

## **PREHOSPITAL CONTINUOUS POSITIVE AIRWAY PRESSURE FOR ACUTE RESPIRATORY FAILURE: A SYSTEMATIC REVIEW AND META-ANALYSIS**

### **ABSTRACT**

#### **INTRODUCTION**

Acute respiratory failure (ARF) is a common problem presenting to emergency medical services and is associated with significant morbidity, mortality and health care costs. Continuous positive airway pressure (CPAP) is an integral part of the hospital treatment of acute respiratory failure, predominantly due to congestive heart failure. Intuitively, better patient outcomes may be achieved when CPAP is applied early in the pre-hospital setting but there are few outcome studies to validate its use in this setting.

#### **AIM**

This systematic review and meta-analysis aimed to examine the effectiveness CPAP in the pre-hospital setting for patients with ARF.

#### **METHODS**

A literature review of bibliographic databases and secondary sources was conducted and potential papers assessed by two independent reviewers. Included studies were those that compared CPAP therapy (and usual care) to no CPAP for ARF in the prehospital setting. Studies of other methods of non-invasive ventilation were not included. Methodological quality was assessed using guidelines from the Cochrane Collaboration. Outcomes included the number of intubations, mortality, physiological parameters and dyspnoea score. Forrest plots were constructed to estimate the pooled effect of CPAP on outcomes.

#### **RESULTS**

Five studies (1,002 patients) met the selection criteria – three randomised control trials (RCTs), a non-randomised comparative study and a retrospective comparative study using chart review. Forty-seven percent of patients were allocated to the CPAP group. Baseline characteristics were similar between groups. The pooled estimates demonstrated significantly fewer intubations (OR 0.31, 95% CI 0.19-0.51) and lower mortality (OR 0.41, 95% CI 0.19-0.87) in the CPAP group.

#### **CONCLUSION**

The studies included in this review showed a reduction in the number of intubations and mortality in patients with ARF who received CPAP in the pre-hospital setting. The results may not be applicable to other health care contexts because of the inherent differences in the

organisation and staffing of the EMS. Information from large RCTs on the efficacy of CPAP initiated early in the pre-hospital setting is critical to establishing the evidence base underpinning this therapy prior to ambulance services incorporating CPAP as routine clinical practice.

## **INTRODUCTION**

Acute respiratory failure (ARF), defined by the presence of hypoxaemia or hypercapnia, is a common problem presenting to emergency medical services (EMS). ARF is most commonly caused by diseases of the cardiac (e.g. left ventricular failure, pulmonary embolus) or respiratory system (e.g. chronic obstructive pulmonary disease [COPD], asthma, pneumonia). Identifying the precise cause of ARF in the pre-hospital setting is challenging: the time window for assessment is limited, it is not possible to obtain a chest x-ray or other diagnostic imaging and environmental considerations (avoiding exposing the patient, noise) make clinical examination difficult.

The most common cause of acute respiratory failure is left ventricular failure causing acute cardiogenic pulmonary oedema (ACPO), a potentially life-threatening medical emergency that is associated with significant morbidity, mortality and health care costs.<sup>1</sup> Other causes of acute pulmonary oedema (APO) are cardiac (includes myocardial ischaemia, hypertension, arrhythmias) and non-cardiac (includes drugs, poisoning). Non-cardiogenic pulmonary oedema is often evident from the patient history surrounding the acute event and is due primarily to a disruption in the alveolar–capillary membrane from an insult (e.g. sepsis, trauma, drugs).<sup>2</sup> While they have distinct causes, acute cardiogenic and non-cardiogenic pulmonary oedema have similar clinical manifestations.<sup>3</sup> Furthermore, patients with COPD often present with ACPO due to coexisting cardiac disease and it may be difficult to differentiate between them<sup>2</sup> especially in the pre-hospital emergency setting. However, it is important to understand the cause of APO because it has important treatment implications. Patients with cardiogenic pulmonary oedema typically are treated with preload and afterload reduction using drugs such as nitrates. Patients with non-cardiogenic pulmonary oedema require support of oxygenation and ventilation and treatment of the underlying cause.<sup>3</sup>

Continuous positive airway pressure (CPAP) is an integral part of the hospital treatment of APO and provides beneficial effects on respiratory and cardiac function.<sup>4-6</sup> This non-invasive

medical therapy maintains positive airway pressure during spontaneous ventilation throughout the whole respiratory cycle, reducing dyspnoea and the work of breathing. Several reports that describe CPAP,<sup>7-12</sup> applied by face or nasal mask, improves gas exchange, reduces the need for endotracheal intubation (and the potential complications of mechanical ventilation),<sup>13</sup> and decrease length of stay (LOS) in the intensive care unit (ICU), coronary care, emergency department (ED) and hospital. CPAP is most beneficial in patients with APCO, but patients with other causes of acute respiratory failure, e.g. acute exacerbations of COPD also benefit.<sup>14</sup> Intuitively, better patient outcomes may be achieved when CPAP is applied early in the pre-hospital setting, but outcome studies in the pre-hospital setting are required to validate its use.<sup>14,15</sup> This information is critical to establishing the evidence base underpinning this therapy prior to EMS incorporating pre-hospital CPAP as routine clinical practice.

## **METHOD**

### **Aims**

We conducted a systematic review and meta-analysis of the evidence of the clinical efficacy of pre-hospital administration of CPAP in patients with acute respiratory failure.

### **Search strategy**

To identify studies eligible for review, computerized searches of bibliographic databases were performed (author TW): MEDLINE (1980–2012), EMBASE (1980–2012), CINAHL (1982–2012) and the Cochrane Library (2004—2012). Terms were mapped to the appropriate MeSH/EMTREE subject headings and “exploded”: (1) [“acute pulmonary oedema” OR “pulmonary oedema” OR “acute heart failure” OR “acute respiratory failure”] AND [“continuous positive airway pressure”] (2) [“continuous positive airway pressure”] AND [“ambulance” OR “emergency medical services” OR “pre-hospital care” OR mobile health units ”OR “paramedic”]. Reference lists of relevant review articles and journals were hand-searched for relevant papers.

