Continuous positive airway pressure plus low flow oxygen versus usual care of severe acute cardiogenic pulmonary edema in the pre-hospital setting: A randomised controlled trial [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Acute cardiogenic pulmonary edema (ACPE) is characterized by acute breathlessness and hypoxia and is associated with poor prognosis. Standard pre-hospital management of ACPE includes high-flow oxygen, nitroglycerin and, in severe cases, assisted ventilation. Patients with ACPE can be supported with newer modalities of non-invasive ventilation, specifically continuous positive airway pressure (CPAP). The aim of this study was to determine whether patients with ACPE treated with CPAP plus low-flow oxygen pre-hospitaly have a lower mortality rate than those treated conventionally.

Methods: This study was a pre-hospital randomised, non-blinded controlled trial conducted July 2009–July 2010. Included were all participants transported by ambulance and admitted to the Royal Hobart Hospital, Tasmania, Australia. The study population was consecutive persons ≥18 years of age with sudden onset of severe respiratory distress, diagnosed as ACPE. Patients were included if they required ventilatory assistance. Patients required a GCS >12 and blood pressure >90 mmHg systolic to safely receive CPAP. The primary outcome was pre- or in-hospital mortality.

Results: In total, 50 patients were enrolled with mean age of 79.8 (±11.9) years. There were two deaths (8.3%) in the CPAP arm and nine (34.6%) in the control arm (RR, −0.24; 95% CI, 0.06–1.00; p=0.051) with a number needed to treat of 4. CPAP plus low-flow oxygen was significantly less likely to result in respiratory acidosis (mean difference in pH, −0.11; 95% CI, −0.04—−0.17; p=0.002), with elevated pCO₂ (mean difference, −10.0 mmHg; 95% CI, −19.2—−0.78; p=0.026). The length of hospital stay was significantly shorter in the surviving patients who received CPAP (ratio of means, 0.45; 95% CI, 0.29—0.70; p=0.001).

Discussion: This study, which provides interim results due to early termination of the trial, shows CPAP in the pre-hospital setting for ACPE is practicable and is associated with improved patient outcomes.
<table>
<thead>
<tr>
<th>Keywords</th>
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<tbody>
<tr>
<td>CPAP, pulmonary edema,</td>
<td>ambulance, NIPPV, out-of-hospital, pre-hospital</td>
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</table>

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- Austin MA: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Visualization, Writing – Original Draft Preparation
- Willis K: Data Curation, Formal Analysis, Methodology, Writing – Review & Editing
- Kilpatrick D: Writing – Review & Editing
- Walters EH: Methodology, Supervision, Writing – Review & Editing

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Introduction
Congestive heart failure occurred in 5.7 million Americans, and in 10 million Europeans. In the United States, 670,000 new cases of acute exacerbations of heart failure (AHF) are diagnosed each year. Unlike other cardiovascular conditions, it is increasing in incidence and prevalence. Its management imposes a substantial burden on the health care system, accounting for 1–2% of total healthcare costs in industrialized nations. About 70% of these costs are related to hospitalization. Acute cardiogenic pulmonary oedema (ACPE) is characterized by acute breathlessness and hypoxia, and is associated with poor prognosis. Standard pre-hospital management of ACPE in most ambulance/paramedic services throughout the world includes high-flow oxygen, nitroglycerin and, in severe cases, assisted ventilation with a bag valve mask or endotracheal intubation (ETI). Some services use frusenide as a diuretic and morphine at low dose as an anxiolytic but these are controversial.

Invasive ventilation increases the risk of complications, including hospital acquired infection (HAI) (pneumonia, sinusitis) and tracheal injury, and consequently may prolong ICU and hospital stay. Pre-hospital intubation is especially difficult in this patient population and is not routinely part of pre-hospital protocols. Therefore in the subset of patients with severe ACPE who are not responding to oxygen and medical therapy, ventilatory assistance is first given non-invasively, conventionally with a valved bag and mask (bagging). However, bagging with a bag and mask in the pre-hospital setting can also have inherent risks: it is difficult to synchronize with the patient’s respiratory efforts while moving in an ambulance, and trying to provide adequate assisted ventilation this way may be counter-productive. Patients with ACPE can be supported with newer modalities of non-invasive positive pressure ventilation (NPPV), specifically continuous positive airway pressure (CPAP). In itself this improves ventilation and therefore oxygenation, through improved V/Q mismatch, reduced breathing effort and increased cardiac output by reducing left ventricular afterload.

