A randomized study of out-of-hospital continuous positive airway pressure for acute cardiogenic pulmonary oedema: physiological and clinical effects

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Aims In acute cardiogenic pulmonary oedema (ACPE), continuous positive airway pressure (CPAP) added to medical treatment improves outcome. The present study was designed to assess the benefit of CPAP as a first line treatment of ACPE in the out-of-hospital environment.

Methods and results The protocol lasted 45 min, divided into three periods of 15 min. Patients with ACPE were randomly assigned in two groups: 1/Early CPAP (n = 63): CPAP alone (T0–T15); CPAP + medical treatment (T15–T30); medical treatment alone (T30–T45) and 2/Late CPAP (n = 61): medical treatment alone (T0–T15); medical treatment + CPAP (T15–T30); medical treatment alone (T30–T45). Primary endpoint: effect of early CPAP on a dyspnoea clinical score and on arterial blood gases. Secondary endpoints: incidence of tracheal intubation, inotropic support, and in-hospital mortality. T0–T15: CPAP alone had a greater effect than medical treatment on the clinical score (P = 0.0003) and on PaO2 (P = 0.0003). T15–T30: adding CPAP to medical treatment (late CPAP group) improved clinical score and blood gases and the two groups were no longer different at T30. T30–T45: in both groups, CPAP withdrawal worsened clinical score. Six patients in ‘early CPAP’ group vs. 16 in ‘late CPAP’ group were intubated [P = 0.01, odds-ratio: OR = 0.30 (0.09–0.89)]. Dobutamine was used only in the ‘late CPAP’ group (n = 5), (P = 0.02). Hospital death was higher in ‘late CPAP’ group (n = 8) than in ‘early CPAP’ group (n = 2) [P = 0.05, OR = 0.22 (0.04–1.0)].

Conclusion When compared to usual medical care, immediate application of CPAP alone in out-of-hospital treatment of ACPE is significantly better improving physiological variables and symptoms and significantly reduces tracheal intubation incidence and in-hospital mortality.

KEYWORDS Pulmonary oedema; Immediate CPAP; Pre-hospital

Introduction

Cardiogenic pulmonary oedema (CPE) is a frequent presenting process for acute out-of-hospital practice. Acute left heart failure may occur from a variety of processes that rapidly deteriorates to this generalized cardiopulmonary disorder. The classical treatment of out-of-hospital CPE includes supplemental oxygen, vasodilators, loop diuretics, and morphine. If not effective, or because of the associated respiratory depression, tracheal intubation and mechanical ventilation are often needed, which, by themselves are associated with a worse prognosis.1 Continuous positive airway pressure (CPAP) has been proposed to avoid mechanical ventilation in severe CPE.2–4 This technique not only decreases intrapulmonary shunt4 and work of breathing5 but also reduces left ventricular afterload, and both right and left ventricular preload.6 The overall effect of CPAP in the acute management of CPE is to improve cardio-respiratory function and sustained tissue oxygenation. Furthermore, the combination of CPAP with medical treatment in patients with CPE significantly reduces the need for intubation3,4 and improves the outcome.7–11

Very limited data are available on the effects of CPAP in the out-of-hospital practice.12,13 Applying CPAP out-of-hospital could shorten the delay for an adequate treatment and therefore reduce the need for intubation. Indeed, due to its combined heart and lung effects and in case of an early application, one can speculate that CPAP alone might be sufficient to re-establish cardio-respiratory stability in these patients. Thus, we evaluated for the out-of-hospital treatment of acute CPE, the effects on physiological and clinical parameters of CPAP alone, or in combination with medical treatment.
Methods

This single centre, prospective, randomized, intention-to-treat clinical trial was performed in the out-of-hospital setting. The Consultative Council for the Protection of Persons Volunteering for Biomedical Research of Lariboisière Saint-Louis University, Paris, approved the study (reference number: AOM03037, P030428, ERN20040504). Patients or their next-of-kin were informed on scene about the principles of the protocol. In order to start the treatment as soon as possible, patients or their next-of-kin had to approve or to refuse the principle to participate before starting the study. Then, a written informed consent was fulfilled and signed before leaving the scene.