Potential studies were limited to studies conducted within the prehospital setting that compared patients with acute respiratory failure who received CPAP and usual care (CPAP group) to those receiving usual care (non-CPAP group) transported to hospital by ambulance. We did not include studies of neonates. Studies that did not specifically compare patients

with acute respiratory failure,<sup>16,17,18,19</sup> did not compare the CPAP group with a non-CPAP group,<sup>20,21</sup> or those that included patients who received bilevel positive airway/pressure support ventilation<sup>22-27</sup> were excluded. Outcomes included changes in physiological values (respiratory rate, oxygen saturation [SpO<sub>2</sub> or SaO<sub>2</sub>], intubation, mortality and intensive care unit (ICU) or hospital length of stay (LOS)). Papers were included if they were published in English. Articles had to be published in peer-reviewed journals but those published only in abstract form were excluded. No time limits on journal publication date were set. If reports described overlapping study populations, we retained the most recent or complete publication.

### **Study selection**

Studies identified during the literature search were assessed for relevance to the review based on the information contained in the title, abstract and subject descriptor/MeSH heading (authors TW and JF). Full text articles were obtained if, after reviewing the abstract, the study was considered relevant or if the title and abstract were inconclusive. All citations selected by either author for abstract review were eligible for selection, and any subsequent disagreement regarding eligibility resolved by consensus.

### **Data extraction**

Data were extracted by two investigators (authors TW and JF) from studies that met the inclusion criteria. We did not get primary data verified from investigators. The data were collected on a form that included study design, patient characteristics (e.g. age, sex, diagnosis), treatments received, emergency medical services, reported outcomes (mortality, physiological changes, dyspnoea score, length of stay [LOS]), direction (and magnitude) of treatment effect.

### **Study quality**

Using guidelines from Ryan et al.<sup>28</sup> and Higgins and Green,<sup>29</sup> study quality was assessed for risk of bias, adherence to the intention-to-treat principle, completeness to follow-up, heterogeneity, and loss to follow-up. In addition, for non-randomised studies similarity of baseline characteristics was examined. If groups were not reasonably equivalent and this was not adjusted through analysis, the study was excluded from the analysis.

### **Assessment of risk of bias in included studies**

Allocation concealment was rated as (a) adequate if the randomisation method would not enable the investigator or participant to know or influence allocation intervention group before an eligible participant was entered in the study; (b) unclear if randomisation stated but no information on the method used is available; (c) inadequate if the method of randomisation used indicated that investigators or participants could influence the intervention group; and (d) randomisation not done.<sup>28</sup>

### **Adherence to the intention-to-treat principle**

If an intention-to-treat analysis was reported to have been undertaken by the investigators and this was confirmed on study assessment then adherence to the intention-to-treat principle was assumed.<sup>28</sup> If not reported and lack of intention-to-treat analysis was confirmed on study assessment, e.g. patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation, it was assumed that there was no adherence to the intention-to-treat principle.

### **Assessment of heterogeneity**

Statistical heterogeneity was assessed using the Higgins  $I^2$  test,<sup>30</sup> which estimates the variability due to heterogeneity rather than chance alone.  $I^2$  values less than 25% are considered low risk, 25 to 50% moderate risk and values greater than 50% high risk of heterogeneity.<sup>30</sup>

### **Sensitivity analysis**

A priori sensitivity analyses were proposed to explore the impact of excluding studies that met the inclusion criteria but not the assessment of study quality on outcomes.

### **Publication bias**

The intubation rate from the studies were used to construct a funnel plot, to investigate the likelihood of overt publication bias.<sup>29</sup> The vertical axis indicates the standard error of the log odds ratio and the horizontal axis the logit odds ratio.<sup>31</sup> In the absence of bias the plot resembles a symmetric inverted funnel, but if there is bias it appears asymmetric with a gap in the bottom right-hand side of the graph.<sup>29</sup>

## Data synthesis

Narrative and tabular summaries of study characteristics, methods and results are presented, guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>32</sup> Summary estimates of treatment effect with their associated 95% confidence intervals (CI) are reported. A protocol was not registered for the systematic review. We pooled dichotomous outcomes (using odds ratio [OR]) using random effects models. Data were analysed using Review Manager (*RevMan*) version 5.1 software (The Cochrane Collaboration, Oxford, UK) and STATA (Release 12: StataCorp LP, College Station, TX, USA). We considered P values < 0.05 to be statistically significant.

## RESULTS

We identified 160 reports of studies. After title and abstract assessment, 95 reports were excluded because it was evident that the publications were not comparative studies or did not include either the target population or the intervention of interest. We retrieved 65 full text reports for further evaluation, and seven were finally included.

*INSERT FIGURE 1 HERE*

### Study characteristics

There were 14 studies of CPAP used in the pre-hospital setting.<sup>14,16-19,22,33-39</sup> We did not include six studies of prehospital CPAP<sup>16-19,22,33</sup> because they did not have a comparison group. The Plaisance et al.<sup>20</sup> RCT was excluded because it did not compare the CPAP group to a non-CPAP group but instead compared 'early' CPAP to 'late' CPAP. Seven studies<sup>14,34-39</sup> compared the effect of prehospital CPAP to no CPAP - three randomised controlled trials (RCTs)<sup>14,35,36</sup>, a non-randomised concurrent comparative study,<sup>38</sup> two before and after studies,<sup>37,39</sup> and a retrospective review of prehospital charts.<sup>34</sup> Only one of the studies involved multiple centers.<sup>35</sup>

The studies included in this review (Table 1) were conducted in different healthcare contexts: one was conducted in Canada,<sup>14</sup> two in France<sup>35,36</sup> and four in the United States of America (USA).<sup>34,37-39</sup> In the mobile ICUs in France, physicians are part of the EMS team, but are not routinely used in the USA and Canada. Differences also exist within the same context. For example, Hubble et al.<sup>38</sup> used two neighbouring EMS counties with different levels of services: one county for the control group and the other for the intervention group.