Despite the potential advantages of CPAP for the management of severe ACPE, there is a lack of high-quality trial evidence evaluating its impact on mortality in its use in the pre-hospital setting. The hypothesis of this randomised clinical trial was that the use of CPAP system would reduce mortality, hospital length of stay and the requirement for intubation for such patients compared with conventional care provided in the pre-hospital setting.

Methods
This study has been reported according to the CONSORT guidelines. A completed checklist can be found in Supplementary File 1.

The full trial protocol can be found in Supplementary File 2.

Study design and setting
This randomised, controlled, parallel-group trial, which was non-blinded but with good concealment of allocation, was undertaken in patients with a diagnosis of severe ACPE from July 2009 to July 2010. The Joint Tasmanian Ethics Committee (Tasmania Health & Medical Human Research Ethics Committee; EC00337) approved the study with patient consent waived (Ethics Reference Number: H0010364), as in such an emergent therapeutic area both treatments were accepted practices, time was of the essence and neither the patients nor relatives were in a position to make informed choices. The study was registered with the Australia New Zealand Clinical Trials Registry (Trial ID, ACTRN12609000410257).

The RCT consisted of two treatment arms: a control arm using standard positive pressure ventilation with high flow oxygen with a bag-valve-mask assisting patients’ ventilations (bagging), versus an active arm using a continuous positive airway pressure (CPAP) device (Whisperflow) and oxygen supplied at 28–33%. All participants were transported by ambulance to the Emergency Department of the Royal Hobart Hospital (RHH). The RHH is the tertiary hospital for the state of Tasmania and is the only major acute public general hospital serving a population of 250,000 in Southern Tasmania, Australia. No changes to the trial were made after commencement.

Selection of participants
Patients were included if they were ≥18 years of age and diagnosed by paramedic ambulance staff with severe ACPE requiring ventilator assistance. Patients were excluded if they were in respiratory or cardiac arrest, had a Glasgow Coma Score (GCS) <12 or had a systolic blood pressure <90 mmHg.

Interventions
Initially, all subjects received standard therapy according to Ambulance Tasmania (AT) guidelines, namely initial high-flow oxygen, sublingual nitroglycerin as a primary therapy in increasing incremental doses from 400–1600 µg, increasing every 5 min as long as systolic blood pressure was >100 mmHg, with 1–2 mg IV morphine as an anxiolytic and 40 mg IV frusenide for severe respiratory distress in patients with a transport time greater than 20 min.

We used computerised random number generation to allocate patients to treatment arms. This procedure ensured that treatment allocation was concealed before randomisation. Neither paramedics nor the research team were blinded to treatment after randomisation. Subjects entered the study and were randomised at the point where the ambulance personnel considered that they required non-invasive ventilatory assistance. This could be immediately on initial contact or after some standard therapy but subsequent deterioration. Patients in the active arm received 10 cm of H₂O CPAP delivered by Whisperflow® (flow created by a mix of oxygen and air delivering a fixed oxygen flow rate providing 28–33% oxygen), with continued concurrent therapy in the AT Protocol for ACPE patients. In the control arm, positive pressure ventilation was provided by a conventional bag-valve-mask system with high flow oxygen at a rate of 8–15 l/min (bagging), again along with the same concurrent per-protocol therapy. Pulse oximeters were used to measure oxygen saturations in both groups. Baseline and
follow-up measurements of oxygen saturation and vital signs, including GCS scores were recorded on the computerized Ambulance Report Form (Victorian Ambulance Clinical Information System). Vital signs recorded at the time of initial assessment were used as baseline measures.

**Measurements**

In total, 98% (62/63) of paramedics from AT agreed to participate and were trained in the use of the CPAP device and the study protocol. Randomization and allocation concealment were achieved using computer-generated numbers printed on cards indicating the assigned device, which were sealed in sequentially numbered opaque envelopes placed with the ventilation/CPAP equipment on every ambulance.