In France, a two-tiered emergency medical services system is responsible for responding to all emergency calls.14,15 The first-tier response consists of fire rescue personnel equipped with basic life support equipment, providing, at most, only supplemental oxygen to the patients. The second-tier response usually arrives 8–10 min after the first responders. It provides advanced life support care (ALS), including advanced airway support and pharmacological therapy. It always includes a physician (anaesthesiologist or emergency physician specially trained in intensive care), an anaesthesiologist nurse, an ambulance driver, and a medical student.

Patient selection

The study was performed in a single ALS team based in Lariboisière University Hospital and which covered the north–north east of Paris, France. Patients with clinical symptoms of acute pulmonary oedema such as orthopnea, diffuse crackles without evidence of pulmonary aspiration or infection, pulse-oximetry (SpO2) ≤ 90% despite supplemental oxygen therapy (15 L min⁻¹ via a reservoir bag face mask, Gamida, France) provided by the first responders were included in the study. Patients were excluded if they had a history of chronic obstructive pulmonary disease, asthma, severe stenotic valvular disease, or if they had cardiovascular collapse or an impaired level of consciousness.

Upon arrival of the medical team, after acceptance of the principle of the protocol, subjects were randomized on scene to CPAP first (Early CPAP = E) or to medical treatment first (Late CPAP = L). Randomization was performed on scene using a computer-generated randomized list of sequentially numbered, sealed envelopes. Day-to-day envelopes were kept on the SAMU truck and opened on scene to know the arm allocation. CPAP was generated by a Venturi device (Downflow®, Gamida, France) connected to a face mask with an expiratory valve that sustained 7.5 cmH₂O CPAP. The airflow provided by such a device was above 120–140 L min⁻¹ ensuring a relatively constant airway pressure during all the respiratory cycle with an constant oxygen fraction (FiO2) ranging from 0.33 to 0.37. During the whole procedure, upper airway pressures were continuously measured by connecting the facemask to a physiological monitor (Propaq Encore®, PhysioControl, France) via a pressure transducer (Sorensen Transpac III®, Abbott Systems, Chicago, IL, USA) to avoid air leaks, but the values were not recorded.

Medical treatment consisted in intravenous bumetamide (0.025 mg kg⁻¹), and, if systolic blood pressure (SBP) was over 100 mmHg, nitroglycerin (400 mcg sublingually followed by 1 mg h⁻¹ intravenously) and nicardipine (1 mg h⁻¹ intravenously) in case of severe sustained arterial hypertension (SBP > 160 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg after nitroglycerin administration). Addition of an inotropic support (dobutamine) was decided by the physician in charge when the previous strategy failed to improve clinical status.

Study design

The baseline time (T0) corresponded to at least 15 min of ALS oxygen therapy. The protocol was divided into three periods of 15 min each (Figure 1). The length of each period was controlled by the medical student of the ALS team using a chronograph. The study began on scene and was continued during patient transport in the ambulance. Only the first 15 min period differed within the two arms. Group E: patients received CPAP alone from T0 to T15 min, whereas Group L, received both medical treatment and supplemental oxygen therapy (15 L min⁻¹ corresponding to a FiO₂ of 0.5–0.7, via reservoir bag face mask, Gamida, France). From T15 to T30 min, CPAP was maintained in Group E and added to Group L, while both groups received medical therapies, as described above. From T30 to T45 min, medical treatment was maintained, whereas CPAP was removed and replaced by 15 L min⁻¹ oxygen therapy in both groups. A protocol step was considered not completed if the patient’s trachea had to be intubated, presented a cardiac or a respiratory arrest, or did not tolerate CPAP. CPAP intolerance was defined as the occurrence of facemask intolerance, a bronchial aspiration, a pneumothorax, or a severe gastric distension.

The intubation criteria were: respiratory arrest, respiratory pauses with loss of consciousness, refractory hypoxemia (SpO2 < 85%), loss of consciousness or psychomotor agitation making care impossible and requiring sedation, a heart rate below 50 beats/min with loss of alertness, and hemodynamic instability with systolic arterial blood pressure below 70 mmHg.