*INSERT TABLE 1 HERE*

### **Study quality**

None of the studies were blinded, as shown in Table 1, but it would be technically and operationally difficult to blind the paramedics. The three RCTs<sup>14,35,36</sup> were considered low risk for bias. Hubble et al.<sup>38</sup> had a moderate risk of bias because it was a well conducted, non-randomised comparative clinical study. Two studies had a high risk of bias.<sup>34,37,39</sup> Hastings et al.<sup>37</sup> described a decrease in the number of intubations from 20% to 1% but did not describe the number of patients or the characteristics of the comparator group and was excluded from the outcome analyses.<sup>37</sup> Warner et al.<sup>39</sup> conducted a before and after study but did not describe the characteristics of the groups and was also excluded from further analyses. Publication bias is shown in Figure 2.

*INSERT TABLE 2 HERE*

*INSERT FIGURE 2 HERE.*

### **Study participants**

There were 1002 patients enrolled across five studies,<sup>14,34-36,38</sup> of whom 471 (47%) were allocated to the CPAP group. The number of patients recruited in each study ranged from 71 to 387. The average age of participants was 76 years non-CPAP group versus 75 years in the CPAP group (when reported) and the proportion of males was similar (50% non-CPAP group versus 47% CPAP group,  $p=0.25$ ). Three studies reported outcomes for patients with severe CHF<sup>34</sup> or ACPO.<sup>35,36</sup> A further study examined outcomes for patients with APO but the majority of patients (76%) were diagnosed in ED with cardiogenic pulmonary oedema.<sup>38</sup> Thompson et al.<sup>14</sup> recruited patients with severe respiratory distress, predominantly CHF, COPD or asthma.

Standard therapy included use of oxygen, nitrates and diuretics (furosemide) although the mode of delivery (oral versus parenteral) varied within and between EMS. The therapies for APO were provided at the discretion of the treating paramedics,<sup>34,38</sup> or protocol-driven<sup>35,36</sup> depending on the EMS but some adjunctive therapies were mandatory.<sup>35</sup> Delivery of CPAP was by facemask.<sup>14,35,36,38</sup> CPAP was generated by oxygen-driven Venturi devices which deliver high gas flow with adjustable fractional inspired oxygen (FiO<sub>2</sub>) in three studies<sup>35,36,38</sup> or fixed-flow generator with pre-set FiO<sub>2</sub> and no allowance for titration of FiO<sub>2</sub>.<sup>34</sup> Four studies set the pressure for CPAP at 10 cm<sup>14,34,36,38</sup> and Ducros et al.<sup>35</sup> initially set the

pressure for CPAP to 7.5 cm H<sub>2</sub>O for 15 minutes and increased it to 10 cm H<sub>2</sub>O if tolerated. Only one study<sup>35</sup> set a target SpO<sub>2</sub>.

## Outcomes

Outcomes from the five studies included in this systematic review are shown in Table 3. The requirement for intubation overall was reported as a primary or secondary outcome in five studies<sup>14,34,36,38,39</sup> or included as part of a composite outcome.<sup>35</sup> Different time points were used to assess intubation rates. The use of CPAP was associated with a 69% reduction in the number of intubations overall, as shown in Figure 2 (OR 0.31, 95% CI 0.19-0.51). Similar results were found when the two French studies were excluded (OR 0.30, 95% CI 0.17-0.53)<sup>35,36</sup> but not significant for pre-hospital intubation only (OR 0.43, 95% CI 0.18-1.02).<sup>14,34,36</sup>

*INSERT TABLE 3 HERE*

*INSERT FIGURE 3*

Composite endpoints were used as the primary outcome in two studies.<sup>35,36</sup> Assessed within 48 hours after inclusion, Ducros et al.<sup>35</sup> combined death, necessity of intubation, persistence of either all inclusion criteria or circulatory failure at 2 hours or reappearance after 2 hours. There was no difference in the composite outcome between the CPAP and usual care group. A secondary outcome was the composite primary endpoint without the intubation criteria. Frontin et al.<sup>36</sup> used treatment success, defined as the respiratory rate less than 25 breaths per minute and SpO<sub>2</sub> greater than 90% at the end of the 1-hour study.

Mortality was measured at different time points (Figure 3). Pre-hospital patient mortality,<sup>34</sup> in-hospital mortality,<sup>35,38</sup> and 30-day mortality<sup>36</sup> were reported. Hubble et al.<sup>38</sup> had the highest decrease in mortality, from 23% in the non-CPAP group to 5.5% in the CPAP group. Pooled results demonstrated an overall 59% decrease in mortality, OR 0.41, 95% CI 0.19-0.87 (Figure 4).

*INSERT FIGURE 4*

The sensitivity analysis could not be performed for the studies excluded because of quality. There was no denominator for the non-CPAP group in one study<sup>37</sup> and there were no intubations in the CPAP group for the other.<sup>39</sup> The studies did not report mortality.



Changes in physiological values - respiratory rate, heart rate and blood pressure were also assessed,<sup>34-36,38</sup> as shown in Table 3. Most studies reported physiological outcomes at 1 hour. Others reported the final set of physiological outcomes used recorded just before ED arrival.<sup>34</sup> One study reported physiological values recorded at several intervals up to 6-hours.<sup>35</sup> When data points were not present in the final set, the immediately preceding complete set was used.<sup>34</sup> Improvements in the changes of physiological values were inconsistent and had high heterogeneity, as shown in Table 4

Length of stay in ICU<sup>35,36</sup> and hospital LOS<sup>36,38</sup> showed no difference (Table 4). The requirement for inotropic support<sup>36 35</sup> was assessed in two studies and in one study BNP levels during the first 24 hours, peak troponin I level; cumulated doses of nitrates and diuretics were reported.<sup>35</sup> Changes in BNP levels in the first 24 hours were similar in both groups.<sup>35</sup>

Dyspnoea score was reported in two studies.<sup>36,38</sup> Patients self-evaluated their perceived breathlessness using a scale ranging from 0 (no breathlessness) to 10 (maximal breathlessness). The reduction in dyspnoea score was significant in one study.<sup>38</sup>

