

# Helmet CPAP versus Oxygen Therapy in Hypoxemic Acute Respiratory Failure: A Meta-Analysis of Randomized Controlled Trials

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**Purpose:** The efficacy of helmet continuous positive airway pressure (CPAP) in hypoxemic acute respiratory failure (hARF) remains unclear. The aim of this meta-analysis was to critically review studies that investigated the effect of helmet CPAP on gas exchange, mortality, and intubation rate in comparison with standard oxygen therapy.

**Materials and Methods:** We performed a meta-analysis of randomized controlled trials (RCTs) by searching the PubMed, Embase, Cochrane library, OVID, and CBM databases, and the bibliographies of the retrieved articles. Studies that enrolled adults with hARF who were treated with helmet CPAP and measured at least one of the following parameters were included: gas exchange, intubation rate, in-hospital mortality rate.

**Results:** Four studies with 377 subjects met the inclusion criteria and were analyzed. Compared to the standard oxygen therapy, helmet CPAP significantly increased the PaO<sub>2</sub>/FiO<sub>2</sub> [weighted mean difference (WMD)=73.40, 95% confidence interval (95% CI): 43.92 to 102.87,  $p<0.00001$ ], and decreased the arterial carbon dioxide levels (WMD=-1.92, 95% CI: -3.21 to -0.63,  $p=0.003$ ), intubation rate [relative risk (RR)=0.21, 95% CI: 0.11 to 0.40,  $p<0.00001$ ], and in-hospital mortality rate (RR=0.22, 95% CI: 0.09 to 0.50,  $p=0.0004$ ).

**Conclusion:** The results of this meta-analysis suggest that helmet CPAP improves oxygenation and reduces mortality and intubation rates in hARF. However, the significant clinical and statistical heterogeneity of the literature implies that large RCTs are needed to determine the role of helmet CPAP in different hypoxemic ARF populations.

**Key Words:** Helmets, continuous positive airway pressure, respiratory failure, meta-analysis, endotracheal intubation, mortality

## INTRODUCTION

Oxygen therapy and endotracheal intubation ventilation are standard medical treatments for hypoxemic acute respiratory

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•The authors have no financial conflicts of interest.

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failure (hARF).<sup>1</sup> Continuous positive airway pressure (CPAP) is a common mode in noninvasive ventilation (NIV) that delivers a constant positive airway pressure during both inspiration and expiration.<sup>2,3</sup> CPAP has been demonstrated to improve oxygen saturation, relieve dyspnea, and avoid complications resulting from intubation, thus playing an important role in treating hARF.<sup>4,5</sup>

A recent multicenter randomized controlled trial (RCT) compared CPAP delivered by a full-face mask with standard oxygen therapy in patients with hARF caused by various etiologies.<sup>5</sup> The authors observed improved oxygenation during CPAP treatment; however, CPAP did not reduce the rates of intubation complications, in-hospital mortality, and adverse events.

The success of NIV is dictated in part by the choice of interface,<sup>6</sup> which greatly affects patient comfort. In Europe, oral-

nasal masks are the most commonly used interface for NIV;<sup>7</sup> however, the helmet interface has gained wide acceptance in some countries, such as Italy, as a more comfortable interface for patients with hARF.<sup>7</sup>

Several studies have evaluated the efficacy of helmet CPAP for hARF,<sup>8-12</sup> and most have found that helmet CPAP significantly reduced the intubation rate and mortality while improving clinical outcomes compared to standard oxygen therapy. However, a robust conclusion has not been reached on the utility of helmet CPAP owing to the small sample size in current RCTs. This problem would remain until a meta-analysis is performed to pool and quantify the results from these studies. For this purpose, the present study was designed and conducted to compare the efficacy of helmet CPAP with standard oxygen therapy in hARF.

## MATERIALS AND METHODS

### Search strategy

According to the guidelines described by the Cochrane handbook for reviews of intervention (version 5.0.1), we searched the PubMed, Embase, Cochrane library, OVID, and CBM databases through March 2015. The literature search was limited to human studies using the following key words: NIV OR non-invasive ventilation OR continuous positive airway pressure OR CPAP OR pressure support ventilation AND acute respiratory failure AND helmet. The reference lists of identified studies were manually reviewed and additional search of related studies were performed if necessary. Two reviewers independently extracted the data using a pre-defined protocol. Any divergence between them was resolved by consensus or by a third reviewer. The following data were recorded from each study: first author, year of publication, study design, trial type, location, primary disease, sample size, experimental and control treatment strategies, and outcome variables.