The following parameters were collected at T0, T15, T30, and T45: heart rate (HR: b.p.m.), respiratory rate (RR/min), non-invasive SBP and DBP, SpO2 (Propaq Encore®, PhysioControl, France), dyspnoea clinical score (DCS; Table 1), and arterial blood gases sampled from a radial arterial catheter inserted under local anaesthesia. After protocol completion, patients were transported to an adapted unit (emergency room, medical, or cardiologic intensive care unit) in the nearest hospital. Since the SAMU system works on geographically defined zones, the four hospitals located in this zone received the patients. Patients did not receive CPAP after protocol completion as far as the technique was not routinely used at the time of the study. The follow-up was then performed by the ALS doctors (daily phone calls and analysis of patients’ files) until patients’ discharge or in-hospital death. The needs for intubation or for an inotropic support were recorded during the protocol but also after its completion, during patients’ hospital stay.

The primary endpoint was the effect of early CPAP administration on the clinical score and arterial blood gases. The secondary endpoint was the impact of early CPAP on the frequency of failure of the care strategy, defined as a need for tracheal intubation or inotropic support or in-hospital death.

Statistical analysis

Sample size was calculated to detect a difference in clinical score of 1.5 considering a standard deviation of 2.5. To detect such effect, with 90% power and a type I error of 0.05, 59 patients per group were required.

Data were analysed on an intention-to-treat basis. All data were expressed as mean ± SD. After verifying the normal distribution, numerical data were analysed using Student’s t-tests whereas qualitative data were analysed using χ² tests. When χ² validity criteria were not present, we used a Fisher’s exact test. Odds-ratios (OR) with their 95% confidence intervals (95% CI) were also computed. All tests were two-sided, at the 0.05 significance level. P-values involving multiple comparisons (at T15, T30, and T45) were corrected using Hochberg method.16 Data analysis was performed using Statview™ software (version 5.0, Abacus concepts, Berkley, CA, USA).

Results

Hundred and seventy six consecutive ACPE were screened between January 1998 and December 1999. Hundred and twenty four consecutive patients were finally included in the study: 63 in group E and 61 in group L. Fifty two were...
excluded: 36 had a history of chronic obstructive pulmonary disease, 10 a history of asthma, and six patients were in cardiovascular collapse (Figure 2). Their general characteristics are summarized in Table 2. No significant differences were found between the two groups at T0.

T0–T15

At T15, DCS and RR (Figure 3A and B) were lower in group E (CPAP alone) than in group L (medical treatment alone) even if, for RRs, the difference did not reach statistical significance (4 ± 2 vs. 7 ± 2 at T15; $P = 0.0003$ and 29 ± 8 b min$^{-1}$ vs. 32 ± 7 b min$^{-1}$ at T15; $P = 0.09$ respectively). After the first 15 min, SBP was significantly lower in group L with no difference in DBP (Figure 3C). HR significantly decreased similarly in both groups (Figure 3D). At T15, patients in group E had a higher PaO$_2$ (group E: 89 ± 18 mmHg vs. 68 ± 10 mmHg in group L at T15; $P = 0.0003$) and a lower PaCO$_2$ even if the difference in PaCO$_2$ was close to statistical significance (42 ± 7 mmHg vs. 45 ± 8 mmHg at T15; $P = 0.06$) (Figure 4A and B). Arterial pH was significantly higher in group E than in group L at T15 (in group E, 7.32 ± 0.08 at T0 vs. 7.35 ± 0.06 at T15; in group L, 7.33 ± 0.08 at T0 vs. 7.33 ± 0.08 at T15). Arterial bicarbonate levels remained stable in both groups during the first 15 min of the protocol.

T15–T30

DCS and RR improved in both groups but significantly more in group L in which CPAP was added to medical treatment. At T30 DCS, RR, and blood pressures were similar within the two groups. PaO$_2$ and PaCO$_2$ improved dramatically in group L during the second period of the protocol. At T30, PaO$_2$ and PaCO$_2$ were similar within the two groups. As a result of arterial pH increase in group L, both groups exhibited a similar arterial pH at T30 (7.36 ± 0.06 vs. 7.36 ± 0.04; $P = 0.92$).