Having identified a suitable study patient, the paramedic opened the next envelope and entered the randomization number into the computerized ambulance reporting system. A list of these patients was sent to the study coordinator each week. As is standard with such severe patients, they were pre-notified to the Emergency Department (ED) at RHH as an impending Category 1 (high priority) patient, but also that the patient should be recorded as part of the CPAP trial. At arrival at the ED, paramedics were asked to request ED personnel to follow the study protocol and to draw arterial blood gas (ABG) within 30 min; the study was then complete and conventional patient care continued under the treating emergency physician.

The randomisation cards were collected and accounted for by the research team (MA and MG) shortly after each use. The team also followed up each set of ambulance case notes to ensure that the correct device had indeed been used, since neither paramedics nor the research team were blinded to treatment after allocation. In addition, a full list of patients during the study period who had been transported by ambulance with an ED and hospital discharge diagnosis of ACPE was collected, and case notes were assessed to determine if any patients who either required ventilatory assistance or who received it were missed during this time.

Two independent physicians blinded to group allocation retrospectively reviewed randomised study patient computerised ambulance and hospital records to confirm that they had met the set diagnostic criteria for severe ACPE (crackles on auscultation, acute onset shortness of breath and hypoxia requiring assisted ventilation); where appropriate, the cause of mortality was also confirmed from the notes and/or death certification. Discrepancies were reviewed by a third physician (EHW) who was blinded to treatment allocation for resolution. Hospital admission data, including arterial blood gas results were obtained from the RHH Patient Information Medical System. Dispatch, arrival and transport data were obtained from dispatch records from AT to calculate length of pre-hospital treatment times. The third physician (EHW) also reviewed the hospital clinical records of those patients who died, while blinded to the treatment arm, to assess at what point critical deteriorations had occurred and crucial management decisions had been made. AT provided in-kind support for consumables, paramedic training and IT, but unfortunately pulled out at the 12-month time point for budgetary reasons, owing to the expense of CPAP consumables.

**Outcomes and statistical analysis**

The primary outcome measure was pre-hospital or in-hospital mortality. The secondary outcomes were: requirement for invasive ventilation, arterial blood gas values upon arrival in the ED (pH, PO$_2$, PCO$_2$, bicarbonate), length of hospital stay (days) for patients who survived their admission to hospital, and vital signs (oxygen saturation, heart rate, blood pressure, respiratory rate and GCS score).

Where only venous blood samples were available for blood gas assessments we used published formulations to estimate corresponding arterial values for pH, carbon dioxide, and bicarbonate$^{15}$. Arterial and converted venous blood gases were compared using Student’s t-tests, and if no difference was detected they were combined for subsequent analyses. It was not possible to convert venous paO$_2$ since respective arterial paO$_2$ values are not directly comparable and so not provided in the conversion equations, so only measured arterial PaO$_2$ values were analysed.

Power calculations for the primary outcome measure were based on the findings of Hubble’s work$^{10}$, who report a mortality rate, although in patients not as severely ill as ours, of 5.4% for ACPE patients receiving CPAP compared with 23.2% for patients receiving standard therapy. A total sample size of 74 participants (37 in each group) would thus provide 80% power to detect this 17.8% absolute reduction in mortality in the CPAP arm. It was estimated from a retrospective review that at least 50 patients per year with a diagnosis of ACPE requiring ventilatory assistance were transported by AT to the RHH; therefore, the trial was intended to run for 18 months (see below). Unlike more conventional randomized controlled trials, it was not envisaged that there would be drop-outs after recruitment, between randomization and arrival, dead or alive, at the ED.

Baseline characteristics for the patient cohort were described using frequencies for categorical variables and mean (±SD) for continuous variables. We used log binomial regression to compare the risk of death for patients in the two treatment arms. For the secondary outcomes, linear regression was used to compare post-treatment vital signs after adjustment for pre-treatment measurement, and to compare blood gas measurements. Non-normally distributed data were transformed as required. Variables that could not adequately be transformed were analysed using the Mann–Whitney test. Negative binomial regression was used to compare length of hospital stay for patients who survived, with the effect estimate presented as a ratio of mean length of stay for the intervention arm relative to the control arm. A ratio less than one would indicate a decrease in length of hospital stay associated with the intervention, whilst a ratio greater than one would indicate an increase. We summarized pre-hospital drug treatments as frequencies and percentages of patients treated with nitroglycerin, morphine or frusemide, and the number of doses received. Only intention-to-treat analyses were
performed. Stata/IC version 12.1\(^\text{17}\) was used for all analyses and a P-value of 0.05 was considered statistically significant.

