 312 patients) were included (mean PaO_2/FiO_2 = 131 (± 48) mmHg, mean respiratory rate = 28 (± 8) breaths*min^{-1}). Compared to standard oxygen, HFNO and CPAP did not affect transpulmonary driving pressure or effort per breath. HFNO and NIV reduced effort per minute (-95 cmH_2O*bpm

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[-140; -49] and -240 cmH_2O*bpm [-284; -196], respectively), whereas CPAP did not. NIV lowered effort per breath (-5.9 cmH_2O [-7.4; -4.4]) but increased driving pressure (3.4 cmH_2O [1.4; 5.4]). All strategies reduced respiratory rate, with HFNO producing the greatest decrease (HFNO: -5 breaths*min^{-1} [-6; -4]; CPAP: -2 breaths*min^{-1} [-4; -1]; NIV: -4 breaths*min^{-1} [-5; -2]); all interventions improved PaO_2/FiO_2, with CPAP and NIV showing greater effects than HFNO (CPAP: 67 mmHg [55; 80]; NIV: 82 mmHg [56; 108]; HFNO: 24 mmHg [5; 43]). None of the strategies affected $PaCO_2$.

Conclusions Noninvasive strategies exert distinct physiological effects: HFNO and NIV reduce effort per minute, while only NIV decreases effort per breath but at the cost of increased driving pressure. CPAP has neutral effects on driving pressure and effort. CPAP and NIV provide greater improvements in oxygenation than HFNO. Individualized selection based on effort levels may help balance the benefits and risks of noninvasive support.

PROSPERO registration: CRD42024564035.

Keywords Hypoxemic respiratory failure, Noninvasive support, Noninvasive ventilation, High-flow nasal oxygen, CPAP, Self-inflicted lung injury, Network meta-analysis

Background

Noninvasive respiratory support is commonly applied to improve oxygenation and avoid endotracheal intubation in patients with acute hypoxemic respiratory failure. While this can be beneficial, it also carries risks [1]. Hypoxemic patients may exhibit increased respiratory drive, resulting in high inspiratory effort and respiratory rate [2, 3]. This can be injurious, causing patient self-inflicted lung and diaphragm injury. Self-inflicted lung injury occurs because high inspiratory effort, eventually coupled with ventilator support, generates high transpulmonary driving pressure. This increases lung stress and regional heterogeneities in lung inflation, leading to local overstretch and worsening lung injury [4, 5]. Moreover, the profoundly negative intrathoracic pressures promote lung oedema, reducing lung compliance and impairing gas exchange. This further increases respiratory drive, finally generating a vicious cycle that perpetuates lung damage [6, 7]. Moreover, diaphragm injury occurs because high inspiratory effort can cause shear stress, ischemia–reperfusion damage, and proteolytic degradation, ultimately leading to diaphragm weakness and impaired function [8, 9].

To interrupt this vicious cycle, endotracheal intubation and sedation constitute a therapeutic option [7]. However, they carry the risk of diaphragm atrophy, ventilator-induced lung injury, ventilator-associated infectious events, and intensive care unit-associated complications [10]. An ideal approach would maximize the benefits of noninvasive support while making spontaneous breathing non-injurious [8]. Accordingly, any noninvasive support technique should balance oxygenation benefits with the impact on inspiratory effort and transpulmonary driving pressure, which are key determinants of lung injury progression [8]. Noninvasive respiratory support strategies include high-flow nasal oxygen (HFNO), noninvasive ventilation (NIV), and continuous positive airway pressure (CPAP). These strategies gained popularity over the last few years, especially during the COVID-19 pandemic [11]. Mechanistically, the optimal strategy depends on the interplay between the patient's breathing pattern phenotype and the physiological effects of the intervention, with the goal of improving oxygenation while minimizing exposure to injurious factors such as high inspiratory effort and transpulmonary driving pressure [12].

However, the respective effects of different noninvasive respiratory support techniques on transpulmonary driving pressure and inspiratory effort have not been systematically investigated, largely due to the inherent difficulty of obtaining a complete set of measurements in physiological studies. Network meta-analyses offer a valuable tool to integrate fragmented evidence and enable indirect comparisons across interventions. We conducted a systematic review and network meta-analysis of the existing literature to assess the respective effects of noninvasive support strategies on inspiratory effort and transpulmonary driving pressure in patients with acute hypoxemic respiratory failure.

Methods

A complete version of the methods is presented in the supplementary material 1: E1, E2.

Search strategy

A systematic search was conducted in Ovid MEDLINE, Embase, Scopus, and PubMed for published randomized and non-randomized controlled trials up to February 16th, 2025 (CRD42024564035). Grey literature was screened using Google Scholar and conference proceedings from the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the American Thoracic Society. The search also included PROSPERO. No language restrictions were applied.

Inclusion and exclusion criteria

We included studies enrolling at least two non-intubated adults (> 18 years) with acute hypoxemic respiratory

failure of non-cardiogenic origin, treated with at least two noninvasive respiratory support strategies (including standard oxygen therapy, NIV, HFNO, CPAP), and reporting at least one measurement of inspiratory effort using esophageal manometry, as the inspiratory swing in esophageal pressure or in trans-diaphragmatic pressure (end-inspiratory minus end-expiratory values). Exclusion criteria are detailed in supplementary material 1: E3.

Outcomes

The primary outcome was the transpulmonary driving pressure. Because its definition varied across studies – with some reporting dynamic values, others as quasi-static, and some omitting it entirely – we calculated it as the sum of set pressure support and the negative swing in esophageal pressure (ΔPes) during NIV, and as ΔPes alone during standard oxygen, HFNO, and CPAP (where no pressure support is applied) [13, 14]. If available, quasistatic transpulmonary pressure values were extracted and are reported in the supplementary material. Secondary outcomes were effort per breath (ΔPes), effort per minute (ΔPes × respiratory rate), respiratory rate, pressure–time product of the esophageal or trans-diaphragmatic pressure, PaO_2/FiO_2, $PaCO_2$, and hemodynamics (only mean arterial pressure and heart rate were reported in most studies). Effort per minute serves as a surrogate for the metabolic work of breathing [15–17]. As not pre-specified exploratory outcome, we computed [4 × transpulmonary driving pressure + respiratory rate ($4\Delta P_L + RR$)] – which was associated with mortality in intubated patients with acute respiratory distress syndrome both during controlled and assisted ventilation [14, 18].

Of note, although effort per breath and transpulmonary pressure are identical for standard oxygen, HFNO, and CPAP, small differences in pooled contrasts (e.g., HFNO vs standard oxygen) may arise in the network meta-analysis because of the anchor effect of NIV. This affects the network structure but not the within-study values, which remain identical.

Study selection

All references were independently screened by author pairs (C.M., N.V., R.d.S., M.M., A.C.). Titles and abstracts were screened based on eligibility criteria. Then, full texts were examined for eligibility. Data extraction was performed independently and in duplicate, including participant characteristics, study design, $PaCO_2$, dyspnea, PaO_2/FiO_2, interventions, and outcomes (L.S.M., E.B., R.d.S, M.M.). Disagreements were resolved by a third reviewer (C.G.). If the results were not reported as mean and standard deviation, we estimated the mean and SD from the reported data [19]. If the data were only displayed in figures, we used WebPlotDigitizer (https://automeris.io, v 5.2) to extract raw values and derive the mean and standard deviation.

