Author's response to reviews

Title: Semi-closed circuit represents a cost-effective way of heliox administration in patients with severe airway obstruction: An economic study

Authors:

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Version: 3 Date: 27 March 2015

Author's response to reviews: see over
Reviewer's report Referee 1:

Title:Semi-closed circuit represents a cost-effective way of heliox administration in patients with severe airway obstruction: An economic study

Version: 2 Date: 28 December 2014
Reviewer: Stefano Baglioni
Reviewer's report:

Major compulsory revisions

1. In abstract and in methods the authors did not describe if the four methods of heliox administration are applied in the same patient (case control study) or always in different subjects. In this second case the authors have to explain the characteristics of patients (age, gender, disease, level of respiratory failure).

Also the setting of the study is not explicated: ICU, ward (this not a "bench study" I think, because the authors do reference to a previous bench study); this extremely important to understand if the system are suitable in real life in different settings. Are there some differences in clinical effect or unwanted effect or applicability of heliox using the four different systems? The cost –effectiveness is critical if the systems works equally well.

Did the authors find better clinical results with heliox in comparison to other treatment of respiratory failure capable to avoid intubation of patient with airway obstruction, such as noninvasive ventilation and/or aggressive medical therapy.

We are aware that it would be much better to evaluate the economic advantage of the semi-closed circuits over an open circuit during a clinical trial with real patients; however, the presented study is solely theoretical economic analysis. Nevertheless, the majority of data used for the analysis has been published and is also in concordance with our experience with heliox application in patients with COPD in clinical setup that we mentioned several times in the manuscript. We realize that this may confuse readers; therefore, we added the following sentences into the manuscript:

At the beginning of the method section (line 87):
Cost analysis of two different ways of heliox administration using four actual systems was conducted in this theoretical study.

In the Discussion (line 236):
The custom-made semi-closed circuit was used in COPD patients and tested in a clinical trial approved by the State Institute for Drug Control, Czech Republic (EudraCT number: 2008-008274-31). For analysis conducted in this study we used published input data and our experience from the clinical trial. Since this study is a theoretical cost analysis, it does not describe the clinical trial and its evaluation.
As the manuscript describes a study focused on economic analysis only, the comparison of treatment efficacy of heliox therapy with other approaches was not the aim of the study, even though this is still a topical and unsolved question.

2. In Methods, in equation 1 and 2 are not indicated the unit of measure

*We have added the units to the text related to the equations 1 and 2 as follows:*

**Lines 148 – 155:**

where $V_{OC}$ (L) stands for the total volume of gas consumed by a patient during the whole therapy using an open circuit, $V_{SCC}$ (L) stands for the total volume of gas consumed by a patient during the whole therapy using a semi-closed circuit, $q_{OC}$ (L/min) is gas flow rate during the high flow therapy using an open circuit, $q_{INH}$ (L/min) is gas flow rate during the inhalation, $q_{DEN}$ (L/min) is gas flow rate during the denitrogenation, $q_{SCC}$ (L/min) is gas flow rate during the low flow therapy, $t_{OC}$ (min) is duration of high flow therapy, $t_{INH}$ (min) is duration of inhalation, $t_{DEN}$ (min) is duration of denitrogenation, and $t_{SCC}$ (min) is duration of low flow therapy.

3. In table 1 the cost of service is indicated for ten years; is this the service sale for the home country of the authors or is valid also for the other European countries?

*The prices of service and lifespan of the medical equipment are the same or very similar in European countries. The equipment is supplied and serviced by international companies having their offices all over the Europe; therefore, the conditions of service and prices are identical.*

4. Table 2, the characteristics of cylinders on row 1 and 2 are identical but the price is different; is there a mistake? The table must be revised.

*We are sorry, we unintentionally deleted the first column of the table, probably during the final formatting of the manuscript. We replaced the wrong table with the correct one.*

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Heliox</td>
<td>50 L at 200 bar</td>
<td>233.87</td>
<td>10 000</td>
<td>0.0234</td>
</tr>
<tr>
<td>Oxygen</td>
<td>50 L at 200 bar</td>
<td>46.77</td>
<td>10 000</td>
<td>0.0047</td>
</tr>
</tbody>
</table>

Abbreviation: A.T.P.D.—Ambient Temperature and Pressure, Dry

5. Figure 1, bottom, semi-closed circuit, authors refer to custom-made circuit or also to the anaesthesia circuits?
The diagram is valid for all the semi-closed circuits analyzed. We have added this information both into the text and into the description of Fig. 2:

Line 140:
The application of heliox in a single patient can be therefore described as $N_C$ repeated cycles consisting of two (for the open circuit) or three (for any realization of the semi-closed circuits) phases as depicted in Fig. 2.