Adverse events/complications such as mask intolerance, barotrauma, vomiting or gastric distension were also assessed. Two patients experienced vomiting in the CPAP group and three in the usual care group but adverse events such as mask intolerance, barotrauma, or gastric distension were not observed.<sup>34,36</sup>

## **DISCUSSION**

This systematic review found seven studies that compared CPAP to non-CPAP treatment for patients with respiratory distress in the pre-hospital setting. Two studies<sup>37,39</sup> did not compare baseline characteristics and were excluded from analyses of outcomes. Pooling the results of the five eligible studies, we demonstrated fewer intubations and decreased mortality when CPAP was used in the prehospital setting. There was wide variation in the intubation and mortality rates, from 0% to 50% for intubation and 0% to 35% for mortality in the non-CPAP

groups. The variability may be related to the differences between health care systems. For example, the French EMS has mobile ICUs staffed by a physician (who is usually an experienced emergency physician or anaesthetist), a nurse and an emergency medical technician.<sup>36</sup> In comparison, EMS systems in North America, United Kingdom and Australia ambulances are often staffed by paramedics who do not have the same clinical resources and expertise as mobile ICUs. Furthermore, Australian studies of critical illness have shown lower baseline and treatment mortality compared to international studies,<sup>40</sup> and hence such dramatic improvements with CPAP may not be replicated in other health care contexts. Also, the exclusion of patients with “do not resuscitate” orders may influence outcomes. Patient outcomes that were not statistically significant in the two French RCTs in this systematic review and meta-analysis were likely due to the studies not being adequately powered for these outcomes.

The cause of respiratory failure may have influenced intubation and mortality rates but this was not examined in four studies. Logistic regression modelling of intubation outcomes by Thompson et al<sup>14</sup> found, after adjustment for allocation to the CPAP group, female sex, age out-of-hospital, peripheral oxygen saturation, out-of-hospital respiratory rate, ED diagnosis of pneumonia and ED diagnosis of acute coronary syndrome that CPAP independently reduced the number of intubations (adjusted OR 0.16; 95% CI 0.04 to 0.7). Studies of the hospital administration CPAP<sup>9-11,41-57</sup> initially targeted APO, particularly ACPO and similarly studies of prehospital CPAP.<sup>17-20,25,34-36</sup> Intubation for acute cardiogenic pulmonary oedema ranged from 5% to 6% for non-CPAP compared to 3 to 5% for the CPAP group and mortality varied for the non-CPAP group from 0% to 11% and CPAP group 0% to 5%.<sup>34-36</sup> Paramedic assessment of the medical history to identify patients with acute congestive heart failure among critically ill patients struggling to breathe in the prehospital-setting can be difficult. Correct identification of patients who meet eligibility criteria or whose treatment decisions depend on these data is important. Hubble and colleague’s study<sup>38</sup> of APO showed that 24% of patients did not have APO and for those who did, the intubation rate was 28% and mortality 25%. With the exception of studies of patients treated by mobile ICU<sup>17</sup> feasibility studies of CPAP for patients with acute cardiogenic pulmonary oedema report 16-32% of cases were misdiagnosed.<sup>16 18</sup> Other diseases such as chronic obstructive pulmonary disease or asthma have also been treated by CPAP.<sup>23,58,59</sup> Thompson et al.<sup>14</sup> recruited patients with acute respiratory failure and reported an intubation rate of 50% and in-hospital mortality of 35% in the non-CPAP group and 20% and 14% respectively in the CPAP group. Including all

cases of severe acute respiratory failure in this systematic review increased the generalisability of the results, but there is a large variation in the number of intubations and mortality. Further research is required.

Mortality as an end point is objective and its clinical relevance is important but requires large sample size for valid assessment in the pre-hospital setting. Recruiting patients for these studies may be difficult. For example, Ducros et al.<sup>35</sup> recruited only half of their estimated sample and had to terminate their study early because data collection time exceeded planned duration due to low patient recruitment. Treatments received and other factors after the patient has been transported to the ED may influence in-hospital or 30-day mortality greater than pre-hospital care. The number of intubations is also an important outcome because of the associated risks with intubation and higher costs associated with the ICU admission and longer hospital stay. The proportion of patients intubated and dying in the field is comparatively low so large sample sizes would need to be recruited to ensure the study has adequate power to detect significant differences. Surrogate measures such as physiological values are a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives<sup>60</sup> are used to assess the effect of the therapy. It is unknown if improvements in physiological values are associated with improved mortality and other patient-centred outcomes. Improvements in physiological values were reported but the results were inconsistent.

Dyspnoea, described as sensations of work or effort, tightness, or air hunger that is unsatisfied on inspiration, is a common and important symptom reported by patients with acute respiratory failure.<sup>61</sup> To manage patients with symptoms of dyspnoea, dyspnoea should be assessed using appropriate measures. Two studies assessed dyspnoea in this systematic review but few reports describe dyspnoea scores in studies of pre-hospital CPAP.<sup>20,36,38</sup> Visual analogue scales<sup>62-64</sup> and the Borg dyspnoea scale<sup>65,66</sup> are sensory–perceptual measures that include ratings of intensity or sensory quality. They are used in the pre-hospital setting but there are no validated instruments for dyspnoea assessment that have accuracy, reliability, reproducibility between observers, and are sensitive to important changes in dyspnoea.<sup>67</sup> Further, assessment of dyspnoea is challenged because dyspnoea scores tend to improve regardless of intervention.<sup>67</sup>

Recent guidelines<sup>68</sup> recommend CPAP in the prehospital setting administered by advanced-level EMS providers in both urban and rural settings.<sup>59</sup> The safety of administering CPAP has been reported in several small observational European and North American observational studies,<sup>16-18,34,37</sup> Early CPAP, when compared to later CPAP, has been shown to have improved outcomes.<sup>20</sup> Nevertheless, consideration must be given to the feasibility to delivering CPAP in the pre-hospital setting. Devices to deliver CPAP are often driven by oxygen and large volumes may be required. Ambulances must have the capacity to carry sufficient amounts of oxygen to ensure availability of oxygen from any distance to definitive care that is required. Furthermore its potential benefit must be weighed against possible transport delays for critically ill patients.