Risk of bias

Risk of bias in the included studies was assessed independently and in duplicate using the modified Cochrane Collaboration's risk of bias assessment instrument (ROB 2.0 for crossover studies, ROBINS-I) (N.V., E.B.). Disagreements were resolved by a third reviewer (L.S.M.).

Statistical analysis

We employed a frequentist approach using the *{netmeta}* package in RStudio [20]. After testing for heterogeneity, we used a random-effects model to account for between-study variability. Treatment effects for continuous outcomes were analyzed using the inverse variance method and expressed as the mean difference (MD) with 95% confidence intervals (CIs). Statistical heterogeneity across studies was assessed using the chi-squared test and the I^2 statistic, decomposing the total heterogeneity within the network, into its two components: within-design heterogeneity and inconsistency between designs. Publication bias was assessed by visually inspecting a funnel plot for potential asymmetry and Egger's test.

To assess the robustness of our results for the primary outcome, we conducted a sensitivity analysis excluding non-randomized trials and studies at high risk of bias. To examine network geometry, we constructed a network graph. Inconsistency was evaluated through heterogeneity test, the direct and indirect evidence plot, and additional techniques such as the Net Heat Plot and the net-splitting method. When interpreting the direct and indirect evidence plot, a mean path length greater than 2 suggests that the comparison estimate should be approached with caution [21]. All statistical analyses were performed using R (v4.1.3, R Foundation for Statistical Computing, Vienna, Austria; URL: https://www.R-project.org). Figures were prepared with GraphPad Prism (version 9.0.0 for Windows, GraphPad Software, Boston, Massachusetts, USA, www.graphpad.com).

Results

We identified 5876 unique citations. We reviewed the full text of 46 studies to assess eligibility. Of these, 14 studies met our inclusion criteria. One study had data already reported in a previous publication [22]: we therefore included only the original dataset [23].

Overall, 13 studies and 312 patients were included (Fig. 1). Reasons for exclusion are listed in the supplementary material 1: E3.

Characteristics of included studies and patients

We included 10 physiological crossover studies and 3 non-randomized studies. Eight studies compared two

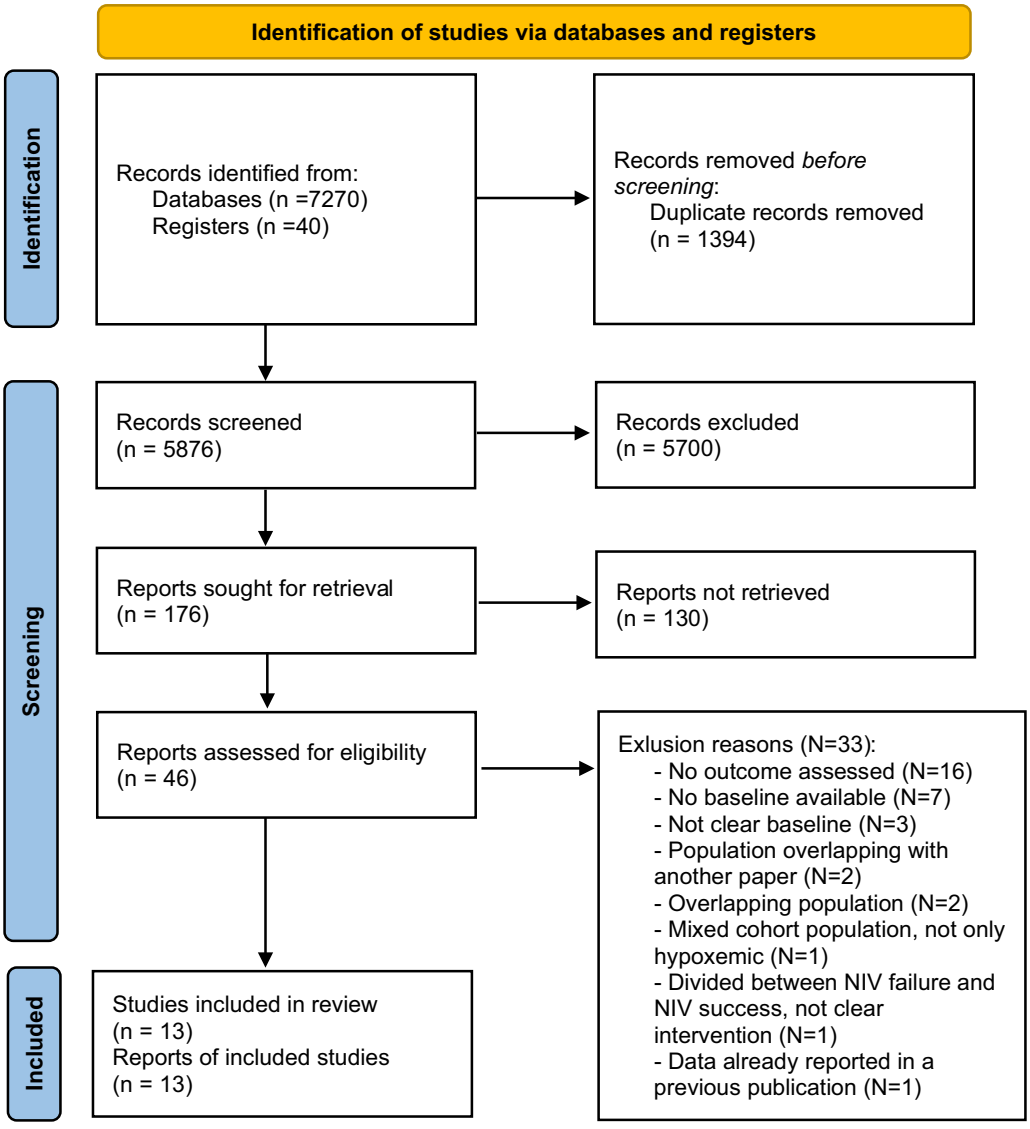

Fig. 1 PRISMA flow diagram of study selection. Flowchart summarizing the identification, screening, eligibility assessment, and inclusion of studies in the systematic review and network meta-analysis

interventions, four compared three, and one compared four. When two PEEP levels were tested, we extracted data from the setting with the highest level [24–26].

Table 1 summarizes patient characteristics. On average, included patients had a moderate-to-severe hypoxemic respiratory failure [mean (SD) PaO_2/FiO_2 ratio 131 (48) mmHg], were hypocapnic [mean (SD) $PaCO_2$ 35 (8) mmHg] and were tachypneic [mean (SD) respiratory rate 28 (8) breaths*min^{-1}]: 113 patients (36%) had COVID-19–related hypoxemic respiratory failure; the remaining 199 (64%) had other causes.

Risk of bias assessment

All studies satisfied the transitivity assumption. We assessed the risk of bias for all included studies using the ROBINS-I and RoB 2.0 algorithms (supplementary material 1: E4-E8). Given the mechanistic nature of the interventions, we adapted the risk of bias assessment in specific domains:

1) The respiratory support strategies are impossible to blind; this domain was not considered.
2) Any study reporting randomization – regardless of method – was considered at low risk of bias. Additionally, we deemed the risk of carryover effect low if any randomization was present and if the respiratory support strategies were tested for sufficient time to allow adaptation of the respiratory drive [27–29].