**Results**

**Study sample**

A total of 377 patients with varying severity of ACPE were treated and transported to the RHH during the first 12 months, before the study was prematurely terminated as a result of budgetary concerns from AT. Of these, 50 (13\%) met the inclusion criteria and were considered eligible for inclusion in the study according to the attending paramedics: 26 were assigned to the conventional bagging arm, and 24 to the CPAP arm (Figure 1). Of the remaining 327 patients transported, none received CPAP or bagging, so no missing patients were identified (Figure 1). All patients received treatment with the allocated device. Although the intended recruitment numbers were not achieved, the CIs decided to continue with the analysis as planned to avoid publication bias and to ensure that the data are

**Figure 1. Participant flow diagram.**
available for meta-analysis. Thus, the analysis was completed on an intention-to-treat basis with the numbers obtained. Baseline characteristics in the two groups were similar for age, initial oxygen saturation, respiratory rate, blood pressure, heart rate, GCS score and pre-hospital treatment time; however, there were more females in the CPAP arm (Table 1). ED diagnosis confirmed the opinion of the ambulance personnel for all patients enrolled as ACPE, and this was also endorsed by a later review of investigator notes. The median treatment time (scene arrival to ED) was 35 mins.

**Comparison of CPAP and bagging**
We found modest evidence for a reduction in overall mortality in the treatment arm (RR, 0.24; 95% CI, 0.06–1.00; p=0.051; Table 2) from 34.6% (9 deaths) in the bagging arm to 8.3% (2 deaths) in the CPAP arm. This represents a 76% relative reduction in mortality. There were 11 deaths, all in hospital, with 8 occurring in the first 24 hours. Of these deaths, nine were due to a cardiac cause (essentially heart failure), one patient died of a stroke, and the final death at 9 days was due to an unexpected abdominal catastrophe (volvulus and secondary necrosis).

The mean (SD) length of hospital stay was 7.2 (5.11) days for surviving patients in the control arm (n=17) and 3.23 (2.37) days for patients in the CPAP arm (n=22). From the regression analysis (Table 2), it is estimated that the expected length of hospital stay would decrease by 55% with CPAP compared with usual care (ratio of means, 0.45; 95% CI, 0.29–0.70; p≤0.001). Blood gas analysis was undertaken within 30 minutes in 78% (39/50) patients; 48% (24/50) were arterial and 30% (15/50) venous. Patients receiving CPAP were significantly less likely to have acidosis (pH <7.35) and hypercarbia (PaCO₂ >45 mmHg) (Table 2); the hospital arrival post-ambulance-treatment oxygen saturation of patients was significantly lower in those who received CPAP (Table 3). Only two patients were intubated in the ED, both having been bagged.

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**Table 1. Pre-treatment baseline characteristics for patients with a diagnosis of ACPE.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (usual care)</th>
<th>Intervention (CPAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Mean (SD)*</td>
<td>n Mean (SD)*</td>
</tr>
<tr>
<td>Males (% (n/N))</td>
<td>61.5% (16/26)</td>
<td>29.2% (7/24)</td>
</tr>
<tr>
<td>Age, years</td>
<td>26 78.3 (11.8)</td>
<td>24 81.5 (11.9)</td>
</tr>
<tr>
<td>Transport time, min (median (IQR))</td>
<td>26 35 (24–48)</td>
<td>24 36 (31–52)</td>
</tr>
<tr>
<td>Pre-treatment vital signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>18 79.7 (12.0)</td>
<td>22 77.1 (14.2)</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>26 32 (11.6)</td>
<td>24 34 (10.8)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>23 161 (61)</td>
<td>24 169 (25)</td>
</tr>
<tr>
<td>Glasgow Coma Scale (median (IQR))</td>
<td>26 15 (14–15)</td>
<td>24 15 (14.5–15)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated.