### Selection criteria

Studies meeting the following criteria were included: RCT; adult subjects (>18 y); helmet CPAP intervention versus standard oxygen therapy; hARF diagnosed according to a respiratory rate  $\geq 25$ /min,  $\text{PaO}_2 < 60$  mm Hg, oxygen saturation  $< 90\%$  while breathing room air as measured by pulse oximetry, and  $\text{PaO}_2/\text{FIO}_2 \leq 300$ ; hARF secondary to acute exacerbation of chronic obstructive pulmonary disease, pneumonia, cardiogenic pulmonary edema, ALI/ARDS, or similar conditions; measurement of gas exchange, intubation, in-hospital mortality.

Studies were excluded according to the following criteria: subjects  $< 18$  years of age; publication as an abstract only; and poor quality (small studies) or sparse data.

### Risk of bias assessment

The two reviewers independently performed a methodologic

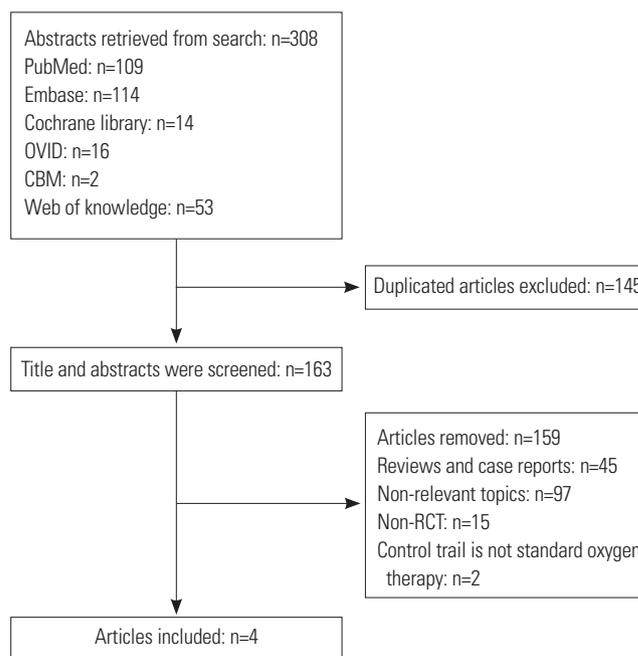
quality assessment with divergences resolved by consensus. The risk of bias was assessed using the Cochrane Risk of Bias Tool and evaluated as high, low, or unclear.<sup>13</sup>

### Heterogeneity assessment

The impact of heterogeneity on the pooled estimates of individual outcomes was assessed using the Cochran Q statistic and  $I^2$  test<sup>14</sup> to identify inconsistencies between the study results. Inconsistencies were considered as approximately the proportion of total variation in the study estimates that was due to heterogeneity rather than sampling error. Because the Cochran Q test has a low sensitivity for evaluating heterogeneity, a  $p$  value of  $< 0.1$  was considered significant for the presence of statistical heterogeneity.  $I^2 < 25\%$ ,  $25\% \leq I^2 < 50\%$ , and  $I^2 \geq 50\%$  were considered to indicate low, moderate, and high significance, respectively.<sup>15</sup>

### Determination of the pooled treatment effect

The statistical analysis was performed using Review Manager (version 5.3.3, The Nordic Cochrane Center, The Cochrane Collaboration; Copenhagen, Denmark). For binary variables in each study, the relative risk (RR) and 95% confidence intervals (95% CI) were calculated, and we computed the weighted mean difference (WMD) and 95% CI for consecutive variables. A fixed effects model was used initially; however, in case of significant heterogeneity across trials, a random effects model was used ( $p < 0.10$  and  $I^2 > 50\%$ ).