### **Limitations**

Five studies were reviewed in this systematic review and meta-analysis. We did not include non-English language papers so we have may have missed some relevant papers. We may have also missed some relevant English-language papers but we conducted an extensive systematic, literature review to minimise this.

We included non-randomised trials and observation studies provided that they compared the baseline characteristics. Non-randomised studies have inherent biases due to the non-random allocation of the intervention. The risk of potential selection bias from the study conducted by Dib et al.<sup>34</sup> was high, e.g. from non-randomization of patients, and patients and paramedics not being blinded to treatment. The investigators also acknowledge that the reason that patients did not receive CPAP was largely because of paramedic inexperience in administering the treatment.<sup>34</sup> The method of data collection also increased the risk for bias. The identification of acute congestive heart failure was made by two physicians who accessed patients' history, treatment and outcomes from a retrospective chart review. Paramedics in the field usually do not have access to this information. Inspired oxygen concentration per CPAP level should be titrated to achieve a target SpO<sub>2</sub> Hyperoxia is potentially linked to worse outcomes (e.g. myocardial infarction, COPD).<sup>33</sup> Titrating oxygen and CPAP levels to achieve a target SpO<sub>2</sub> should be evaluated in future trials. The use of concurrent controls and adjustment for potential confounding factors in regression models<sup>38</sup> reduces the potential risk for bias. It is likely that some potential confounders are unknown. For example, there is no way to know that more than one episode for a patient has been included in the study unless declared by the authors and this information may not be reported.

Also, not knowing whether intubation has been withheld could be significant to the interpretation of the findings. We assessed studies for methodological quality, based on the evaluation system recommended by Ryan et al.<sup>28</sup> and the Cochrane Collaboration.<sup>29</sup> All of the papers were from developed countries and it is unknown if the results from this systematic and meta-analysis would be different if studies had been conducted in other settings.

## **CONCLUSION**

The studies included in this review showed a reduction in the number of intubations and mortality in patients with acute respiratory failure who received CPAP in the pre-hospital setting. The results may not be applicable to other health care contexts because of the inherent differences in the organisation and staffing of the EMS. Limitations of this systematic review and meta-analysis are the small number of studies and even fewer RCTs. Information from large RCTs on the efficacy of CPAP initiated early in the pre-hospital setting is critical to establishing the evidence base underpinning this therapy prior to ambulance services incorporating CPAP as routine clinical practice.

Several small studies have shown a reduction in the rate of intubations and mortality in patients administered CPAP for acute respiratory failure in the pre-hospital setting. The results may not be applicable to other health care contexts because of the inherent differences in the organisation and staffing of the EMS. Information on the efficacy of CPAP initiated early in the pre-hospital setting is critical to establishing the evidence base underpinning this therapy prior to ambulance services incorporating CPAP as routine clinical practice.

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## **CONFLICT OF INTEREST STATEMENT**

TAW is a NH&MRC Clinical Research Postdoctoral Fellow

JF receives partial salary support from St John Ambulance (WA)

GDP - no conflict of interest

IJ is the Clinical Services Director for St John Ambulance (Western Australia).

St John Ambulance (WA) played no role in the study design, conduct or interpretation of the results.

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## FIGURE LEGEND

Figure 1. Flow diagram of study selection

Figure 2. Publication bias

Figure 3. Forrest plot showing the pooled estimate of effect of CPAP on the risk of intubation

Figure 4. Forrest plot showing the pooled estimate of effect of CPAP on the risk of mortality