One study exhibited missing data for > 20% of the population [23] and three were non-randomized trials [26, 30,

Table 1 Patient's characteristics and demographics at study inclusion

Study	Population	N	Age (years)	SAPS II	SOFA	PaO_2/FiO_2 (mmHg)	$PaCO_2$ (mmHg)	Respiratory rate (breaths*min^{-1})
Calderini [67] (1999)	P. Carinii (4); Aspergillus (2)	6	44 (13)	42 (12)	N.R	N.R	N.R	N.R
Fraticelli [68] (2009)	Acute Cardiac Failure (2); pneumonia in immunodepressed (3); aspiration pneumonia (1); community acquired pneumonia (1)	7	59 (18)	33 (15)	N.R	N.R	34 (4)	31 (8)
Giosa [25] (2023)	COVID-19 (28)	28	65 (10)	N.R	3 (1)	107 (55)	36 (4)	25 (5)
Grieco [44] (2020)	Infectious pulmonary (13); non-infectious pulmonary (1); extrapulmonary (1)	15	70 (11)	50 (27)	6 (5)	126 (51)	32 (3)	N.R
L'Her [24] (2005)	P. Carinii (1); community acquired pneumonia (5); aspiration pneumoniae (2); eosinophilic pneumonia (1); nosocomial pneumonia (1)	10	61 (17)	41 (17)	N.R	131 (61)	42 (11)	29 (10)
Lassola [26] (2023)	COVID-19 (30)	30	66 (10)	31 (6)	4 (1)	128 (46)	40 (6)	23 (5)
Mauri [42] (2016)	Infectious pulmonary (13); extrapulmonary (2)	15	60 (14)	38 (9)	N.R	130 (35)	41 (6)	24(3)
Mauri [41] (2017)	Infectious pulmonary (8); extrapulmonary (9)	17	62 (10)	48 (13)	11(3)	167 (46)	38 (5)	24(8)
Menga [43] (2023)	COVID-19 (10); infectious pulmonary (5)	15	68(11)	32 (7)	2 (0)	120 (29)	33 (8)	N.R
Schifino [23] (2022)	COVID-19 (15)	15	64(9)	22 (6)	N.R	121 (36)	34 (4)	24 (5)
Tonelli [31] (2024)	AHRF of non-covid origin	82	72 (9)	N.R	5 (4)	130 (57)	33 (3)	30 (8)
Tonelli (Covid-19) [30] (2021)	COVID-19 (30)	30	67 (16)	N.R	3 (1)	N.R	34 (6)	28 (4)
Tonelli (non Covid-19) [30] (2021)	Non COVID-19 (30)	30	68 (16)	N.R	3 (1)	N.R	35 (8)	36 (9)
Vargas [69] (2015)	Community acquired pneumonia (7); pneumonia in immunocompromised (3); nosocomial pneumonia (1); health-care associated pneumoniae (1)	12	65 (11)	46 (18)	N.R	146 (51)	35 (6)	22 (9)
Weighted mean (SD) **N**	COVID-19 (113); non COVID-19 (199)	312	67 (13) 312	37 (16) 142	5 (4) 232	131 (48) 299	35 (6) 306	28 (8) 276

Data are reported as mean (SD)

In the last row, the weighted mean (sd) with the number of patients (n) is reported

Non COVID-19 patients were distributed as follows: non-specified non COVID-19 AHRF (112); non-specified pulmonary infections (39); community acquired pneumonia (13); extrapulmonary (12); pneumonia in immunocompromised (6); P. Carinii (5); aspiration pneumonia (3); Aspergillus (2); nosocomial pneumonia(2); acute cardiac failure (2); non-infectious (pulmonary) (1); eosinophilic pneumonia (1); healthcare associated pneumonia (1)

SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; N.R., not reported

31]. These studies were deemed at high risk of bias and were excluded from the sensitivity analysis.

Statistical heterogeneity and inconsistency

No substantial differences between direct and indirect estimates (*mean path length* > 2) were detected for the primary outcome (supplementary material 1: E9). The *heat plot* identified only 4/169 designs at strong risk for inconsistency (supplementary material 1: E10-E12); these inconsistencies were no longer evident after sensitivity analysis (supplementary material 1: E13-E14).

The *net-splitting analysis* showed a significant difference between the network estimate and the direct and indirect estimate for the comparison between HFNO and NIV only ($I^2 = 78.9\%$, $p = 0.037$); of note, all the effects were on the same side of the neutrality line (supplementary material 1: E11-E12). The sensitivity analysis showed no inconsistencies (supplementary material 1: E15-E16).

The inspiratory effort had low heterogeneity and inconsistency between direct and indirect evidence estimates in the *mean path length*, in the *heat plot* and in *the net-splitting analysis* alike. (supplementary material 1: E17-E20). The detected publication bias was low (supplementary material 1: E21-E22).

Effects of intervention

The effects of the interventions on study outcomes are detailed in Table 2.

Primary outcomes

Transpulmonary driving pressure

Transpulmonary driving pressure was available for 13 studies, with 24 pairwise comparisons and 312 patients (Fig. 2).

Compared to standard oxygen, HFNO and CPAP did not affect transpulmonary driving pressure (MD −0.9 cmH_2O, 95% confidence interval [95% CI] [−2.9; 1.1] and MD 0.6 cmH_2O, 95% CI [−1.4; 2.5]), while NIV increased it (MD 3.4 cmH_2O, 95% CI [1.4; 5.4]) (Fig. 3).

Compared to HFNO, CPAP did not affect transpulmonary driving pressure (MD 1.49 cmH_2O, 95% CI [−0.46; 3.44]), while NIV increased it (MD 4.33 cmH_2O, 95% CI [2.03; 6.62]) (Fig. 3).

The effects of the strategies on the quasi-static transpulmonary driving pressure did not differ from the main analysis (supplementary material 5: E-Fig. 1).

Heterogeneity was moderate-high ($I^2 = 57.9\%$, 95% CI [27.9%; 75.4%]), and primarily driven by between-design differences ($Q = 33.03$, $p = 0.0003$) rather than within-design variability ($Q = 4.98$, $p = 0.5463$). Design-specific decomposition confirmed that different comparisons did not contribute significantly to inconsistency. This supports the appropriateness of the random-effects model in accounting for between-study variability.

Inspiratory effort

Effort per breath

Effort per breath was available for 13 studies, with 24 pairwise comparisons and 312 patients (Fig. 2).

Compared to standard oxygen, HFNO and CPAP did not affect effort per breath (MD −1.2 cmH_2O, 95% CI [−2.7; 0.3] and MD 0.9 cmH_2O, 95% CI [−0.5; 2.34]; respectively).

NIV decreased effort per breath (MD −5.9 cmH_2O, 95% CI [−7.4; −4.4]) (Fig. 4).

Compared to HFNO, CPAP increased the effort per breath (MD 2.1, 95% CI [0.7; 3.6], while NIV significantly decreased it (MD −4.7 cmH_2O, 95% CI [−6.4; −3]) (Fig. 4).

Heterogeneity was moderate ($I^2 = 27\%$, 95% CI [0.0%; 59.4%]).

Effort per minute

Both respiratory rate and effort per breath were available in 12 studies, with 23 pairwise comparisons and 304 patients, allowing calculation of effort per minute.

Compared to standard oxygen, HFNO reduced effort per minute (MD −95 cmH_2O*bpm, 95% CI [−140; −49]), while CPAP did not affect it (MD −21 cmH_2O*bpm, 95% CI [−64; 22]), and NIV decreased it the most (MD −240 cmH_2O*bpm, 95% CI [−284; −196]) (Fig. 4).

Compared to HFNO, CPAP increased effort per minute (MD 73 cmH_2O*bpm, 95% CI [22; 125]), while NIV decreased it (MD −146 cmH_2O*bpm, 95% CI [−196; −96]).