**Fig. 1.** Flow chart of the study selection process. RCT, randomized controlled trial.

**Table 1.** Main Characteristics of Included Studies

First author	Year	Location	Study design	Trial type	Inclusion criteria	Experimental strategy	Control strategy		Outcomes	
							Experimental	Control		
Squadrone, et al. <sup>11</sup>	2005	Italy	RCT	Multicenter	Postoperative patient with acute hypoxemic	Oxygen at FiO <sub>2</sub> of 0.5 plus a helmet CPAP of 7.5 cmH <sub>2</sub> O	Oxygen through a venturi mask at an FiO <sub>2</sub> of 0.5	105	104	Gas exchange, intubation, in-hospital mortality, adverse events, intolerance
Squadrone, et al. <sup>10</sup>	2010	Italy	RCT	Single-center	Hematologic malignancy with hypoxemic ARF	Oxygen at FiO <sub>2</sub> of 0.5 plus a helmet CPAP of 10 cmH <sub>2</sub> O	Oxygen through a venturi mask at an FiO <sub>2</sub> of 0.5	20	20	Gas exchange, intubation, in-hospital mortality, adverse events, intolerance
Cosentini, et al. <sup>9</sup>	2010	Italy	RCT	Multicenter	Community-acquired pneumonia with hARF	Helmet CPAP with an initial PEEP of 10 cmH <sub>2</sub> O and with an FiO <sub>2</sub> set to maintain a SpO <sub>2</sub> ≥ 92%	Oxygen through a venturi mask with an FiO <sub>2</sub> set to maintain a SpO <sub>2</sub> ≥ 92%	20	27	Gas exchange, intubation, in-hospital mortality, intolerance
Brambilla, et al. <sup>8</sup>	2014	Italy	RCT	Multicenter	Pneumonia with hARF	Helmet CPAP with an initial PEEP of 10 cmH <sub>2</sub> O and with an FiO <sub>2</sub> set to maintain a SpO <sub>2</sub> ≥ 92%	Oxygen through a venturi mask with an FiO <sub>2</sub> set to maintain a SpO <sub>2</sub> ≥ 92%	40	41	Gas exchange, intubation, in-hospital mortality, intolerance

RCT, randomized control trial; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure; hARF, hypoxemic acute respiratory failure; FiO<sub>2</sub>, fraction of inspiration O<sub>2</sub>; SpO<sub>2</sub>, pulse oximetry.

## RESULTS

### Search and study selection

The database search yielded 308 studies (Fig. 1). Of these, 304 studies were excluded for the following reasons: 145 duplicate studies; 45 case reports and abstracts; 97 studies without examination of hARF; 15 non-RCTs; one incomplete hARF study carried out by Fasano, et al.,<sup>16</sup> and one study by Antonaglia, et al.<sup>17</sup> using facial NIV in the control group.

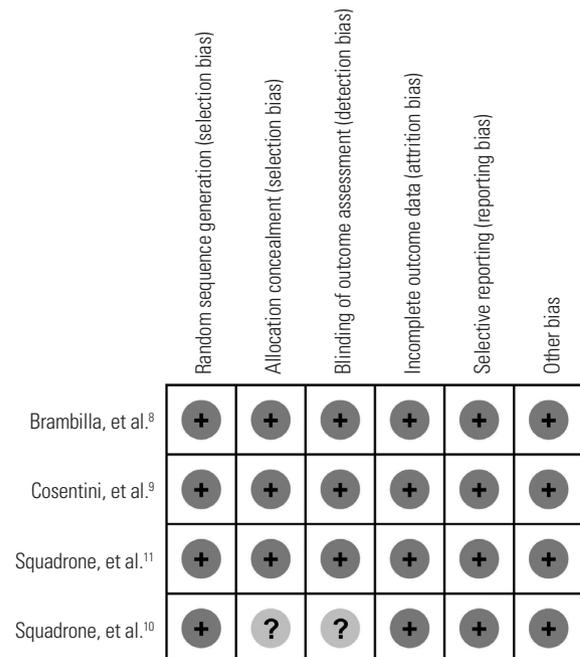
Four clinical<sup>8-11</sup> trials comprising 377 subjects met the inclusion criteria (Table 1). All trials were RCTs, and three of these, were multicenter studies,<sup>9-11</sup> and one<sup>9</sup> was a single center study.