Figure 1. Flow diagram of study selection

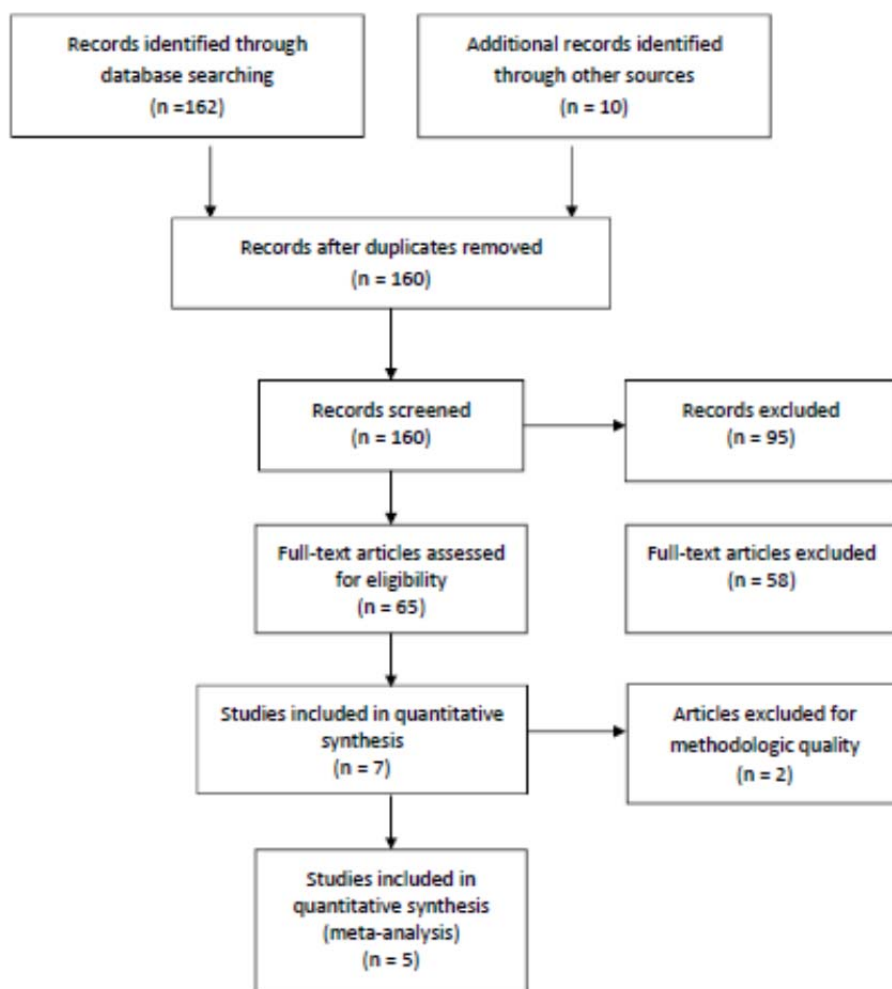


Figure 2. Publication bias

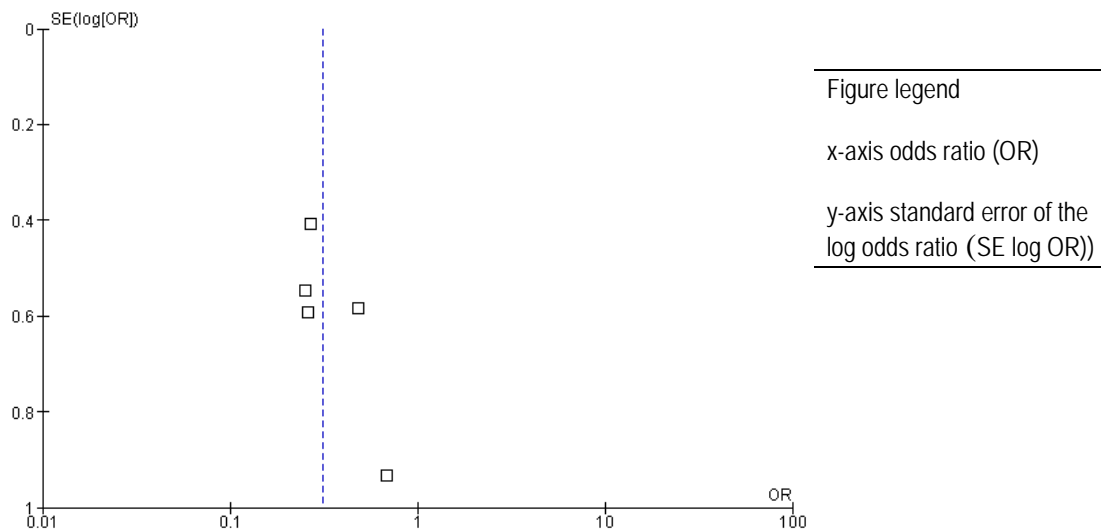


Figure 3. Forrest plot showing the pooled estimate of effect of CPAP on the risk of intubation

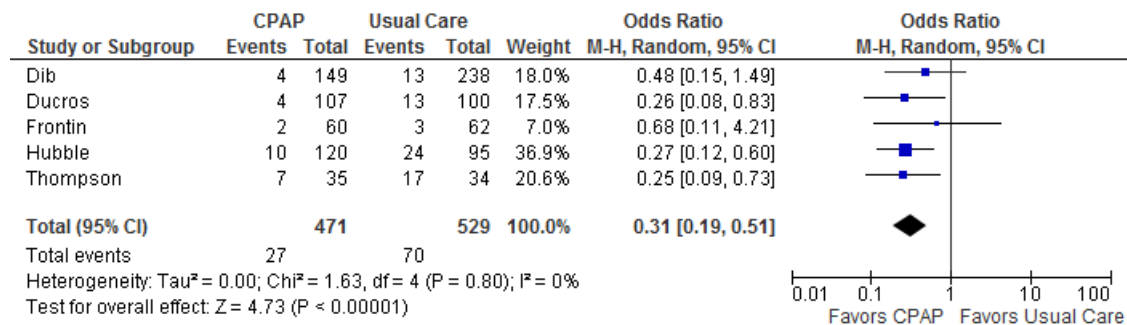


Figure 4. Forrest plot showing the pooled estimate of effect of CPAP on the risk of mortality

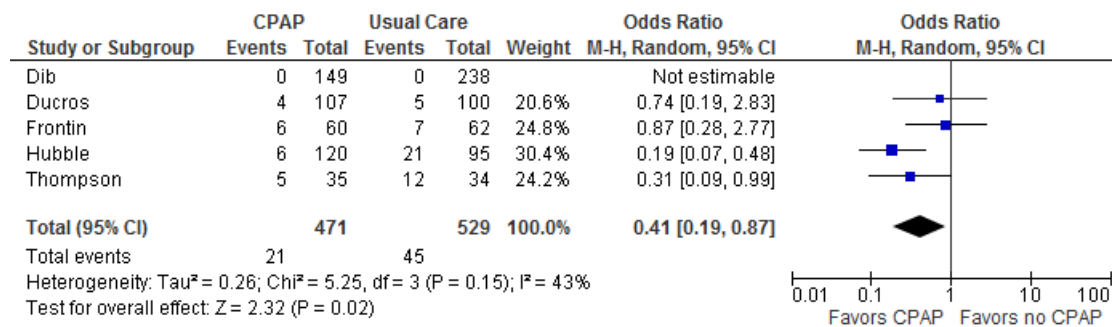


Table 1. Studies that met the inclusion criteria for this systematic review before assessment of the study quality