Heterogeneity was high (I2 = 97% [96.1%; 97.7%]).

Secondary outcomes

Respiratory rate

Respiratory rate was reported in 12 studies, with 23 pairwise comparisons and 304 patients (Fig. 5).

Compared to standard oxygen, HFNO, CPAP and NIV reduced respiratory rate by −5 breaths per minute (bpm) (95% CI [−6; −4]), −2 bpm (95% CI [−4; −1]), and −4 bpm, (95% CI [−5; −2]) respectively (Fig. 5).

Compared to HFNO, CPAP increased respiratory rate (MD 3 bpm, 95% CI [1; 4]), while NIV did not modify it (MD 1 bpm, 95% CI [−1; 3]) (Fig. 5).

Heterogeneity was low ($I^2 = 0\%$, 95% CI [0.0%; 52.3%]).

Gas exchange

PaO_2/FiO_2 ratio was reported in 10 studies, with 23 pairwise comparisons and 214 patients, while $PaCO_2$ in 11 studies, with 20 pairwise comparisons and 259 patients.

Compared to standard oxygen, HFNO, CPAP and NIV increased PaO_2/FiO_2 ratio by 24 mmHg (95% CI [5; 43]), 67 mmHg (95% CI [55; 80]) and 82 mmHg (95% CI [56; 108]), respectively (Fig. 5).

Due to the unreliability of FiO_2 estimation in patients receiving standard oxygen therapy, we excluded all comparisons involving standard oxygen, and compared the interventions to the HFNO. Compared to HFNO, both CPAP and NIV increased PaO_2/FiO_2 ratio by 54 mmHg (95% CI [30; 79]) and 62 mmHg (95% CI [34; 91]), respectively. I^2 was 4.7% [0.0%; 75.8%] (Fig. 5).

None of the interventions affected $PaCO_2$ compared to standard oxygen (supplementary material 5: E-Fig. 2). CPAP decreased $PaCO_2$ compared to HFNO (MD −0.8 mmHg, 95% CI [−1.6; 0]) (supplementary material 5: E-Fig. 2).

Heterogeneity was low ($I^2 = 0\%$, 95% CI [0.0%; 53.6%]).

Hemodynamics

Hemodynamics were assessed in 6 studies, reporting heart rate and mean arterial pressure in a total of 12 pairwise comparisons and 84 patients. Compared to

Table 2 Characteristics of included studies

Study	Comparison (N)	Inspiratory effort (cmH_2O)	Transpulmonary pressure (cmH_2O)	PaO_2/FiO_2 (mmHg)	$PaCO_2$ (mmHg)	Respiratory rate
Calderini [67] (1999)	Standard Oxygen (6)	14 (5)	14 (5)	N.R	N.R	N.R
	Face-mask NIV (6)	13.0 (2)	23 (5)	N.R	N.R	N.R
Fraticelli [68] (2009)	Standard Oxygen (7)	14.7(5.9)	14.7 (5.9)	117 (106)	33 (3)	29 (4)
	Face-mask NIV (7)	8.8 (7.2)	18.8 (7.1)	185 (106)	33 (5)	27 (7)
Giosa [25] (2023)	Standard Oxygen (28)	5 (3.7)	5 (3.7)	118 (61)	36 (4)	25 (5)
	Helmet CPAP (28)	8.3 (3.9)	8.3 (4)	172 (60)	36 (4)	24 (6)
Grieco [44] (2018)	Standard oxygen (15)	N.R	N.R	121 (39)	32 (4)	N.R
	HFNO (15)	14 (9)	14 (9)	137 (58)	32 (7)	29 (5)
	Helmet NIV (15)	7.3 (5.7)	17.7 (5.7)	231(130)	32 (5)	26 (7)
L'Her [24] (2005)	Standard oxygen (10)	11 (5.4)	11 (5.4)	131 (61)	42 (11)	29 (10)
	Face-mask CPAP (10)	10.3 (7.1)	10.3 (7.1)	184 (74)	N.R	N.R
	Face-mask NIV (10)	5.8 (4.4)	15.8 (4.4)	206 (120)	40 (14)	28 (11)
Lassola [26] (2023)	Standard oxygen (30)	11 (4.8)	11 (4.8)	N.R	N.R	22.5 (4.9)
	Helmet CPAP (30)	12 (3.7)	12 (3.7)	N.R	N.R	19 (4.2)
Mauri [42] (2016)	Standard oxygen (15)	9.9 (4.2)	9.9 (4.2)	130(35)	40.7 (5.7)	23.7 (5.7)
	HFNO (15)	8 (3.4)	8 (3.4)	184 (53)	41.1 (5.9)	21 (5.7)
Mauri [41] (2017)	Standard oxygen (17)	9.4 (4.4)	9.4 (4.4)	151 (60)	38.2 (5)	24 (8)
	HFNO (17)	7.1 (3.4)	7.1 (3.4)	205 (61)	38.3 (5.4)	18 (7)
Menga [43] (2023)	HFNO (15)	10.3 (4.1)	10.3 (4.1)	125.3 (34.3)	31 (7.36)	26.3 (9)
	Helmet CPAP (15)	14 (7.4)	14 (7.4)	204.6 (100.6)	33.3 (7.36)	29.7 (7.36)
	Helmet NIV (15)	5.67 (4.9)	15.67 (4.9)	172.3(64.61)	33 (9)	28 (8)
Schifino [23] (2022)	Standard oxygen (15)	10.2 (5)	10.2(5.1)	120.6 (36.1)	33.7 (3.7)	23.6 (5.3)
	HFNO (15)	9.9 (3.8)	9.9 (3.8)	207 (94)	N.R	22.8 (5)
	Helmet CPAP (15)	7.6 (4.3)	7.6 (4.3)	170.9 (61.8)	N.R	23.2 (4.3)
	Face-mask NIV (15)	3.9 (3.4)	8.8 (3.6)	152.2 (75.4)	33.24 (4.2)	20.4 (5.6)
Tonelli [31] (2023)	Standard oxygen (82)	18 (15.1)	18 (15.1)	130 (57.3)	33 (3)	29.67 (8.3)
	HFNO (82)	15 (15.8)	15 (15.8)	142.6 (65.6)	34.2 (3.24)	23.33 (6.04)
Tonelli [COVID-19] [30] (2021)	Standard oxygen (30)	13.9 (4.3)	13.9 (4.3)	N.R	34 (6)	28 (4)
	Face-mask NIV (30)	7.9 (3.1)	18.9 (3.4)	135 (28)	35 (4)	24 (4)
Tonelli [Non-Covid] [30] (2021)	Standard oxygen (30)	33.7 (10.9)	33.7 (10.9)	N.R	35 (8)	35 (9)
	Face-mask NIV (30)	21 (14.4)	37 (10.1)	139 (30)	34 (3)	31 (11)
Vargas [69] (2015)	Standard oxygen (12)	11.1 (5.8)	11.1 (5.8)	146 (51)	35 (6)	26 (10)
	HFNO (12)	8.7 (2.3)	8.7 (2.3)	169 (23)	37 (7)	22 (6)
	Face-mask CPAP (12)	9.4 (4.4)	9.4 (4.4)	234 (54)	36 (7)	25 (9)

Data are reported as mean (SD)