### Risk of bias assessment

The risk of bias in all four trials is shown in Fig. 2. A random number generator was used to generate allocation sequences in all four trials. Appropriate allocation and concealment methods were used in three trials<sup>8,9,11</sup> but were not specified in the fourth.<sup>17</sup> Blinding was not performed in any trial. Since the appearance of the various NIV masks and treatment devices cannot be identical, the subjects were able to recognize easily the treatment they had received. As a result, trials with adequate randomization and a clear follow-up protocol were considered to be at low risk of bias. According to their random sequence generation, attribution bias, and reporting bias, all trials were at low risk.

### Effect of helmet CPAP on gas exchange

All four trials (377 subjects) reported gas exchange data, which are pooled and summarized in Fig. 3 and 4. In patients treated



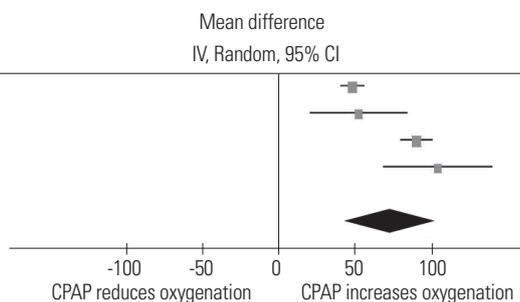
**Fig. 2.** The reviewers made judgments about risk of bias for each item in each included study. +, low risk; ?, unclear risk; -, high risk.

by helmet CPAP, the WMD PaO<sub>2</sub>/FiO<sub>2</sub> was significantly higher at 73.40 (95% CI: 43.92 to 102.87, *p*<0.00001) (Fig. 3) despite the significant heterogeneity between the trials (*I*<sup>2</sup>=93%). Helmet CPAP also decreased the WMD arterial carbon dioxide to

-1.92 (95% CI: -3.21 to -0.63, *p*=0.003) (Fig. 4), compared to patients receiving standard oxygen therapy.

Study or subgroup	Experimental			Control			Weight	Mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Squadrone, et al. <sup>10</sup>	441	10	20	392	15	20	29.0%	49.00 [41.10, 56.90]
Brambilla, et al. <sup>8</sup>	209.5	80.7	37	156.4	53.7	32	21.9%	53.10 [21.13, 85.07]
Squadrone, et al. <sup>11</sup>	432	45	105	341	32	104	28.5%	91.00 [80.42, 101.58]
Cosentini, et al. <sup>9</sup>	349	69	20	244	51	27	20.6%	105.00 [69.16, 140.84]
Total (95% CI)			182			183	100.0%	73.40 [43.92, 102.87]

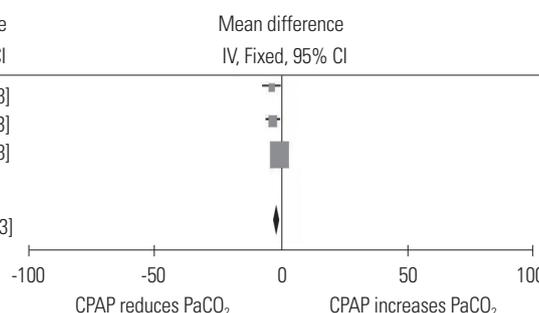
Heterogeneity: tau<sup>2</sup>=764.31; chi<sup>2</sup>=44.27, df=3 (*p*<0.00001); *I*<sup>2</sup>=93%  
 Test for overall effect: Z=4.88 (*p*<0.00001)



**Fig. 3.** Forest plot: effect of helmet CPAP on oxygenation (PaO<sub>2</sub>/FiO<sub>2</sub>) in patients with hARF. CI, confidence interval; CPAP, continuous positive airway pressure; hARF, hypoxemic acute respiratory failure.

