Author's response to reviews

Title: Boussignac continuous positive airway pressure for the management of acute cardiogenic pulmonary edema: prospective study with a retrospective control group

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Author's response to reviews: see over
Dear Editor,

Hereby we submit a revised version of our manuscript “Boussignac continuous positive airway pressure for the management of acute cardiogenic edema: prospective study with a retrospective control group”. We wish to thank the reviewers for their valuable comments. Below we address these comments on a point-by-point basis.

Before addressing these remarks point-by-point we wish to clarify one major problem that was signaled by both reviewers: the type of groups and the shift of patients between these groups. Since we wanted to assess the use of BCPAP for all ACPE patients admitted to our hospital, we included all ACPE patients whether admitted to the CCU, ICU or CCU and thereafter ICU. Although BCPAP treatment in the CCU was intended to be provided to all candidates, this did not happen for all patients, as we truthfully have pointed out. This was because the patients were either deemed too ill or deemed too good for BCPAP treatment. We think intention-to-treat analysis is the most appropriate to assess the value of BCPAP. Two patients who received ineffective BCPAP were later transferred to the ICU.

Yours sincerely,
also on behalf of all authors

Willem Dieperink,

Remarks of the Editor (Dr. Ektaa Rohra)

Remark 1: Please expand the abbreviation CPAP in the title.
Answer: We expanded the abbreviation accordingly.

Remark 2: Please document in the methods whether verbal or written consent was obtained from the patients.
Answer: As further clarified in the Methods section, the study that evaluated a control group with a prospective BCPAP group was approved by our IRB. Verbal consent was obtained and recorded from patients to use their medical data.

Remarks of Reviewer 1 (Dr. Gaetano Iapichino)

Remark: Clearly state that a facial mask was used.
Answer: We now added in the Abstract as well as in the Introduction and Methods section that Boussignac CPAP was delivered by a face mask.

Remark 1: The reviewer asks if we rely on the CPAP level obtained by flow delivery or if we measured the CPAP level with an independent device. Furthermore the reviewer noticed that the reported flow/pressure relationship was in contrast with experimental studies and data supplied by the manufacturer.
Answer: With respect to the question how the CPAP pressure was obtained; this was measured during CPAP treatment with an independent handheld electronic pressure analyzer. This is now
stated more clearly in the text. We now added in the Methods section, last sentence of paragraph 1 *(Boussignac CPAP system)* “This was measured during CPAP treatment with a handheld electronic pressure analyzer (Testo 505-P1, Almere, the Netherlands).”

Before patients were included in our study we also performed a bench test to determine the flow/pressure relationship as well as the inspired oxygen fraction. For the flow/pressure relationship we used 3 independent pressure analyzers 1. Testo (Testo 505-P1, Almere, the Netherlands) 2.VT plus (Fluke Biomedical, Carson City, USA) 3.RT 200 (Calibration Analyzer, Timeter instrument Corporation, St. Louis, USA). In multiple tests we measured approximately 5 cm H$_2$O CPAP with an oxygen flow of 15 L/min and 10 cm H$_2$O with an oxygen flow of 23 L/min. Leman et al. *Emerg Med Australas* 2005, reported a CPAP pressure of 5 cm H$_2$O with a flow of 18 L/min. Hildewine *JEMS* 2006 reported that an oxygen flow of 10L/min provides 2.5-3.0 cm H$_2$O CPAP and a flow of 15 L/min 4.5-5 cm H$_2$O CPAP. In information we received from the manufacturer (Vygon) “Bibliographie CPAP, Résumés et conclusions d’études cliniques portant sur la CPAP, dd 15-06-2003) is was written that 20 L/min provides 6.3 cm H$_2$O CPAP. Is summary, we assume that it is possible that local conditions may influence the flow/pressure measurements. Therefore in our study CPAP was also measured and not predicted from flow delivery. The reason that we did not mention this in the text was that we observed that gas leakage was the main cause of lower pressure and that this leakage was readily observed. We also found that measuring pressures was of little use for the treatment with BCPAP, especially since the patients response was the main determinant of treatment.

In the Results section we now refer to the pressure measurements that were performed.

Remark 2: The reviewer asks if it is accurate that all patients who improved while on BCPAP maintained stable gas exchange for more than 6 hours or that they needed additional CPAP or more invasive treatment.

Answer: All except two patients could be managed with BCPAP. One patient had to be intubated, the other received ventilator mask-CPAP in the ICU. We now added in the Result section “Sixty-four of 66 patients maintained stable gas exchange after BCPAP was stopped. Two of the 66 patients required follow-up respiratory support in the ICU after BCPAP treatment in the CCU. One patient with a large infarction and support with an intra-aortic balloon pump had to be intubated and the other received ventilator mask-CPAP.

Remark 3: The reviewer remarks that although different in some points, as explained by Authors, nevertheless the pharmacological treatment in both groups must be specified.

Answer: Both groups were treated with loop-diuretic, opioids and nitroglycerine. We now specified that information in Table 1.

Remark 4: The reviewer remarks that the baseline values of mean arterial pressure are relevant.

Answer: We now added the requested information in Table 2.

Remark 5: The reviewer asks if there were severe coexisting diseases such as COPD, chronic renal failure or else in the patients that failed BCPAP.

Answer: This information is now mentioned in the Results section (see Remark 2).

Remark 6: The reviewer remarks that a tight fitted face mask can cause discomfort but it is fundamental for having adequate positive pressure at the patient airway during CPAP especially for a relatively short treatment.
Answer: We now changed the sentence accordingly in the Discussion part.