Study	Emergency Medical Service	Design	Selection criteria	Number of patients
Dib et al. (2012) <sup>34</sup>	EMS, New Jersey Paramedics Two-tier EMS system: BLS and ALS ALS only to those calls requiring possible ALS care and intervention, e.g. shortness of breath	Retrospective review prehospital charts January 2005 –December 2006 Ethic Committee approval	Patients treated for severe acute CHF if <ul style="list-style-type: none"> <li>• Respiratory rate &gt; 25 breaths per minute</li> <li>• Laboured and shallow breathing</li> <li>• Bilateral rales</li> <li>• History of CHF</li> <li>• Intact mental status</li> </ul>	387 patients: CPAP = 149 Non-CPAP = 238
Ducros et al. (2011) <sup>35</sup>	French mobile medical units (Physician staffed)	Multicentre RCT Control group - standard treatment Experimental group - standard treatment plus CPAP Ethic Committee approval	Included patients with cardiogenic pulmonary oedema if <ul style="list-style-type: none"> <li>• Orthopnoea</li> <li>• Respiratory rate &gt; 25 breaths per minute</li> <li>• SpO<sub>2</sub> less than 90% in room air</li> <li>• Diffuse crackles</li> </ul> Excluded <ul style="list-style-type: none"> <li>• History of COPD, asthma, severe stenotic valve disease</li> <li>• Immediate indication for intubation (severe impairment of consciousness, bradypnoea)</li> <li>• Cardiovascular collapse or suspicion of STEMI</li> </ul>	207 patients: CPAP = 107 Non-CPAP = 100 Baseline demographics and physiological values similar between groups Sample size estimated at 200 patients per group Data collection time exceeded planned duration due to low patient recruitment, trial stopped after 207 patients
Frontin et al. (2011) <sup>36</sup>	Mobile ICU (Physician staffed) Prehospital emergency service of University Hospital in metropolitan area Toulouse, France	Single centre RCT September 2006 and March 2008 Ethic Committee approval	Out-of-hospital patients in severe acute cardiogenic pulmonary oedema Included <ul style="list-style-type: none"> <li>• Age &gt;= 18 years</li> <li>• Respiratory rate &gt; 25 bpm</li> <li>• Orthopnoea</li> <li>• Diffuse crackles without evidence of pulmonary aspiration or infection</li> <li>• SpO<sub>2</sub> &lt;90%</li> </ul> Excluded <ul style="list-style-type: none"> <li>• cardiovascular collapse</li> <li>• Impaired consciousness</li> <li>• AMI</li> <li>• Immediate need for intubation</li> <li>• History gastric surgery (&lt;8 days)</li> <li>• Vomiting</li> </ul>	124 patients: CPAP = 60 Non-CPAP = 62 2 did not consent Similar baseline characteristics and non-significant trend toward difference in rate of previous ACPE between the groups
Hastings et al.(1998) <sup>37</sup>	Paramedics Galveston, United States of America	Before and after 6-month study Before: Retrospective chart review of patients matching study inclusion criteria pre introduction of nasal CPAP After Data collection Ethics approval not stated	Severe respiratory distress with APO secondary to congestive heart failure and renal failure. Signs and symptoms include: <ul style="list-style-type: none"> <li>• Tachypnoeic</li> <li>• Tachycardia</li> <li>• Diaphoretic</li> <li>• Hypertension</li> <li>• Verbal impairment</li> <li>• SpO<sub>2</sub> &lt;90%</li> </ul>	CPAP group=32 Age ranged from 50 to 90 years Comparator group: number and characteristics of patients not stated

Hubble et al. (2006) <sup>38</sup>	Two EMS systems Two-tiered EMS - BLS team dispatched to all emergency calls, and ALS Paramedics dispatched only to calls requiring possible ALS care and intervention e.g. chest pain or shortness of breath United States of America	Non-randomised comparative study 1/7/2004 – 30/6/2005 Ethic Committee approval	All consecutive patients presenting with APO as identified by paramedics	215 patients: CPAP =120 Non-CPAP = 95 CPAP group younger, greater dyspnoea, baseline respiratory rate and diastolic blood pressure higher
Thompson et al. (2008) <sup>14</sup>	Emergency Medical Services, transferred to academic tertiary care center) or General Hospital Paramedics Public utility model in which the government owns all ambulances and equipment and provides fully integrated medical oversight, including continuous online physician coverage	RCT Canada, July 2002 – December 2006 Paramedics contacted dispatcher by radio who randomly assigned patient to usual care or CPAP Randomization sequence generated from random-numbers table. Customized tool permitted sequential exposure to allocation sequence via numbered, opaque stickers Ethic Committee approval	Acute respiratory failure - severest subset of the out-of-hospital "shortness of breath" Included <ul style="list-style-type: none"> <li>Severe respiratory distress with failing respiratory efforts (paramedic judgment)</li> <li>Accessory muscle use</li> <li>Respiration rate &gt;25 breaths/min</li> <li>Hypoxia</li> </ul> Excluded <ul style="list-style-type: none"> <li>Respiratory arrest or near arrest (paramedic judgment)</li> <li>Respiration rate &lt;8 breaths/min</li> <li>Periods of apnoea</li> </ul>	CPAP = 35 Non-CPAP = 34 Groups similar in demographics, baseline physiologic characteristics, proportions of patients with exacerbations of CHF, chronic obstructive pulmonary disease, or asthma
Warner (2010) <sup>39</sup>	Paramedics Alabama, US EMS advanced life support (ALS) ambulance provider serving suburban-rural population	8-month, before and after observational, non-blinded study Before November 2007- February 2008 After March to June 2008 Ethics approval not stated	Respiratory distress (dyspnoea, respiratory rate >25 bpm, and/or retractions or accessory muscle use, arterial hypoxemia SpO <sub>2</sub> < 95% in spite of administration of supplemental O <sub>2</sub> ) PLUS <ul style="list-style-type: none"> <li>mental alertness (GCS&gt;10)</li> <li>ability to maintain open airway</li> <li>SBP &gt;90 mmHg</li> </ul> Excluded <ul style="list-style-type: none"> <li>ventilatory arrest</li> <li>suspected pneumothorax / penetrating chest trauma</li> <li>tracheostomy</li> <li>agonal ventilations</li> <li>unconsciousness</li> <li>persistent nausea and vomiting</li> <li>facial trauma or malformation</li> <li>active upper gastrointestinal bleeding or recent gastric surgery (&lt;2 weeks)</li> <li>patients &lt;12 years of age and of average size</li> </ul>	195 patient CPAP group n=106 Non-CPAP group n=89 No description of patient characteristics
ACPE	Acute Cardiogenic Pulmonary Oedema	ALS	Advanced Life Support	
ASPE	Acute Severe Pulmonary Oedema	BLS	Basic Life Support	
bpm	Breaths per minute	CHF	Chronic Heart Failure	
CPAP	Continuous Positive Airway Pressure	EMS	Emergency Medical Services	
ETI	EndoTracheal Intubation	GCS	Glasgow Coma Score	
ICU	Intensive Care Unit	RCT	Randomised Controlled Trial	
SpO <sub>2</sub>	Oxygen saturation from pulse oximetry			