N.R., not reported

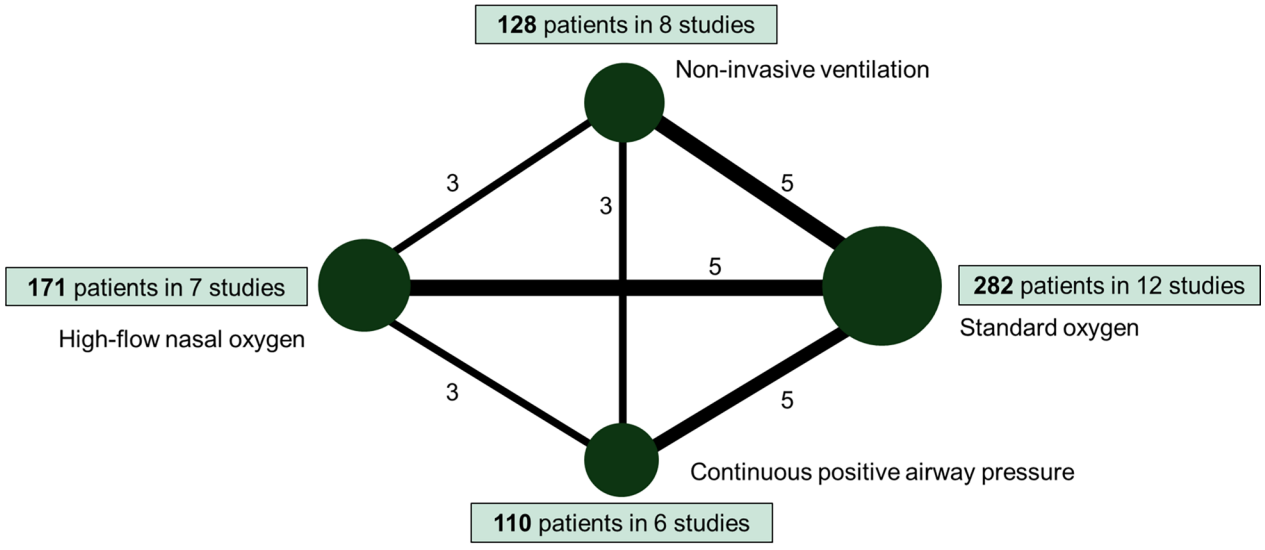

Fig. 2 Network geometry of included studies. Each node represents a noninvasive respiratory support strategy; node size is proportional to the total number of patients receiving each intervention. Lines between nodes represent direct head-to-head comparisons; line thickness is proportional to the number of studies

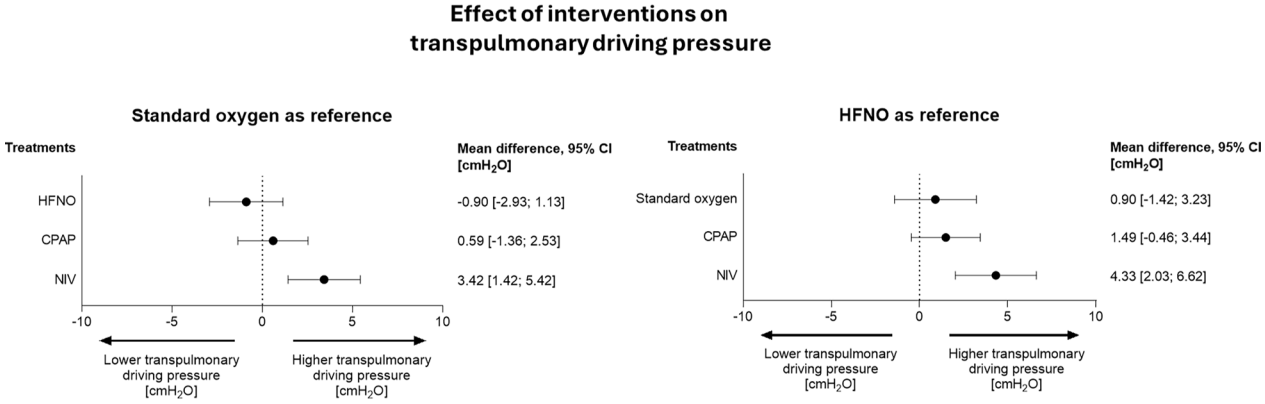

Fig. 3 Effects of noninvasive respiratory strategies on transpulmonary driving pressure. Left panel: standard oxygen therapy as comparator. Right panel: high-flow nasal oxygen (HFNO) as comparator. Dots indicate mean difference estimates; bars represent 95% confidence intervals (CIs)

standard oxygen, no significant differences were found in any parameter for HFNO, CPAP, or NIV. Heterogeneity was negligible ($I^2 = 0\%$, 95% CI 0–70.8%) (supplementary material 1: E23-E24).

Exploratory analysis

Both respiratory rate and effort per breath were available in 12 studies, with 23 pairwise comparisons and 304 patients, allowing calculation of $4\Delta P_L + RR$.

Compared to standard oxygen, HFNO reduced $4\Delta P_L + RR$, (MD −7.33 cmH_2O + bpm, 95% CI [−14.51; −0.14]), while CPAP did not affect it (MD 1.69 cmH_2O + bpm, 95% CI [−5.58; 8.97]), and NIV increased it (MD 9.04 cmH_2O + bpm, 95% CI [1.40; 16.67]) (supplementary material 5: E-Fig. 3).

Compared to HFNO, both CPAP and NIV increased 4ΔPL + RR, with a greater effect observed for NIV (MD 9 cmH_2O + bpm, 95% CI [1.7; 16.3] and 16.4 cmH_2O + bpm, 95% CI [7.6; 25.2], respectively).

Heterogeneity was low ($I^2 = 18.6\%$, 95% CI [0.0%; 54.8%]).

Sensitivity analysis

We analyzed separately the effects of the interfaces used to deliver CPAP and NIV – helmet or face-mask (supplementary material 5: E-Fig. 4). The small number of direct comparisons on the primary outcome, and the consequent high heterogeneity, precluded drawing meaningful conclusions. The results are reported in the supplementary material 1: E25.

We performed a sensitivity analysis by removing 4 studies deemed at high risk of bias [23, 26, 30, 31]. When excluding non-randomized trials and those deemed at high risk of bias, the main findings remained consistent