T30–T45

At T45, DCS, RR, HR, and blood pressures were similar within the two groups. PaO$_2$ was significantly higher in group E than in group L after completion of the three steps of the protocol (97 ± 29 mmHg vs. 85 ± 19 mmHg; $P = 0.018$). At the end of the protocol, PaCO$_2$ in group E was lower but not statistically different than in group L (42 ± 7 mmHg vs. 44 ± 9 mmHg; $P = 0.27$). At T45, no statistical difference in arterial pH was observed within the two groups (7.35 ± 0.07 vs. 7.35 ± 0.06).

Secondary end-points

Intubation rate: Nine patients were intubated during the 45 min of the study period (one in group E and eight in group L, within the first 15 min, $P = 0.01$). Globally, 22 patients out of the 124 needed a tracheal intubation during or after the study period [six in group E vs. 16 in group L; $P = 0.01$, OR = 0.30 (0.09–0.89)]. As a consequence, 13 patients were intubated after hospital admission (five in group E and eight in group L, $P = 0.23$).

Inotropic support: Five patients needed addition of dobutamine in group L, while none of the patients required inotropic support in group E ($P = 0.02$).

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**Figure 1** Protocol design: $n$ is the actual number of patients in each group who completed the study period. When a patient had to be intubated, he was considered as not having completing the study period. Hundred and twenty four patients were included, 115 patients finally completed the three steps of the protocol.
Figure 2. Flowchart. COPD: chronic obstructive pulmonary disease.

Table 2. Patients' characteristics at study entry

<table>
<thead>
<tr>
<th></th>
<th>Group E</th>
<th>Group L</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>76.7 ± 8.8 (n = 63)</td>
<td>77.9 ± 11.7 (n = 61)</td>
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<td>Gender, M/F (no. of patients)</td>
<td>31/32 (n = 63)</td>
<td>30/31 (n = 61)</td>
<td>0.99</td>
</tr>
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<td>Aetiology (no. of patients)</td>
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<td>0.61</td>
</tr>
<tr>
<td>Myocardioopathy</td>
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<td>46</td>
<td></td>
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<tr>
<td>Patient myocardial ischemia</td>
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<td>14</td>
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<tr>
<td>Other aetiologies</td>
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<td></td>
</tr>
<tr>
<td>Acute hypertensive episode</td>
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<td>8</td>
<td></td>
</tr>
<tr>
<td>Acute arrhythmia</td>
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<td></td>
</tr>
<tr>
<td>Physiological measurements</td>
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<td></td>
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</tr>
<tr>
<td>SBP (mmHg)</td>
<td>176 ± 38</td>
<td>174 ± 40</td>
<td>0.70</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>95 ± 23</td>
<td>96 ± 23</td>
<td>0.81</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>104 ± 23</td>
<td>105 ± 21</td>
<td>0.92</td>
</tr>
<tr>
<td>RR (breath/min)</td>
<td>34 ± 8</td>
<td>34 ± 7</td>
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<tr>
<td>DCS (score/10)</td>
<td>8 ± 1</td>
<td>8 ± 1</td>
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<tr>
<td>SpO2 (%)</td>
<td>82 ± 6</td>
<td>81 ± 5</td>
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<tr>
<td>PaO2 (mmHg)</td>
<td>50 ± 6</td>
<td>49 ± 6</td>
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</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>46 ± 10</td>
<td>46 ± 8</td>
<td>0.84</td>
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<tr>
<td>CO2t (mmol/L)</td>
<td>23 ± 2</td>
<td>22 ± 2</td>
<td>0.81</td>
</tr>
<tr>
<td>pH</td>
<td>7.32 ± 0.09</td>
<td>7.32 ± 0.09</td>
<td>0.99</td>
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<tr>
<td>SaO2 (%)</td>
<td>86 ± 3</td>
<td>86 ± 3</td>
<td>0.98</td>
</tr>
</tbody>
</table>
Figure 3  Respiratory indexes of patients of 'early CPAP' group (lozenges) and 'late CPAP' group (squares). Values are mean ± SD. (A) DCS denotes our 'Dyspnoea Clinical Score'; (B) RR respiratory rate; (C) systolic and diastolic blood pressures (SBP, DBP); and (D) HR heart rate. T0–T15: CPAP alone in 'early CPAP' group, medical treatment alone in 'late CPAP' group; T15–T30: both treatments in the two groups; T30–T45: CPAP withdrawal in both groups. Asterisk – comparison between the two groups: *P < 0.05.