Table 2 Study quality and potential risk of bias

	Dib et al. (2011) <sup>34</sup>	Ducros et al. (2011) <sup>35</sup>	Frontin et al. (2011) <sup>36</sup>	Hubble et al. (2006) <sup>38</sup>	Hastings et al. (1998) <sup>37</sup>	Thompson et al. <sup>14</sup>	Warner et al. <sup>39</sup>
Allocation concealment	Randomisation not done	Adequate*	Adequate*	Randomisation not done	Randomisation not done	Adequate*	Randomisation not done
Study blinded	No	No	No	No	No	No	No
Adherence to intention-to-treat principle	No	Yes	No, 2 patients (2%) randomised but consent withdrawn (both CPAP group)	Yes	No	No	No
Patients lost to follow-up	Nil	Nil	2 patients (2%) randomised but consent withdrawn (both CPAP group)	Nil	Not stated	One	Not stated
Informed consent obtained	Yes	Yes	Yes	Waiver of consent	No	Yes	No
Groups comparable at baseline	Yes	Yes	Yes	Yes	Unknown	Yes	Unknown

\* adequate = randomisation method would not enable the investigator or participant to know or influence allocation intervention group before an eligible participant was entered in the study<sup>28</sup>

Table 3. Summary of results from comparative studies

Study	Outcome	Non-CPAP	CPAP	'p' value / OR & CI
Dib et al. (2011) <sup>34</sup> Non-CPAP = 238 CPAP = 149	Pre-hospital time* (minutes)	31	30	>0.01
	Physiological changes			
	• Respiratory rate decrease	4.09 bpm	5.63 bpm	<0.01
	• SaO <sub>2</sub> increased	5%	9%	<0.01
	• SBP reduction	19.9 mm Hg	27.1 mm Hg	<0.01
	• DBP reduction	7.4 mm Hg	14.1 mm Hg	0.01
	• Heart rate reduction	9.6 beats/min	17.2 beats/min	< 0.01
Pre-hospital intubation n (%)	11 (5.5%)	4 (2.6%)	< 0.01	
Mortality	Nil	Nil		
Ducros et al. (2011) <sup>35</sup> Non-CPAP =100 CPAP = 107	Median time between recruitment and hospital admission (IQR)	82 min (69, 95)	88 min (75, 104)	
	Physiological changes Time 0 (H0) to 6 hours (H6)			
	• Respiratory rate reduction	6 bpm	8 bpm	0.001
	• SBP reduction	35 mm Hg	19 mm Hg	0.52
	• DBP reduction	25 mm Hg	16 mm Hg	0.035
	• Heart rate reduction	20 beats/min	6 beats/min	0.023
	Successful treatment within first 48 hours = absence of death, intubation criteria & persistence of either all inclusion criteria or circulatory failure 2-48 hours	63 (63%)	84 (79%)	OR 2.1; 95% CI 1.2 to 4.0
	Persistence of inclusion criteria after 2 hours	23 (26%)	12 (12%)	OR 2.5; 95% CI 1.2 to 5.5
	Met intubation criteria within 48 hours	13 (14%)	4 (4%)	OR 3.9; 95% CI 1.2, 12.5
	Intubated within 48 hours	6 (6%)	5 (5%)	OR 3.9; 95% CI 1.2 to 12.5
Mortality n (%)	5 (5%)	4 (4%)	OR 1.4; 95% CI 0. 4 to 5.2	
Median ICU LOS	2 days	2 days	0.67	
Frontin et al. (2011) <sup>36</sup> Non-CPAP = 62 CPAP = 60	Treatment success, i.e. respiratory rate < 25 bpm and oxygen saturation > 90% at the end of 1-hour study	22 (35.5%)	19 (31.7%)	0.65
	Physiology changes at 1 hour			
	• Mean respiratory rate (bpm)	8.5	4.9	
	• Mean SpO <sub>2</sub>			
	• Mean heart rate			
	• Mean systolic pressure			
	• Mean diastolic pressure			
	Prehospital intubation	1 (2%)	0	
	Intubation within 1 month	3 (5%)	2 (3%)	0.52
	Died within 30 days	7 (11%)	6 (10%)	0.52
Median ICU LOS	8.2 hours	8 hours	0.27	
Median hospital LOS	6 days	6 days	0.50	
Dyspnoea score	4.8	5.3	0.47	
Hubble et al. (2006) <sup>38</sup> Non-CPAP=95 CPAP=120	Pre-hospital time	30	32	
	Physiology changes			
	• Improvement in respiratory rate	-1.81	-4.55	0.001
	• Improvement in pulse rate	0.82	-4.77	0.013
• Improvement in dyspnoea	-1.36	-2.11	0.008	

	score			
	Pre-hospital intubation	7 (7%)	5 (4%)	0.48
	Intubation anytime	25%	9%	OR 4.0; 95% CI 1.6 to 9.9
	In-hospital mortality	23%	5%	OR 7.5; 95% CI 2.0 to 28.5
	Hospital LOS	8 days	6 days	0.76
Thompson et al. <sup>14</sup> Non-CPAP=35 CPAP=34	Scene time	21 minutes	22 minutes	
	Prehospital intubation	9 In addition 2 pts had attempted intubation	0	
	Prehospital to hospital discharge intubation	17 (50%)	7 (20%)	Unadjusted OR 0.25; 95% CI 0.09 to 0.73; adjusted OR 0.16; 95% CI 0.04 to 0.7
	Mortality	12 (35%)	5 (14%)	Unadjusted OR 0.3; 95% CI 0.09 to 0.99
	Number of critical care admissions	16 (47)	13 (37)	
	Median critical care LOS	3 days	6.5 days	
	Hospital LOS	9 days	7 days	

\*Pre-hospital time = arrival at scene to arrival at emergency department

bpm breaths per minute  
CI Confidence Interval  
DBP Diastolic Blood Pressure  
LOS Length of Stay  
OR Odds Ratios  
SBP Systolic Blood Pressure  
SaO<sub>2</sub> Arterial Oxygen Saturation  
SpO<sub>2</sub> Peripheral Oxygen Saturation