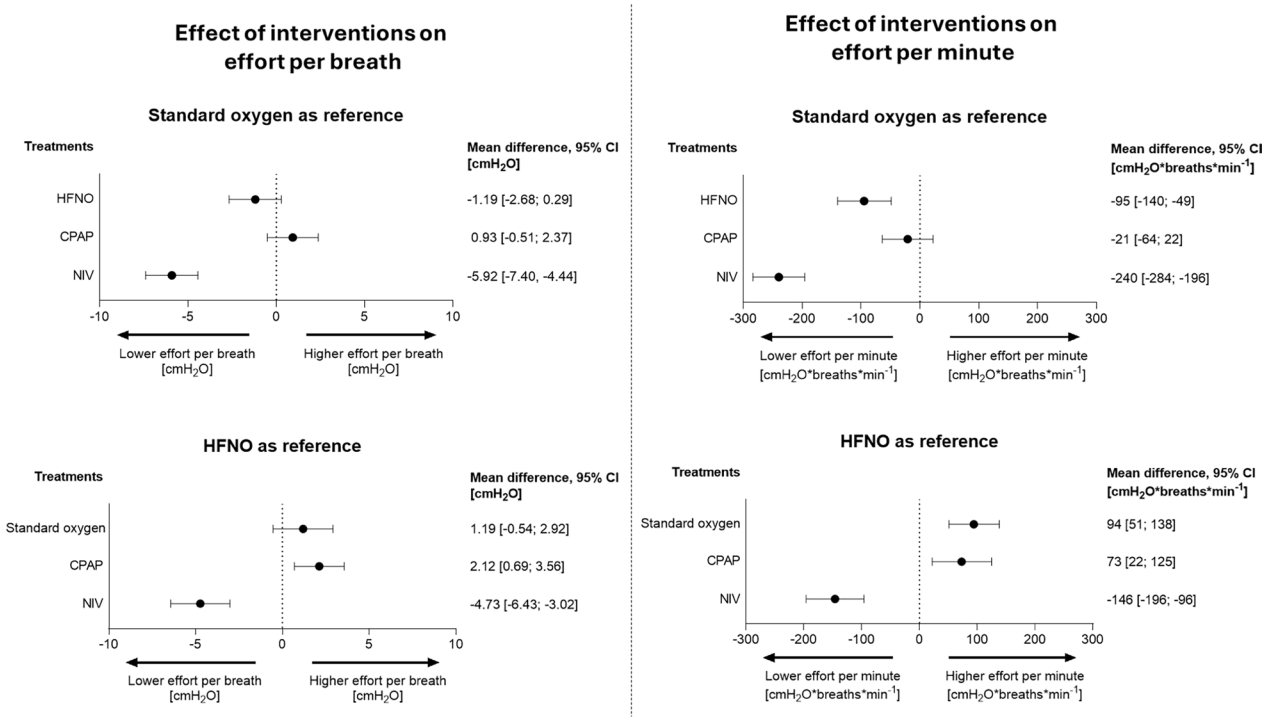

Fig. 4 Effects of noninvasive respiratory strategies on inspiratory effort. Upper panels: standard oxygen therapy as comparator. Lower panels: HFNO as comparator. Left side: effort per breath. Right side: effort per minute. Dots represent mean difference estimates; bars represent 95% CIs

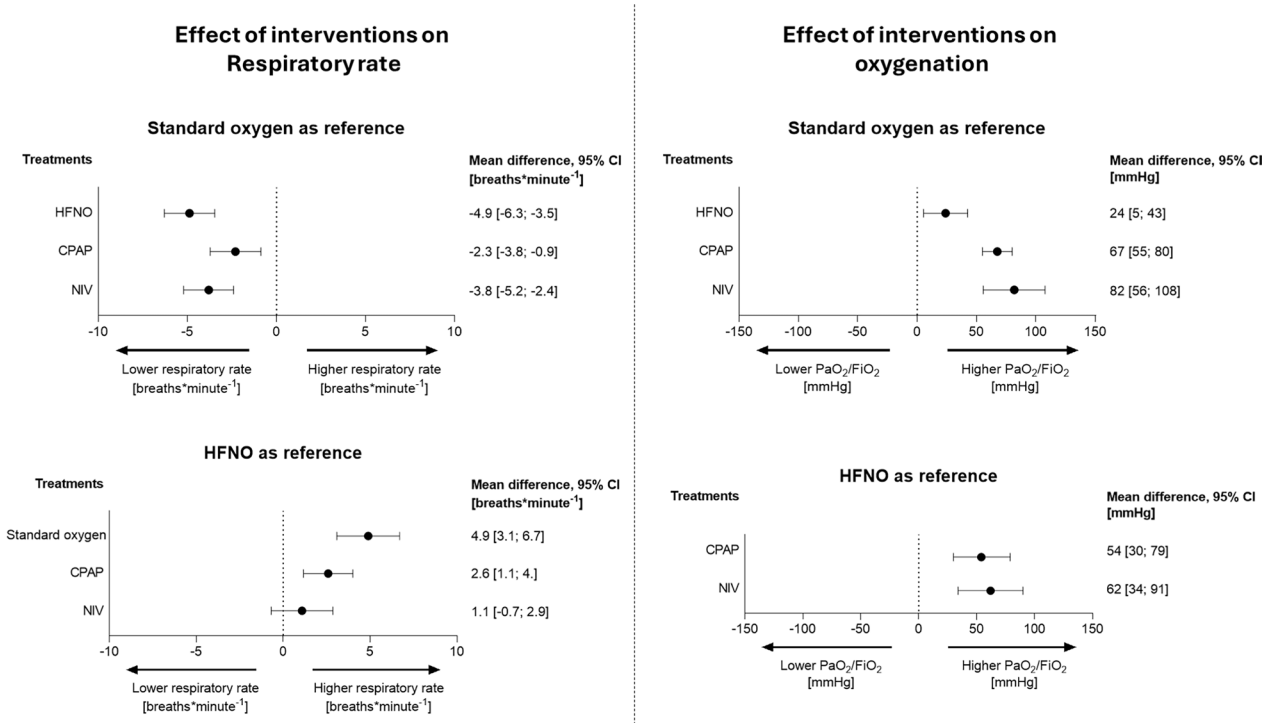

Fig. 5 Effects of noninvasive respiratory strategies on respiratory rate and oxygenation (PaO_2/FiO_2 ratio). Upper panels: standard oxygen therapy as comparator. Lower panels: HFNO as comparator. Left side: respiratory rate. Right side: PaO_2/FiO_2 ratio. Dots represent mean difference estimates; bars represent 95% CIs

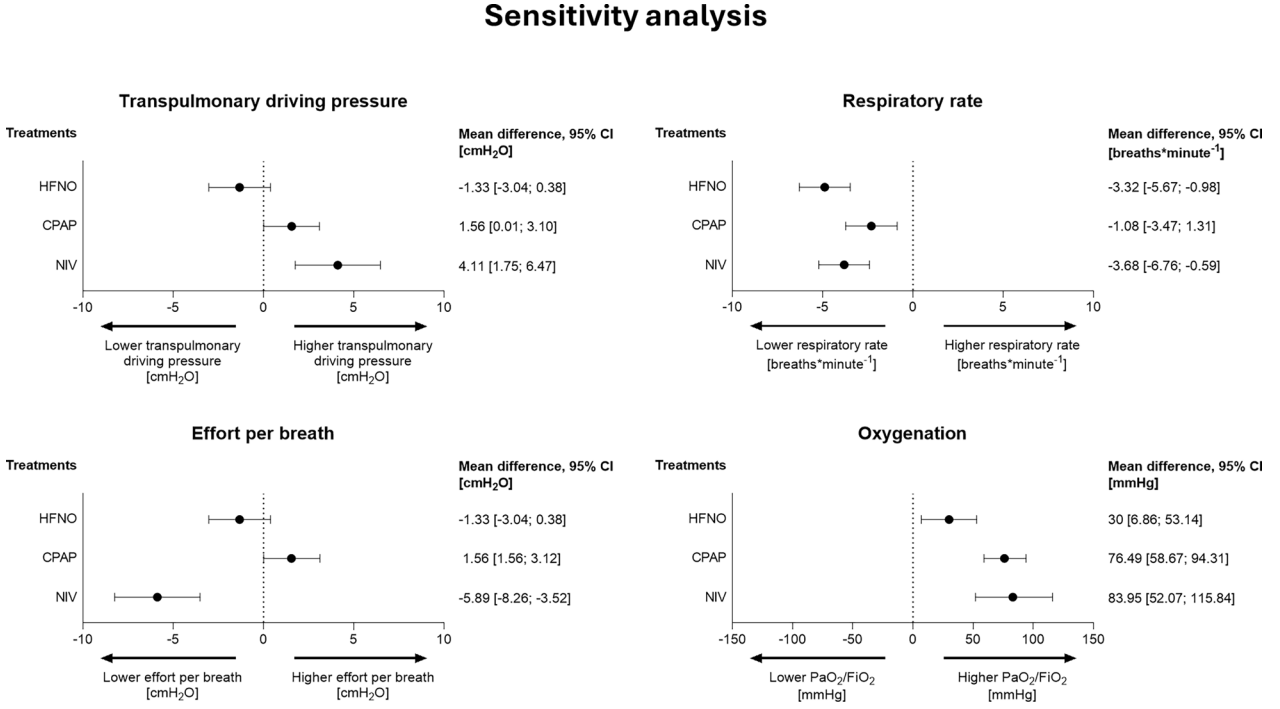

Fig. 6 Sensitivity analysis of noninvasive respiratory strategies. Panels display effects on transpulmonary driving pressure (upper left), inspiratory effort (lower left), respiratory rate (upper right), and oxygenation (PaO_2/FiO_2 ratio; lower right). Standard oxygen is the comparator in all panels. Dots represent mean differences; bars indicate 95% CIs