Study or subgroup	Experimental			Control			Weight	Mean difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Cosentini, et al. <sup>9</sup>	33	5.6	20	37	6.7	22	12.0%	-4.00 [-7.72, -0.28]
Brambilla, et al. <sup>8</sup>	32.3	3.7	36	35.9	7.2	32	21.6%	-3.60 [-6.37, -0.83]
Squadrone, et al. <sup>10</sup>	41	2	20	42	3	20	66.4%	-1.00 [-2.58, 0.58]
Total (95% CI)			76			74	100.0%	-1.92 [-3.21, -0.63]

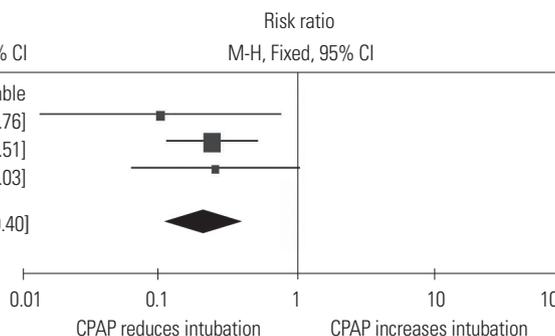
Heterogeneity: chi<sup>2</sup>=3.91, df=2 (*p*=0.14); *I*<sup>2</sup>=49%  
 Test for overall effect: Z=2.92 (*p*=0.003)



**Fig. 4.** Forest plot: effect of helmet CPAP on PaCO<sub>2</sub> in patients with hARF. CI, confidence interval; CPAP, continuous positive airway pressure; hARF, hypoxemic acute respiratory failure.

Study or subgroup	Experimental		Control		Weight	Risk ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Cosentini, et al. <sup>9</sup>	0	20	0	27		Not estimable
Squadrone, et al. <sup>11</sup>	1	105	10	104	23.0%	0.10 [0.01, 0.76]
Brambilla, et al. <sup>8</sup>	6	40	26	41	58.7%	0.24 [0.11, 0.51]
Squadrone, et al. <sup>10</sup>	2	20	8	20	18.3%	0.25 [0.06, 1.03]
Total (95% CI)		185		192	100.0%	0.21 [0.11, 0.40]

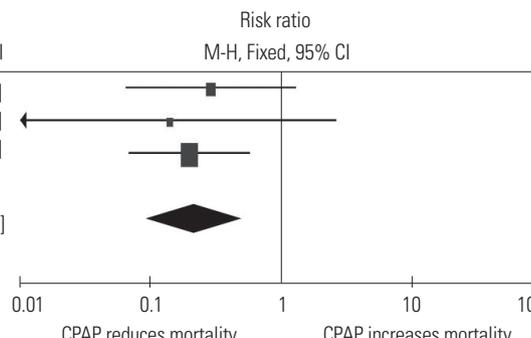
Total events: 9 (Experimental), 44 (Control)  
 Heterogeneity: chi<sup>2</sup>=0.68, df=2 (*p*=0.71); *I*<sup>2</sup>=0%  
 Test for overall effect: Z=4.75 (*p*<0.00001)



**Fig. 5.** Forest plot: effect of helmet CPAP on intubation in patients with hARF. CI, confidence interval; CPAP, continuous positive airway pressure; hARF, hypoxemic acute respiratory failure.

Study or subgroup	Experimental		Control		Weight	Risk ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Brambilla, et al. <sup>8</sup>	2	40	7	41	27.2%	0.29 [0.06, 1.33]
Squadrone, et al. <sup>11</sup>	0	105	3	104	13.8%	0.14 [0.01, 2.71]
Squadrone, et al. <sup>10</sup>	3	20	15	20	59.0%	0.20 [0.07, 0.59]
Total (95% CI)		165		165	100.0%	0.22 [0.09, 0.50]

Total events: 5 (Experimental), 25 (Control)  
 Heterogeneity: chi<sup>2</sup>=0.25, df=2 (*p*=0.88); *I*<sup>2</sup>=0%  
 Test for overall effect: Z=3.56 (*p*=0.0004)



**Fig. 6.** Forest plot: effect of helmet CPAP on in-hospital mortality in patients with hARF. CI, confidence interval; CPAP, continuous positive airway pressure; hARF, hypoxemic acute respiratory failure.