Line 377:
Figure 2 The basic treatment cycles during heliox administration using an open circuit (top) and any realization of a semi-closed circuit (bottom).

Minor issue

6.
Background: author show a list of different pathologies with airway obstruction but some of that are not treatable with heliox (i.e. tumor or foreign body obstruction) and are not interesting and pertinent for this work.

We have revised the statements and excluded irrelevant information as follows:

Line 54:
Nosological units characterized by airway obstruction include bronchial asthma, chronic obstructive pulmonary disease (COPD), epiglottitis, laryngitis, tracheitis, bronchiolitis, tracheal or bronchial stenosis.

7.
Row two: asthma bronchiale (probably authors figure bronchial asthma)

We have exchanged the term “asthma bronchiale” with the term “bronchial asthma”.

8.
In line 81 the authors state: “Heliox is relatively expensive compared to oxygen, but is certainly much less expensive than some other respiratory therapies such as mechanical ventilation and inhaled nitric oxide (NO)” but inhaled NO is used for arterial pulmonary hypertension and not for respiratory failure due to airway obstruction and so the comparison between heliox and NO is not logical, in my opinion. The reference number six is not appropriate in this case because in the work there is not a concern to NO therapy.

Yes, now we understand that this statement is misleading. Originally, we did not intended to compare the clinical applications of the gases, but only comparison of their prices, which is not clear from the text. Therefore, we deleted the part concerning the nitric oxide:

Line 73:
Heliox therapy using the open circuit is associated with high costs. Heliox is relatively expensive compared to oxygen, but is much less expensive than mechanical ventilation [6].

9.
In the seven and eight references the authors did not indicate the journal.
Thank you, we made a mistake probably during the final formatting of the references using a reference manager. We have fixed these problems:

**Line 342:**

**Line 344:**

10. Methods: paragraph 8, other paragraphs and table, gasses is incorrect, correct form is gases.

*We are sorry. We have corrected the misspelling.*

11. Discussion: this section is too long; a more concise style would be appreciable.

*We agree. We have reformulated three paragraphs dealing with only technical details into several sentences as follows:*

Airflow resistances of the inspiratory and expiratory limbs of a semi-closed circuit increase patient’s imposed work of breathing, which represents a disadvantage of a semi-closed circuit over a standard way of heliox administration using an open circuit. So that the increased airflow resistance and hence increased imposed work of breathing would not compromise the positive effect of heliox in the obstructed airways, the airflow resistance of the semi-closed system should be minimized. Based on our former bench tests, older and simpler anesthesia machines and their components have very often less airflow resistance than the modern systems. Our first experimental custom made semi-closed heliox system was an old anesthesia machine N7 (Chirana, Stará Turá, Slovakia) still present but not used any longer at our department of anesthesia and critical care.

A substantial part of the imposed work of breathing associated with the semi-closed system is caused by airflow resistance of the expiratory valve (also referred to as Adjustable Pressure Limiting valve, APL) releasing excessive gas from the semi-closed circuit. A majority of commercially available APL valves have a significant airflow resistance even in a fully open condition that increases the imposed work of breathing and thus compromises the benefit of heliox in the airways. We reached the lowest resistance with a simple water seal (underwater bubbler), which is used nowadays for bubble continuous positive airway pressure (Bubble CPAP) [8].

Bacterial and viral breathing filters, often in combination with heat and moisture exchangers (HME), are widely used during general anesthesia; nevertheless, these components are not suitable for a semi-closed system for heliox application. Breathing filters have quite a high airflow resistance that even increases when the filters become wet [9]. Although this airflow resistance often does not cause a problem in anesthetized patients without any respiratory problem, it may compromise the expected positive effect of heliox in patients with airway obstruction. Therefore, the analyzed semi-closed systems did not contain any breathing filter.

**Line 225:**
Airflow resistances of the inspiratory and expiratory limbs of a semi-closed circuit should be minimized as they increase patient’s imposed work of breathing, which represents a disadvantage of a semi-closed circuit. A substantial part of the imposed work of breathing may be caused by the high resistance of the expiratory valve (Adjustable Pressure Limiting valve). We reached the lowest resistance with a simple water seal, which is used for bubble continuous positive airway pressure [8]. Bacterial and viral breathing filters have relatively high airflow resistance that even increases when the filters become wet [9]. Therefore, the analyzed semi-closed systems did not contain any breathing filter.