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**Table 2. Primary and secondary outcomes.** Intention-to-treat analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Intervention</th>
<th>Treatment effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n  Mean (SD)*</td>
<td>n  Mean (SD)*</td>
<td>Value  (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Mortality (% (n/N))</td>
<td>34.6% (9/26)</td>
<td>8.3% (2/24)</td>
<td>0.24† (0.06, 1.00)</td>
<td>0.051</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>7.2 (5.11)</td>
<td>3.2 (2.37)</td>
<td>0.45§ (0.29, 0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endotracheal Intubation (% (n/N))</td>
<td>7.7% (2/26)</td>
<td>0% (0/24)</td>
<td>1.92#</td>
<td>0.166</td>
</tr>
<tr>
<td>Blood gases (&lt;30 min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>19  7.21 (0.12)</td>
<td>20  7.32 (0.08)</td>
<td>0.11‡ (0.04, 0.17)</td>
<td>0.002</td>
</tr>
<tr>
<td>pCO₂, mmHg</td>
<td>19  56.1 (15.2)</td>
<td>19  46.1 (12.7)</td>
<td>−10.0‡ (−19.2, −0.78)</td>
<td>0.026</td>
</tr>
<tr>
<td>Bicarbonate, mmol/l</td>
<td>19  21.4 (3.94)</td>
<td>19  22.9 (3.57)</td>
<td>1.48‡ (−0.99, 3.95)</td>
<td>0.233</td>
</tr>
<tr>
<td>paO₂, mmHg</td>
<td>14  107.2 (92.6)</td>
<td>9  95.7 (48.6)</td>
<td>−11.5‡ (−81.5, 58.4)</td>
<td>0.788</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated; †relative risk; §incidence rate ratio; #chi-squared statistic; ‡mean difference.
and both died in the ED. There were no significant differences in ED arrival heart rate, blood pressure and GCS between the two study arms (Table 3).

Use of out-of-hospital medications was similar between the two groups: sublingual nitroglycerin was used in 73% (19/26) of patients in the control arm and all patients (24/24) in the CPAP arm; frusemide was used in 50% (13/26) of patients in the control arm, and in 75% (18/24) of patients in the CPAP arm; low-dose morphine was used in 23% (6/26) of patients in the control arm and 25% (6/24) of patients in the CPAP arm. Of those patients receiving drug treatment, the median (IQR) total doses for sublingual nitroglycerin sprays (400 ug/spray) was 2.8 sprays (2.8) for the control arm and 2 sprays (2.8) for the CPAP arm. For frusemide, most patients (92% in the control arm and 89% in the CPAP arm) received a total dosage of 40 mg, one in each arm received 20 mg and one in the CPAP arm received 80 mg. Dosage data were recorded for 9/12 patients receiving morphine: the range of total dosage in the control arm was 1–3 mg and was 1–2 mg in the CPAP arm.

Although the overall number recruited was smaller than intended, for the logistic ambulance service managerial decision given, our results, are consistent with most of the limited pre-hospital literature11,12,16,18,19. Two recent before-and-after studies showed no differences in mortality, although the population studied had less severe acute exacerbations of heart failure20,21. The population around Hobart is reasonably urbanized, but there are significant outlying rural areas, offering a mixed population, which makes our study reasonably generalizable for other similar rural urban setting. Whilst we found evidence for a difference in mortality between the management strategies trialled, we did not recruit the required sample size so did not reach the required level of power. This investigation should perhaps be best regarded as preliminary and of a “pilot” nature. Although, by chance, we had an imbalance in the sex composition of the treatment groups, there is no evidence to indicate an association between sex and mortality, so it is unlikely to have been a confounding factor.

A second limitation of this study was that decision-making about patient eligibility was left to the discretion of the paramedics on the scene, with no validated physiological or clinical scores used22,23. However, given that the paramedic did not know which regimen would be allocated at the time of decision to enrol each patient, this approach is unlikely to have confounded the outcome. Studies have shown that field discrimination between ACPE and other causes of respiratory distress is poor24, even by in-field physicians25. However, our review of hospital records for all patients with heart failure who were transported to hospital over this period indicated that all suitable patients were randomised, and all randomised patients had an admission diagnosis of ACPE and received the allocated treatment. It does not appear that any suitable patients were missing from the recruitment.