### Effect of helmet CPAP on in-hospital mortality and intubation rates

The intubation rate in patients receiving helmet CPAP was significantly lower than that in patients receiving standard oxygen therapy (RR=0.21, 95% CI: 0.11 to 0.40,  $p<0.00001$ ) (Fig. 5). The in-hospital mortality rate was also reduced in patients treated by helmet CPAP (RR=0.22, 95% CI 0.09 to 0.50,  $p=0.0004$ ) (Fig. 6).

## DISCUSSION

The present meta-analysis may add to the currently lacking data comparing helmet CPAP and oxygen therapy in hypoxemic acute respiratory failure. Our results suggest that helmet CPAP improves gas exchange and decreases the intubation and in-hospital mortality rates. However, these results are limited by the presence of significant clinical and statistical heterogeneity.

CPAP does not rely on intubation and is still competent to improve the low alveolar ventilation, functional residual capacity, which ultimately relieves dyspnea, ameliorate gas exchange, and reduces the respiratory muscle load.<sup>18-20</sup> CPAP improves gas exchange ability during hypoxemic ARF caused by various causes.<sup>5,20-22</sup> Similarly, L'Her, et al.<sup>23</sup> found that the use of CPAP in patients with acute lung injury, improved oxygenation. Most studies have examined NIV delivered through a face mask or oro-nasal mask. Recent studies suggest differentiating use of CPAP and NIV in ARF according to the specific clinical condition, but strong clinical evidence is still lacking.<sup>24</sup> The efficacies of helmet CPAP and facial mask CPAP in hARF patients were evaluated by Tonnelier, et al.,<sup>25</sup> who found that both helmet and face mask CPAP increased oxygenation and produced similar outcomes. In the present meta-analysis, we found that helmet CPAP significantly improved gas exchange in patients with hARF, similar to previous reports. However, the statistical heterogeneity was significant between the trials due to the presence of clinical heterogeneity and variations in the timing of blood gas analysis between the primary diseases.

CPAP improves oxygenation and relieves dyspnea, which should decrease the intubation rate and in-hospital mortality rate. CPAP can improve gas exchange ability in patient with ARF; however, robust clinical data indicating that CPAP delivered by facial mask cannot reduce the intubation and mortality rates in hARF in different clinical conditions are lacking.<sup>5,26,27</sup> This failure was attributed to the disadvantages of face mask NIV,<sup>2,11</sup> such as intolerance, leakage, and discomfort, which hinder its continuous use.<sup>28</sup> As a result, the success of NIV relies on properly establishment of the interface.<sup>6</sup> Due to mostly favorable characteristics of the helmet, such as less air leakage and the absence of any contact with the face, the result in the present study indicates fewer complications and

better tolerance of the helmet interface compared with a face mask.<sup>21,25,28-30</sup> In contrary to the earlier study on facial mask CPAP, the present meta-analysis found that helmet CPAP reduced the intubation and mortality rates significantly.

The present meta-analysis had several limitations. First, the major limitation of the present meta-analysis is the clinical heterogeneity of subjects and the statistical heterogeneity in the included trials. Among the 377 subjects, 128 had moderate-severe acute respiratory failure from pneumonia, whereas 209 had moderate acute respiratory failure in post-operative hypoxemia, and 40 subjects had acute lung injury with hematologic malignancy where pneumonia had been excluded. In addition, none of the included trials were blinded; although the interventions, clinical decisions, and measured variables were prioritized in the literature search, bias remained beyond our control. Second, the number of eligible studies was relatively small, and we found high heterogeneity in their measurement of oxygenation and intolerance between the studies. We attempted to mitigate this heterogeneity by stratifying the studies, based on potentially important variables such as primary disease, hypoxemia severity, and patient age. However, due to the small number of eligible studies, this type of analysis was not feasible or yielded unreliable results. Hence, the results should be interpreted with prudence because they might have been influenced by the paucity and heterogeneity of analyzed data. Additional studies are needed comparing the efficacies of helmet CPAP and face mask CPAP.

In conclusion, the results of this meta-analysis suggest that helmet CPAP improves oxygenation and reduces mortality and intubation rates in hypoxemic acute respiratory failure. However, the significant clinical and statistical heterogeneity of the literature implies that large RCTs are needed to determine the role of helmet CPAP in different hypoxemic ARF populations.

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