12.
Quality of written English: Needs some language corrections before being published

We have asked a native English speaker from the USA, to conduct proofreading of our manuscript. His specialties are mechanical ventilation and management of medical equipment. We hope, the manuscript does not contain wrong language any more.

Reviewer's report 2

Discretionary Revisions: (which are recommendations for improvement but which the author can choose to ignore)

Diagrams or pictures of the numerous systems would be helpful for the readers to appreciate the technical aspects and differences of each design.

We have added simple schemes of open and semi-closed circuits as Fig. 1. The original figures were therefore renumbered.

Line 96:
The comparison of the semi-closed circuit with an open circuit is illustrated in Fig. 1.

Line 375:
Figure 1 The schemes of an open circuit and a semi-closed circuit. FGF—Fresh Gas Flow, APL—Adjustable Pressure Limiting valve.
Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. The Background section is entirely too long and should focus on the administration of heliox.

We agree. We have reformulated this paragraph into several sentences as follows:

**Line 53:**
Severe airway obstruction accompanies many diseases of various etiologies. Nosological units characterized by airway obstruction include bronchial asthma, chronic obstructive pulmonary disease (COPD), epiglottitis, laryngitis, tracheitis, bronchiolitis, tracheal or bronchial stenosis. Severe airway obstruction induces increased work of breathing, decreased alveolar ventilation and development of respiratory insufficiency leading to respiratory failure often treated by mechanical ventilation. Initiation of invasive mechanical ventilation is associated with pulmonary and extrapulmonary complications and complications caused by the upper airway management. Ventilator-associated pneumonia (VAP), ventilator-induced lung injury (VILI), pulmonary barotrauma, breathing muscles atrophy, deterioration of circulatory function, gastrointestinal tract and kidneys belong to the main complications of invasive mechanical ventilation [1]. Invasive mechanical ventilation is associated with pulmonary and extrapulmonary complications and complications caused by the upper airway management [1].

2. The flow of heliox is quoted as “typically more than 18 l/m”. This liter flow is not universal and may be excessive for some patients.

We have selected the heliox flow rate according to a fundamental principle that fresh gas flow required to prevent re-breathing should be 2-3 times higher than minute ventilation (MV, typically 7.5 L/min) of a patient [for example: Milner, Q., Anaesthetic Breathing Systems, Update in Anaesthesia, 1997]. As the reviewer states, the MV may be significantly higher in some diseases; therefore, we conducted the sensitivity analysis for increased MV to 10, 12.5 and 15 L/min as described in the text starting at line 257 of the manuscript.

Considering the average minute ventilation in a healthy adult of 7.5 L/min [12], the basic fresh gas flow through the open circuit was assumed to be 22.5 L/min. In respiratory diseases such as COPD and bronchial asthma the minute ventilation increases significantly [13–15]. Therefore, the economic simulations for the open circuit were conducted for minute ventilations which were increased to 10 L/min, 12.5 L/min and 15 L/min. In contrast, an increase in minute ventilation of a patient does not affect the required fresh gas flow into the semi-closed circuit due to the rebreathing principle and exhaled CO₂ removal.

3. According to the manufacturer, “The 7500 V2 Mask is intended to provide a patient interface for applications of noninvasive ventilation. The mask is intended for use as an accessory to ventilators which have adequate alarms and safety systems for ventilator failure and which are intended to administer positive pressure ventilation for treatment of respiratory failure or respiratory insufficiency”. Are the authors advocating the use of positive pressure ventilation to deliver heliox with these masks?

The authors did not study and did not intend to use non-invasive ventilation or positive pressure ventilation with heliox. The 7500 V2 Mask is primarily intended for non-invasive
ventilation with positive pressure, nevertheless in our study the mask was used for spontaneous breathing of a patient connected to a semi-closed circuit. The reason for using this mask is a very good fit and therefore low gas leak required for proper functioning of the semi-closed circuit.

4. The proposed masks have leaks of 3-5 l/m and dead space volumes of 104-169ml. Are these factors accounted for in the heliox delivery calculations?