Figure 4  (A) PaCO2 arterial carbon dioxide tension evolution and (B) PaO2 arterial oxygen tension evolution. T0–T15: CPAP alone in 'early CPAP' group, medical treatment alone in 'late CPAP' group; T15–T30: both treatments in the two groups; T30–T45: CPAP withdrawal in both groups. Asterisk – comparison between the two groups: *P < 0.05.
Mortality: No patient died on scene. Eight patients died during their hospital stay in group L vs. two in the group E ($P = 0.05$, OR = 0.22 (0.04–1.0)).

No patients presented adverse CPAP events, such as mask intolerance, barotrauma, vomiting or gastric distension.

Discussion

This study demonstrates for the first time that the acute out-of-hospital management of CPE can be effectively initiated by the immediate application of CPAP alone, and that the treatment delay of only 15 min, relative to time of initiation of acute out-of-hospital care had profound effects on patient outcomes like mortality, need for subsequent tracheal intubation or subsequent cardiovascular deterioration requiring further medical care. These benefits are acutely manifest by easily monitored physiological variables. After the first 15 min, patients treated with CPAP alone exhibited a lower in RR, DCS, and PaCO$_2$ together with a higher PaO$_2$ and pH. Addition of pharmacological treatment to CPAP did not result in any measurable improvement. Finally, a short but immediate CPAP support (30 min primary care in the E group vs. 15 min secondary care in the L group) seems to improve patients’ outcome with lower rates of tracheal intubation, less need of inotropic support, and lower hospital mortality.

Our study was designed to ascertain that the known mechanisms by which CPAP works in CPE would result in an improved outcome when used immediately and alone. CPAP acts both on gas exchange and left ventricular performance. The effect on oxygenation may result from the generated PEEP. PEEP may improve arterial oxygenation by several mechanisms, particularly by a reduction in intrapulmonary shunt. In the present study, when adding CPAP in both groups, patients exhibited significantly less symptoms of respiratory fatigue, which may relate to a reduction in the work of breathing and alveolar hypoventilation. These results are consistent with the literature showing a reduction in the work of breathing, an increase in pulmonary compliance and a decrease in airway resistances. Positive pressure ventilation also supports left ventricular contraction, by minimizing the negative swings in intrathoracic pressure seen during inspiration and thus, by decreasing aortic impedance and left ventricular transmural pressure.

Indeed, it has been shown that CPAP increases stroke volume, cardiac index and oxygen delivery, improve hemodynamics and decreases myocardial oxygen consumption during severe CPE as compared with medical treatment.

The second period of the protocol provided information concerning both the tolerance of sustained CPAP (group E) and the benefit of associating CPAP to medical treatment (group L). These data supported clearly that the observed cardiorespiratory benefit was due to CPAP. We did not observe any clear benefit of adding medical treatment to CPAP, whereas the addition of CPAP to medical treatment was associated with a dramatic improvement in all parameters. Several authors reported, on scene, an immediate benefit with the use of large doses of medical treatment (either nitrates or diuretics). Our results are somehow conflicting with Sharon et al. study in which medical treatment was superior to positive pressure ventilation for the treatment of severe CPE. This could be explained by important differences between the two protocols. In the study by Sharon et al. which also took place in mobile ICU, high doses of nitrates were used and positive pressure ventilation consisted in a Bilevel Positive Airway Pressure (BiPAP) ventilation. BiPAP was performed with relatively low levels of PEEP (4.2 ± 3.1 cmH$_2$O) and such a ventilatory device implies the necessity for the patient to reach a trigger threshold to open the inspiratory valve, which can be responsible for an increase in the work of breathing. Nevertheless, the data published by Sharon et al. strongly suggest that a medical treatment based upon high doses of nitrates should be considered for severe CPE, especially in case of acute hypertensive crisis.