(Fig. 6 and supplementary material 1: E26-E28). Specifically, NIV was the only strategy increasing transpulmonary driving pressure (MD 4.1 cmH_2O, 95% CI [1.8; 6.5]) and reducing effort per breath (MD −5.9 cmH_2O, 95% CI [−8.3; −3.5]). HFNO did not affect the transpulmonary driving pressure or the effort per breath (both MD −1.3 cmH_2O, 95% CI [−3; 0.4]). Unlike the main analysis, CPAP increased both transpulmonary driving pressure (1.6 cmH_2O, 95% CI [0; 3.1]) and effort per breath (1.5 cmH_2O [0.1; 3.1]) compared to standard oxygen.

Risk of bias

Visual inspection of funnel plots for the two primary outcomes (ΔP_L and ΔPes) did not reveal major asymmetry (supplementary material 1: E21-E22). Egger's test confirmed the absence of significant small-study effects ($p = 0.205$ for ΔP_L and $p = 0.245$ for ΔPes). These findings suggest a low risk of publication bias.

Discussion

The results of this network meta-analysis of physiological studies involving adults with acute hypoxemic respiratory failure can be summarized as follows:

- No intervention reduces transpulmonary driving pressure compared to standard oxygen; NIV increases transpulmonary driving pressure compared to both standard oxygen and HFNO.
- Compared to standard oxygen, HFNO and NIV decrease effort per minute; CPAP increases effort per minute compared to HFNO.
- Only NIV reduces effort per breath compared to both standard oxygen and HFNO; CPAP increases effort per breath compared to HFNO.
- All strategies decrease respiratory rate compared to standard oxygen, and HFNO reduces it the most.
- All strategies increase PaO_2/FiO_2 ratio, with CPAP and NIV having a greater effect than HFNO.

To achieve lung protection, noninvasive support should yield lung recruitment—improving oxygenation and reducing lung strain – while maintaining both inspiratory effort and transpulmonary driving pressure within safe limits [8, 10]. In intubated ARDS patients, limiting tidal volumes and driving pressure can improve clinical outcome by preventing lung injury progression [18, 32, 33]. However, this alone does not ensure lung protection in spontaneously breathing patients, as strong inspiratory effort can yield lung injury even in the presence of limited tidal volumes [12, 31, 34–37]. In non-intubated patients, the optimal approach depends on the interplay of each patient's unique characteristics, particularly their individual effort per breath, and the distinct physiological effects exerted by different forms of noninvasive support.

Compared to standard oxygen therapy, HFNO does not significantly affect inspiratory effort per breath nor

transpulmonary driving pressure. However, compared to standard oxygen, CPAP, and NIV, HFNO reduces respiratory rate, effort per minute, and 4ΔPL + RR, the latter possibly resulting in mechanical unloading on the lung parenchyma and justifying the beneficial effects of HFNO on clinical outcomes [38]. These beneficial physiological effects likely result from anatomical dead-space clearance in the upper airways; this reduces minute ventilation under isocapnic conditions and alleviates dyspnea. Moreover, HFNO increases expiratory resistance, prolongs expiratory time and consequently lowers respiratory rate [39, 40]. Together, these mechanisms explain why HFNO reduces respiratory rate without increasing $PaCO_2$, despite unchanged inspiratory effort per breath [41, 42].

In contrast, NIV modifies the work of breathing through different physiological mechanisms. NIV consistently reduces effort per breath, effort per minute, thus showing the greatest potential for unloading inspiratory muscles: this may protect the diaphragm from excessive effort, and prevent injurious lung inflation patterns related to high inspiratory effort (i.e. pendelluft) [4, 8, 10, 43, 44]. Both NIV and HFNO reduced respiratory rate compared with standard oxygen, but no significant difference was observed between them. However, NIV can simultaneously increase transpulmonary driving pressure, tidal volume, and minute ventilation. These increases in lung stress, coupled with potential to delay endotracheal intubation, may exacerbate lung injury in more severe cases, potentially worsening clinical outcomes. This observation aligns with results from large randomized clinical trials indicating potential harm associated with NIV use in severe hypoxemic respiratory failure [34, 35, 38]. Clinically, when inspiratory effort per breath is high, NIV can effectively reduce it, sometimes by a magnitude exceeding the applied level of pressure support, potentially lowering transpulmonary driving pressure, or at least preventing its increase [43, 44]. However, if high inspiratory effort persists despite NIV, the marked improvement in oxygenation and partial relief of dyspnea caused by the intervention may eventually mask the severity of respiratory failure; this potentially delays the clinical decision to intubate the patient and may favor progression of lung injury [31, 37]. Thus, NIV may carry substantial risks, particularly in clinical settings lacking reliable measures of inspiratory effort [45]. This complexity partly explains the conflicting results reported across clinical trials, observational studies and meta-analysis, and may justify the observed inferiority, or at least lack of superiority, of NIV compared to HFNO [1, 34, 38]. Notably, we observed some inconsistency in the HFNO vs. NIV comparison (supplementary material 1: E11), which should be interpreted with caution.

Differently, HFNO exerts milder effects on oxygenation and demonstrates a more neutral impact on both inspiratory effort and transpulmonary driving pressure. Consequently, HFNO represents a pragmatic first-line option, especially in clinical scenarios where precise physiological phenotyping based on inspiratory effort is unavailable, as it usually is in clinical practice. While HFNO does not provide significant additional benefit – and might even be insufficient – in patients exhibiting intense inspiratory effort, it may pose a considerably lower risk of delaying intubation, and avoids substantial increases in tidal volume and transpulmonary driving pressure. Therefore, HFNO generally offers a more favorable risk–benefit profile across a broader patient population. These considerations explain the robust evidence from clinical trials supporting HFNO as first-line treatment of hypoxemic patients [38, 46, 47], and guidelines recommendations on the topic [48–50].