The gas leak 3-5 l/min described by the manufacturer is valid for ventilation with positive pressure (at 10-30 cm H_2O). During spontaneous ventilation with a semi-closed circuit, the pressure in the circuit and thus in the mask do not differ significantly from the ambient pressure. Therefore, the leak is reduced substantially. According to our experience, fresh gas flow rate of about 3 l/min is sufficient to fully compensate all leaks in the semi-closed circuit (i.e. including the mask).

5. According the manufacturer, “Contraindications: Need for ventilation or ventilatory support > 12 hours per day”. How will this impact heliox delivery and cost calculations?

Need for ventilation or ventilatory support > 12 hours per day is a relative contraindication and for example in patients with COPD is not taken into account. Nevertheless, the patients during spontaneous breathing of heliox do not wear the mask continuously for 12 hours due to the aerosol therapy, peroral nutrition, drinking, etc. The total (summary) length of the heliox therapy may however be longer than 12 hours.

6. These masks are available in five sizes: (L, M, S, XS, P). Selecting the proper size for patient will be imperative for the accuracy of cost calculations. Was the possibility of having to use multiple masks for the same patient considered for cost analysis?

Possibility of having to use several masks for the same patient was not considered for the cost analysis, even though this situation may occur. We are unable to assess in how many patients require multiple masks, nevertheless, we think it is well below 20%. We have recalculated the results of the analysis considering requirement for multiple masks (affecting the durability of the mask due to number of sterilizations and associated sterilization cost). The result do no differ significantly from the original results in the manuscript as the changes are in the order of 1/10 and after the numbers are rounded, the results are the same (17.3 vs. 17.4, which is 18 patients for the custom made circuit; 31.7 vs. 31.9, which is 32 patients for the low cost anesthesia machine and 68.7 vs. 69.0, which is 69 patients for the advanced anesthesia machine).

As this is a real issue that may affect the results of the analysis, we added the following statement into the Discussion section (line 283):

In some patients, multiple masks may be used in order to find a mask that properly fits and is comfortable for the patient. This fact increases costs of consumables and costs of sterilization. These extra costs have a negligible effect on the results of the study. Considering that 20% of patients may require multiple masks, our cost analysis does not change.

7. The mask and swivel port components are expected to stay in service for minimum of 25 disinfection or steam sterilization cycles or 6 months of use under normal conditions,
whichever occurs first. The headgear is expected to stay in service for 6 months of use. If the demand for heliox services fluctuates, will the costs change in a linear direction?

The same mask is frequently used also for “standard” non-invasive ventilation. Considering the number of patients at our Dep. of Anaesthesia and Critical Care Medicine, it seems impossible that a mask will not be used for 6 months or longer.

8. Heliox is of often delivered in conjunction with aerosol therapy. Several statements in the paper imply otherwise.

The frequent termination of heliox therapy due to the aerosol inhalation therapy is evident from the diagram presented in Fig. 2. There is also a sentence in Methods emphasizing this fact:

Line 134:
Heliox cannot be administered continuously because of the intermittent need for aerosol therapy, personal hygiene and nutrition.

9. The statement, “As the total length of the heliox therapy is considered 25 hours and each cycle lasts 150 min (2.5 h)” suggests heliox is given in intermittently to patients. This is contrary to clinical practice and requires supportive evidence with multiple references.

We corrected the ambiguous statement so that it is clear, that the therapy was not continuous and that it involved the interruptions due to the aerosol inhalation therapy:

Line 143:
As the total length of the heliox therapy including the periods of aerosol inhalation therapy is considered to be 25 hours and each cycle lasts 150 min (2.5 h)…

10. The authors should include if these system have been used on human subjects or tested in a clinical trial.

The custom-made system was used on human subjects and tested in a clinical trial approved by the State Institute for Drug Control, Czech Republic (EudraCT number: 2008-008274-31). During conducting the analysis described in the manuscript we used some input data and our experience earned during this clinical trial; nevertheless, the manuscript does not describe the clinical trial at all. We understand that this is important and therefore we added the following sentences into the Discussion section of the manuscript:

Line 236:
The custom-made semi-closed circuit was used in COPD patients and tested in a clinical trial approved by the State Institute for Drug Control, Czech Republic (EudraCT number: 2008-008274-31). For analysis conducted in this study we used published input data and our experience from the clinical trial. Since this study is a theoretical cost analysis, it does not describe the clinical trial and its evaluation.

Quality of written English: Not suitable for publication unless extensively edited

As we stated above, we have asked a native English speaker from the USA, to conduct proofreading of our manuscript. His specialties are mechanical ventilation and management of medical equipment. We hope, the manuscript does not contain wrong language any more.