The third period provided information concerning the tolerance of an early and abrupt CPAP withdrawal. In most of the previous studies of CPAP therapy for CPE, CPAP duration exceeded 2 h, and few data are available concerning a very short treatment. In this study, CPAP withdrawal was followed by a slight impairment in cardio-respiratory status and was less tolerated after only 15 min of treatment (group L) as compared with 30 min (group E), especially in terms of PaO$_2$.

Although the present study has not been designed to analyse outcome, patients’ evolution was significantly different between the two groups. Consistently with the literature, patients who benefited from 30 min of CPAP were less likely to be intubated during and after the study period. Moreover, the early CPAP group required less inotropic support and showed a greater hospital survival rate. The delay for CPAP application and the total duration of CPAP were the major differences between the two groups. Interestingly, if one considers CPAP therapy as appropriate therapy for CPE, then the delay in initiating appropriate resuscitation, as in septic shock, appears to be a primary determinant of outcome. These data suggest that the right treatment needs to be applied as soon as possible and delaying even 15 min may be less efficient. CPAP alone appears to initiate cardiorespiratory recovery, as supported by the impressive improvement in all measured variables during the first 15 min of treatment. Moreover, in our ‘late CPAP’ group, eight patients needed tracheal intubation during the first 15 min, vs. only one in ‘early CPAP’ group. Park et al. recently reported that, in severe CPE treated by medical therapy alone, the time to intubation was 17 ± 10 min. This reinforces the idea that CPAP should be started as soon as possible. Since early CPAP application seems to be crucial in out-of-hospital practice, its routine application suggests that medical and paramedical personnel should be trained and instructed to use it early in resuscitation of patients with CPE as suggested by Kosowsky et al. Craven et al. recently confirmed that even BiPAP could be effectively used on scene by emergency medical technicians trained in advanced life support. Nevertheless, BiPAP is more complicated to use than CPAP and should not be used without a minimal training. Concerning the duration of CPAP application, our data suggest that even 30 min of CPAP result in beneficial results. Consistently with our results, recent studies reported reduction of mortality using the association of CPAP to medical treatment in patients with CPE. A recently published meta-analysis reported, with the use of CPAP, an OR for tracheal intubation of 0.40 (95% CI 0.27–0.58, $P < 0.001$) and of 0.53 for death (95% CI 0.35–0.81, $P = 0.003$). The Task Force for Acute Heart Failure of the European Society of Cardiology
recently supported the use of non-invasive positive pressure ventilation and especially CPAP in severe CPE as a class IIa recommendation (level of evidence A).

A major limitation of this study was that it was unblinded. As a consequence, a bias related to non-blinded investigators cannot be ruled out. Although the indications for endotracheal intubation during the study period were standard, we cannot exclude the possibility that investigators delayed intubation in the early CPAP group. Nevertheless, even if part of the primary endpoints is subjective (i.e. DCS), objective criteria, such as gas exchange, were better improved within the first 15 min in the E group than in the L group. Furthermore, this potential bias had not been confirmed by the post-study period intubation rate, which remained different between the two groups. Our data confirmed the numerous previous studies showing that CPAP therapy for CPE reduces intubation rate. Finally, although the study was not powered pre hoc to test the impact of CPAP on outcome, early CPAP therapy reduced in-hospital mortality. The investigators were concerned about the potential problem of delay of 15 min to the medical treatment in the early CPAP group. This delay was considered as acceptable because of the already proven benefit of CPAP,3,4,18 because the duration under CPAP alone was very short (15 min) and finally because it was the only way to assess the benefit of CPAP alone.

In conclusion, out-of-hospital CPAP therapy, as mono-therapy within the first 15 min of management is superior to standard medical therapy in the initial management of patients presenting with severe CPE. Furthermore, early CPAP therapy appeared to augment the subsequent medical response later on. Because of the simplicity of immediate CPAP use and its immediate efficacy, and lack of serious side effects, this technique should be encouraged as a first line therapy in severe CPE not only in the hospital but also in the out-of-hospital setting.

Conflict of interest: none declared.

References