Compared with HFNO, CPAP was associated with higher effort per breath, but had no impact on effort per minute or transpulmonary driving pressure compared to either HFNO or standard oxygen; however, this latter result should be interpreted with caution given the high heterogeneity in the pooled estimate ($I^2 = 97\%$). CPAP reduced respiratory rate, and its most notable physiological effect was improved oxygenation, primarily attributable to PEEP-induced lung recruitment in dorsal regions [43, 51]. In experimental lung injury, high PEEP increases compliance, flattens the diaphragm, thereby yielding neuro-muscular diaphragmatic uncoupling, and finally reduces both respiratory rate and effort per breath [5, 52]. In non-intubated patients, instead, PEEP alone does not systematically reduce effort per breath. While dorsal lung recruitment may occur in humans as well, PEEP effects are interindividually variable and mostly dependent on heterogeneous patients' response in terms of respiratory system compliance changes [53–55]. In this context, while HFNO may generate a moderate-to-high PEEP level, particularly when delivered with the mouth closed, it is likely lower than the PEEP levels used in most NIV and CPAP studies [40]. Among NIV trials, PEEP < 10 cmH_2O (5–6 cmH_2O) was applied in 2 studies (25%), 10 cmH_2O in 5 studies (62.5%), and 13 cmH_2O in 1 study (12.5%). In CPAP trials, PEEP was set at 5 cmH_2O in 1 study (16.7%), 10 cmH_2O in 3 studies (50%), and > 10 cmH_2O (12–14 cmH_2O) in 2 studies (33.3%), generally exceeding what HFNO would deliver. While higher PEEP may not decrease the effort per se, dorsal recruitment may reduce the amount of *solid-like tissue*, homogenizing the distribution of the effort across different lung regions and avoiding injurious inflation patterns (i.e. pendelluft) [4, 43]. In animal models, this reduced self-induced lung injury [56], but other authors hypothesized that this may be associated to diaphragm injury due to

excessive flattening and harmful geometrical changes in its structure [57, 58]. How this translates to non-intubated patients undergoing non-invasive respiratory support is unknown, and how to achieve diaphragm and lung protective ventilation is still an unsolved problem, without clear evidence on the topic [10, 55, 59].

Moreover, technical aspects might significantly affect helmet CPAP performance in terms of changes in effort to breathe, as bench studies showed that too high or too low flow rate, the applications of HEPA filters, and flow-dependent PEEP valves can worsen the pneumatic performance of the helmet [60].

Overall, CPAP can be a useful tool to improve hypoxemia; however, it should not be considered to modulate effort per breath per se, but rather to potentially homogenize lung inflation through recruitment of dorsal regions.

Finally, in patients with ARDS, heart–lung interactions are influenced by PEEP, transpulmonary pressure, chest wall elastance, and spontaneous effort. During spontaneous breathing, reduced intrathoracic pressure enhances venous return and increases right ventricular transmural pressure while decreasing pulmonary arterial transmural pressure, with effects on right heart function depending on fluid responsiveness [61–63]. At the same time, the impact of PEEP and positive pressure ventilation on the left ventricle also depends on its function, on the preload dependence, and ultimately on the indirect effects of PEEP on right chambers performance [64–66]. In our analysis, we found no significant differences in mean arterial pressure or heart rate across noninvasive respiratory strategies; however, confidence intervals were wide, likely due to the limited number of studies reporting these outcomes. Moreover, heart rate and arterial pressure are rough surrogates for changes in cardiac output and may fail to capture more subtle hemodynamic alterations.

Limitations

This study has limitations. First, network meta-analysis is more commonly used for clinical outcomes and we applied it to physiological endpoints; however, heterogeneity across included studies was low, and all measurements were based on validated methods. These factors support the validity of our comparative estimates. Second, assumptions of network meta-analyses are that populations and intervention protocols are similar across different studies, therefore analysis with high inconsistency should be taken with caution. Third, several crossover studies did not incorporate formal washout periods, raising the possibility of carryover effects, however, the physiological adaptation of the respiratory centers is usually fast, and in most studies measurements were taken after at least 20–30 min of stabilization. For this reason, the risk of residual effects influencing the reported values is likely minimal. Fourth, the effects of noninvasive respiratory support on physiological outcomes may be influenced by fine-tuning of ventilatory parameters, the precise onset time of the disease, and the specific equipment used, and we could not control for these variables. Fifth, all measurements were performed without the occlusion test, and it cannot be guaranteed that the esophageal pressure signal was perfectly calibrated to estimate pleural pressure changes. This limitation may have introduced some imprecision in the absolute values of effort per breath, although relative differences between interventions are likely less affected. Sixth, most of the included studies assessed only short-term physiological responses, without addressing the long-term effect of the studied strategies or patient-centered outcomes.

Finally, our findings are applicable to the specific population represented by the included trials, namely patients with moderate-to-severe acute hypoxemic respiratory failure. As such, our findings cannot be translated to patients with milder disease severity or with acute respiratory failure of different etiologies.

Conclusions

Noninvasive respiratory support techniques have distinct physiological effects. NIV is the only technique that reduces effort per breath and per minute, but is associated with increases in transpulmonary driving pressure; HFNO does not affect effort per breath, and reduces effort per minute without increasing driving pressure; CPAP has a neutral impact on effort and driving pressure. CPAP and NIV provide greater improvements in oxygenation than HFNO. These findings may indicate that individualized selection based on inspiratory effort levels may help achieve an optimal balance between efficacy and safety: NIV benefits are primarily limited to the subgroup of patients in whom it successfully lowers effort per breath to non-injurious levels with minimal increases in driving pressure; although less efficient in patients with high effort per breath, HFNO reduces effort per minute and does not increase driving pressure, potentially offering a safer and more practical alternative, particularly in settings where inspiratory effort cannot be reliably assessed.

Abbreviations

CPAP	Continuous positive-airway pressure
HFNO	High-flow nasal oxygen
NIV	Noninvasive ventilation
MD	Mean difference
95%CI	95% Confidence interval
RoB	Risk of bias

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05670-7.

Supplementary material 1: E1 - E28

Supplementary material 2: Customization log.

Supplementary material 3: PRISMA checklist.

Supplementary material 4: Risk of bias (ROB) assessment.

Supplementary material 5: **E-Figure 1.** Effects of noninvasive respiratory strategies on quasi-static transpulmonary driving pressure. Left panel: standard oxygen as comparator. Right panel: high-flow nasal oxygenas comparator. Dots represent mean differences; bars indicate 95% confidence intervals. **E-Figure 2.** Effects of noninvasive respiratory strategies on arterial carbon dioxide. Left panel: standard oxygen as comparator. Right panel: HFNO as comparator. Dots represent mean differences; bars indicate 95% CIs. **E-Figure 3.** Effects of noninvasive respiratory strategies on the composite variable 4ΔPL × respiratory rate. Left panel: standard oxygen as comparator. Right panel: HFNO as comparator. Dots represent mean differences; bars indicate 95% CIs. **E-Figure 4.** Network geometry of included studies. Each node represents an intervention; node size is proportional to the number of participants. Lines indicate direct head-to-head comparisons; line thickness is proportional to the number of studies.

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Author contributions
LSM, EB and DLG conceived the study and are responsible for data extraction and analysis. LSM and EB drafted the manuscript. CG, CM, NV, RDS, MM, AC, LDC, TR and SDA made substantial contributions to data acquisition. EB and LSM conducted statistical analysis. SMM, MA, LB, MA, GB and DLG participated in the study design and revised the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
LSM has received a scholarship from the European Respiratory Society and the Canadian Lung Association. LB'S laboratory has received support for research by Covidien (PAV), Air Liquide (CPR), Philips (equipment for sleep), Fisher & Paykel (high flow therapy) and GE healthcare.MA has received payments for Board participation from Maquet, Air Liquide and Chiesi, and a research grant by GE. DLG has received payments for travel expenses by Getinge, Draeger and Hamilton, personal fees by Draeger, and research grants by Fisher and Paykel and GE.

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