**Remarks of Reviewer 2** (Dr. Geraldo Lorenzi-Filho)

Remark 1: The rationale that Boussignac CPAP has not been tested in the coronary care unit is too weak. There is not a strong argument to believe that the treatment of acute pulmonary edema should be different in different settings (unless some kind of rationale is provided to the reader). The reviewer suggests that one argument could be that in a setting where the staff is not prepared to treat acute pulmonary edema, the use of CPAP could be dangerous, and would delay a proper treatment in the ICU.

Answer: We agree with the reviewer. Accordingly we put more emphasis on the organizational obstacles in the introduction of BCPAP on the CCU. We now added in the second last sentence of the Introduction section “….we found no convincing medical arguments why BCPAP could not be effective in the CCU. We hypothesized that the major obstacle in treating patients with BCPAP in the CCU would be organizational.”

Remark 2: The definition of acute pulmonary edema is difficult. The threshold to distinguish respiratory discomfort and acute pulmonary edema is based in a rather subjective definition that includes respiratory rate > 25 breaths. min (and breathing frequency is very difficult to be registered in a regular basis) and SpO2< 95% while receiving oxygen.

Answer: We agree that acute cardiogenic pulmonary edema can be difficult to diagnose following standard criteria as now also referenced in the Methods section. We stressed this difficulty in the limitation section of the Discussion.

Remark: No clear definition on how much oxygen was given to the patient when oxygen was delivered by catheter or mask – how many liters – and what was the FiO2.

Answer: We added in the Method section the liters of oxygen delivered and the resulting FiO2 achieved with the various modalities.

Remark: It is very difficult to compare prospective data with historical controls. It is impossible to assure that the severity of the acute pulmonary edema was the same in the 2 periods. One can easily hypothesize that in the retrospective chart review, the authors included more severe cases (that deserved a written report). In contrast, during the prospective part of the study, because the staff was aware of the new protocol, there would be a clear tendency to include mild cases of acute pulmonary edema (that would not be reported in the previous period).

Answer: We agree that optimal comparison is not possible with historical controls. Our study included screening of all patients admitted to our hospital with ACPE, whether they were treated at the CCU or ICU. Our data do not suggest that the historical controls were in a worse condition than the prospectively treated patients, since baseline SpO2 in the patients treated in the CCU was significantly lower in the prospective group than in the historical group (Table 2: 88% vs. 91%). Moreover the CCU patients who did not receive BCPAP had milder ACPE as now mentioned in the Results. Removing those patients out of the analysis would make the statistics more significant.
Remark 3: Another issue that is problematic is that during the prospective study period, a considerable number of patients (19 out of 108) did not receive the proposed treatment with BCPAP. If the study was trying to determine the effects of BCPAP in the CCU they would be forced to only consider the 66 patients that received BCPAP in the CCU. In this new analysis out of 90 patients, 66 received BCPAP and 24 were transferred to the ICU. I am sure the statistics would be quite different and much less significant for all parameters analyzed.

Answer: Both in the text and in the tables we now clarify the difference between intention-to-treat comparison and the physiological comparison for the subgroup of patients treated in the CCU. As pointed out more clearly now all patients admitted to our hospital who fulfilled the ACPE criteria according to [3] were studied, whether treated at the CCU or the ICU, regardless of the treatment form. We chose this design to avoid the error that only “easy” patients would receive BCPAP. Also since we wanted to know if BCPAP reduced intubations (in the ICU) we had to include this patients. Likewise, our statements regarding costs necessitate the inclusion of all patients with ACPE.

In contrast, the patients who were only treated at the CCU were compared to underscore the physiological improvement observed in the CCU with the modern treatment compared to the conventional treatment in the historical group (table 2).

Remark 4: The reviewer notes that tables 1 and 2 are misleading because they give the impression that all 108 patients received BCPAP.

Answer: We now have clarified this in the text and the tables.

Remark 5. The reviewer notes that never is mentioned how many patients treated with BCPAP had to be transferred to the ICU, and what happened to these patients.

Answer: see Remark 2 for Reviewer 1.

Remark: [Safety and effectiveness of BCPAP] are the most important piece of information in this study. The authors could for instance reframe the study and report on the safety of using a simple CPAP in the CCU.

Answer: We certainly agree with the first statement, but leaving out all ACPE patients who did not receive BCPAP would have raised the suspicion that difficult patients were intubated and treated at the ICU. As also alluded to in the answer to remark 3, we therefore chose to compare the historical and prospective groups on an intention-to-treat basis.

Remark 6. The reviewer asks for a report on medications.

Answer: We now added this information in Table 1.

Remark/Minor comment 1: Introduction must make more clear what a Boussignac CPAP is.

Answer: We added more information on the Boussignac CPAP system in the Introduction.

Remark/Minor comment 2: I was confused with Figure 1. It is my impression that patients on both arms started the study in the CCU. The authors state in the legend that there was a shift from ICU admission to CCU admission. If I understood correctly, all patients (BCPAP group, n = 108) and control group (n= 66) were in the CCU in the beginning of the study. If my assumption is correct, the numbers of patients transferred from the CCU to the ICU decreased from 47% to 22%. I would reframe the legend of Figure 2 – as it is stated now “there was a considerable shift
of ICU admissions …”, gives the impression that the patients were treated in another setting (neither CCU or ICU) and were then transferred either to the CCU or the ICU.
Answer: We clarified the legend for Figure 1 and assume that the reviewer referred to Figure 2 with respect to the patient shifts. As stated more explicitly now, patients started the study in the emergency department and were transferred to either the CCU or to the ICU and in two cases from the CCU to the ICU.