The rate of arterial blood gas sampling for study patients was low, with only 48% of arterial samples drawn within 30 minutes of arrival. We recognize that ABGs are not standard of care; however, with the variability of VBG results, we felt ABGs would be a better lab value of respiratory status. Despite the request by research staff in meetings leading up to the study, this rate of compliance by hospital staff is consistent with the literature26,27. Potential reasons for this low compliance include patient

**Table 3. Vital signs after pre-hospital treatment at arrival to ED for patients with a diagnosis of ACPE.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Intervention</th>
<th>Treatment effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)*</td>
<td>n</td>
<td>Mean (SD)*</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>19</td>
<td>95.1 (4.84)</td>
<td>20</td>
<td>87.5 (7.14)</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>20</td>
<td>28.9 (6.66)</td>
<td>24</td>
<td>32.3 (9.72)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>21</td>
<td>143 (32)</td>
<td>24</td>
<td>137 (23)</td>
</tr>
<tr>
<td>Pulse rate, beats/minute</td>
<td>23</td>
<td>105.1 (19.9)</td>
<td>24</td>
<td>111.7 (24.2)</td>
</tr>
<tr>
<td>Glasgow Coma Scale (median (IQR))</td>
<td>18</td>
<td>15 (14–15)</td>
<td>21</td>
<td>15 (15–15)</td>
</tr>
</tbody>
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**Discussion**

We found that treatment with CPAP plus low-flow oxygen, in the pre-hospital setting, for patients with ACPE reduced the risk of death by 76% compared with conventional care. Of the 377 patients transported to hospital with ACPE during the year of the study, we recruited all those eligible in the most severe group requiring assisted ventilation. The difference in mortality between the active and control groups was greater than anticipated, because of a larger than expected number of deaths in the control group. This may be due to the greater severity of patient condition at the time of randomisation in our study compared to that used as the basis for the power calculation16. Although baseline vital signs were not different between groups, patients were more likely to have respiratory acidosis with conventional care, and it may be construed that conventional care may have contributed to this increase in mortality.

Use of out-of-hospital medications was similar between the two groups: sublingual nitroglycerin was used in 73% (19/26) of patients in the control arm and all patients (24/24) in the CPAP arm; frusemide was used in 50% (13/26) of patients in the control arm, and in 75% (18/24) of patients in the CPAP arm; low-dose morphine was used in 23% (6/26) of patients in the control arm and 25% (6/24) of patients in the CPAP arm. Of those patients receiving drug treatment, the median (IQR) total doses for sublingual nitroglycerin sprays (400 ug/spray) was 2.8 sprays (2.8) for the control arm and 2 sprays (2.8) for the CPAP arm. For frusemide, most patients (92% in the control arm and 89% in the CPAP arm) received a total dosage of 40 mg, one in each arm received 20 mg and one in the CPAP arm received 80 mg. Dosage data were recorded for 9/12 patients receiving morphine: the range of total dosage in the control arm was 1–3 mg and was 1–2 mg in the CPAP arm.

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The rate of arterial blood gas sampling for study patients was low, with only 48% of arterial samples drawn within 30 minutes of arrival. We recognize that ABGs are not standard of care; however, with the variability of VBG results, we felt ABGs would be a better lab value of respiratory status. Despite the request by research staff in meetings leading up to the study, this rate of compliance by hospital staff is consistent with the literature26,27. Potential reasons for this low compliance include patient
refusal, reluctance of doctors to perform the test or be involved in other investigators’ research and limited time and staff resources. Conversion of VBG samples is also a limitation of our study. Arterial and converted venous blood gases were compared using Student’s t-tests and no significant group differences were found. In addition, a sensitivity analysis using only the ABG results showed similar results. Therefore, we feel confident in combining these data.

We were unable to determine whether pre-hospital management itself had an effect on in-hospital management, except perhaps that related to the presenting state of the patient. The RHH has a BiPAP/CPAP protocol for breathless patients who present with severe respiratory distress with a clinical picture of ACPE, but any change in management that occurred after arrival at the ED would have reduced the differences between the treatment arms. However, the hospital chart review suggested that those who died tended to do so quite quickly after arrival in hospital.

The number needed to treat with CPAP to avoid a cardiac-related death was 4. Our mortality rate in the CPAP arm was consistent with published data. Notably, our study provides additional evidence to underpin recent recommendations that CPAP be used in the pre-hospital setting for severe ACPE patients. However, the use of controlled oxygen delivered with CPAP in this study is a potential confounder. Thus, we cannot be sure whether the advantage in the active group was through the direct mechanical effects of CPAP, different oxygen regimes in the two systems used, or both. Previous results with CPAP in patients with milder heart failure would certainly support the use of this modality. It would probably not be ethical to undertake a trial of CPAP versus low-flow oxygen at this stage.

Overall, carbon dioxide blood levels were higher in the “bagging” group, with secondary acidosis, indicating relatively worse ventilation, while the oxygen saturations were higher; this raised the question of whether relative hyperoxia was contributing to a V/Q mismatch or suppressing ventilation in a vulnerable group, or whether both are merely features of the respective systems being used. The relative hypercarbia and acidosis when patients were bagged with high-flow oxygen (Table 3) is consistent with that seen in previous hospital studies. Supporting the use of CPAP in these patients.

The overall incidence of endotracheal intubation was low, and was nil in patients with CPAP use, which is consistent with the findings of Thompson et al. However, this raises the question of why those that died were not intubated, especially on arrival in extremis in the ED. Review of the ED notes suggested that the commonest scenario in those who died was an elderly patient presenting with severe heart failure and ventilatory failure being trialled on BiPAP in the ED, with concurrent discussions taking place with family about the decision not to progress to intubation and mechanical ventilation. With family agreement, the patient was then allowed to die comfortably (i.e. a palliative approach was taken). None of the patients had documented “do not resuscitate” advanced directives prior to arrival to the ED. From the baseline characteristics, the severity of the ACPE event appeared similar in each group, so use of the CPAP regime appeared to have prevented this scenario. This strongly indicates that optimal pre-hospital treatment is vital to prevent clinical deterioration to a point where the ED staff are faced with what is essentially an “end-stage” patient thought unsuitable for intubation and ICU care. The length of hospital stay in survivors was significantly longer in the control group compared to the CPAP group, consistent with both the literature and with CPAP allowing patients to arrive in hospital in a better physiological state.

**Conclusion**

In conclusion, our trial, although truncated, found that pre-hospital CPAP plus low-flow oxygen resulted in a 76% relative reduction in the risk of mortality for severe ACPE patients compared with the conventional form of ambulance service management with assisted mask and bag ventilation. Patients that underwent CPAP were less likely to have respiratory acidosis and their length of hospital stay was significantly reduced. Our findings provide evidence to support CPAP with controlled oxygen in severe ACPE patients in the pre-hospital setting. Given the early termination of this study, a further trial of this combination should be considered reasonable.

**Data availability**

Dataset 1. All raw demographic and experimental data from the present study. DOI: 10.5256/f1000research.14577. d201292.

**Competing interests**

No competing interests were declared.

**Grant information**

The authors declare that no grants were involved in supporting this work. Fisher and Paykal (suppliers of the Whisper-flow® CPAP device) had no involvement in the study design, conduct, analysis or interpretation of data, nor in writing this report. The NHMRC through the CRE supported the statistician and co-investigator KW. Ambulance Tasmania provided in-kind support for consumables, paramedic training and IT, but for budgetary reasons, due to the expense of CPAP consumables, pulled out at the 12-month time point. AT did not have access to the study data and had received no information about study progress when they withdrew support. Furthermore, the trial investigators had no involvement in or prior knowledge of the decision.

**Acknowledgements**

We would like to thank the patients who participated in the study, clinical and clerical staff of Ambulance Tasmania and the Emergency Department at the Royal Hobart Hospital, laboratory staff at the Royal Hobart Hospital and members of the Respiratory Department at the Royal Hobart Hospital whose participation made this project possible.
Supplementary material

Supplementary File 1. Completed CONSORT checklist.

Click here to access the data.

Supplementary File 2. Research protocol for the trial.

Click here to access the data.

References


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This is a well designed randomized controlled trial about an important patient-oriented outcome (mortality). This trial had the potential to add to the literature with high quality evidence in the prehospital setting about the management of ACPE with CPAP, and it is unfortunate that the target sample size was not met due to early termination. Though the study is underpowered, the authors appropriately note that the results are promising and suggest it supports another attempt at a similar study. The results are also available for inclusion in future meta-analysis. One concern I have regarding feasibility is that the reason for early termination was the cost of the consumables for the intervention itself.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.
Reviewer Expertise: EMS/paramedicine, health services research

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 28 August 2018

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The study was designed to investigate the impact of prehospital CPAP in the mortality of patients with cardiac acute pulmonary edema, in comparison to bag-valve-mask (BVM). Patients were elected by paramedics according to their perception of severity after protocolized medical treatment, and randomized to CPAP or BVM. Authors conclude that CPAP is better than BVM in improving respiratory acidosis and reducing mortality.

Design and implementation of studies that involve interventions in prehospital setting entails a great effort of coordination, an important leadership and are difficult to carry out. My congratulations to the authors for being able to do it. In the other hand, demonstrate the impact of a short time of treatment on the overall evolution of patients is complicated and it requires studies with a large number of patients and many controlled variables.

The objective proposed in this study has been subject to some meta-analyses that have not been cited in this article. These meta-analyses concluded that the use of prehospital CPAP in patients with suspected acute pulmonary edema leads to a reduction in intubation rate and mortality of these patients. The presented results can help to do the evidence more solid.

Major considerations

1. It would be interesting to discuss about the most important methodological differences with other prehospital protocols, especially regarding the respiratory support received by the control group, which does not include the possibility of intubation. As authors comment in the discussion, respiratory support with bag-valve-mask during out-of-hospital assistance in control group is not easy and could partially explain the gasometrical deterioration of these patients. BVM is not the most commonly used ventilatory support in other countries and its potential influence on the high mortality of the control group could be discussed. Considering that the included patients were aware (taking into account the initial vital signs), the ventilation technique could appear unnecessary. It would be interesting that authors justify in the discussion section their use instead of oxygen therapy alone in the control group. It is not clear what the clinical situation before randomization was. To expand the table 1 with vital signs and oxygen saturation at this moment would provide valuable information.

2. The absence of physiological criteria of inclusion is an important limitation already commented by the authors. This issue make the study difficult to reproduce in other areas.
3. The authors should clarify when the data in the Dataset 1 has been collected. When studied in detail, it seems that most of the deceased patients in the control group (and one of the CPAP group) had exclusion criteria (if data marked with the number 1 are initial) such as Glasgow less than 12 or systolic blood pressure lower than 90 mmHg or unregistered. Is this interpretation correct? What does each column correspond to?

4. I have understood that out-of-hospital treatment protocol was maintained during the first 30 minutes of hospital assistance. This issue may have caused or magnified the observed differences in the prognosis and deserves consideration in the discussion, which also includes ethical aspects of this decision. It would be interesting to report the total treatment times in both groups as well as when non invasive ventilation or CPAP was initiated in the control group, if needed. Regarding the differences in blood gases, the persistence of important respiratory acidosis in patients in the control group is not coherent with clinical situation, since vital signs at hospital arrival were not worse in the control group. It is also important to clarify whether these patients received no respiratory support on arrival and during the first 30 minutes irrespective of what their situation was (as I have understood in the methods/measurements and discussion sections), which would mean an important ethical conflict.

Other considerations

5. The fact that only two of the nine patients who died in the control group were finally intubate does not allow concluding about mortality, as they not received all the alternative treatment. It would be desirable to add a reference to this type of patients in the final conclusion of the article.

6. Further details on the baseline cardiopathy status, severity indices and treatments received would help to conclude that the difference in mortality can be attributed to the different prehospital management. As the authors mentioned, the impact of 30 minutes in the stay of 3 to 7 days is very difficult to demonstrate and all the previous factors and significant treatments received would have to be taken into account.

7. Nothing has been said about the tolerance of both methods.

8. The last section of the abstract does not refer to the discussion but to the conclusions.

9. Taking into account the method used and its limitations, the first sentence of the discussion and the conclusion could be rewritten to better reflect the results.

10. The refereed study by Cheskes² includes not only patients with less severe acute exacerbations of heart failure but also respiratory patients (almost 50% and 50%).

11. Frusemide usually appears in the literature as furosemide.

References


Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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