PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in intensive care units in Asia
AUTHORS	Pisani, Luigi; Algera, Anna; Serpa Neto, Ary; Ahsan, Areef; Beane, Abi; Chittawatanarat, Kaweesak; Faiz, Abul; Haniffa, Rashan; Hashemian, Reza; Hashmi, Madiha; Imad, Hisham; Indraratna, Kanishka; Iyer, Shivakumar; Kayastha, Gyan; Krishna, Bhuvana; Moosa, Hassan; Nadjm, Behzad; Pattnaik, Rajyabardhan; Sampath, Sriram; Thwaites, Louise; Tun, Ni Ni; Yunos, Nor'Azim; Grasso, Salvatore; Paulus, Frederique; De Abreu, Marcelo Gama; Pelosi, Paolo; Dondorp, Arjen; Schultz, Marcus

VERSION 1 – REVIEW

REVIEWER	Arnal Jean-Michel Hopital Sainte Musse Toulon France
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	Dr Pisani and colleagues present an observational study protocol focusing on the practice of mechanical ventilation in ICU in Asian middle income countries. The topic is definitely interesting and the results of this study will provide opportunities for interventional studies in these countries. The manuscript is well written and very clear. I have a few comment in order to improve the interpretation of the results. Comment 1: Driving pressure seems to be an important variable to consider when assessing the risk of VILI in all mechanically ventilated patients. I suggest mentioning it in the introduction (1st paragraph) and collecting this variable in all patients passively ventilated (not only in volume control mode as stated in method). Comments 2: Because the effect of PEEP and large VT are not the same in passive and spontaneous breathing patients, I suggest collecting the information if the patient is passive or in spontaneous breath using a clear definition. The ventilation mode is not precise enough for this as we can imagine a patient ventilated in volume assist control mode triggering all the breaths. Comment 3: Also, it would add a lot to collect the use of sedation and any kind of sedation score. Comment 4: This study will mix low and middle income countries. As stated in the discussion, level of care does not depend only on the country income. Will there be other criteria to assess the type of participating ICU such as nurse/patient ratio, medical staff/patient ratio, specialized medical staff, overnight coverage…

	Additional comments: 1) Is there a minimal duration of MV to include the patients? 2) Will the bedside clinician be aware that their ICU participate in this study? This may be a bias in ventilator settings.

REVIEWER	James Blum Emory University, USA
REVIEW RETURNED	04-Jan-2018

GENERAL COMMENTS	Overall, this is an excellent description of the study design for PRoVENT–iMIC. I have a few minor concerns. 1) The authors describe the current state of prospective data collection from high income countries, but do not discuss any retrospective data. In terms of epidemiology, it may be good for the authors to discuss the benefits of collecting such data prospectively, compared with a retrospective analysis. It may be worthwhile to discuss some of the retrospective work that has been done in high income countries as well for reference 2) The authors do not discuss the diagnosis of pneumothorax imaging modalities that may be used. In particular, the use of ultrasound. This has become a more common technique of late, and may be of real use in low resource areas. 3) Although the study likely will collect the necessary data, considering the recent interest in drive pressures, it may be reasonable to specifically address this data element and its calculation. In particular, if the plateau pressure is not available, will the peak inspiratory pressure be substituted? 4) There are no specific dates for the potential execution of the trial. Adding such information would be helpful for readers.

VERSION 1 – AUTHOR RESPONSE

Editor Comments:

1. Please do not abbreviate ICUs in the title.

Corrected.

Reviewer 1:

1. Driving pressure seems to be an important variable to consider when assessing the risk of VILI in all mechanically ventilated patients. I suggest mentioning it in the introduction (1st paragraph) and collecting this variable in all patients passively ventilated (not only in volume control mode as stated in method).

We thank this reviewer for the suggestion. Driving pressure is now also mentioned in the Introduction, as follows:

'Furthermore, the driving pressure seems to be another key variable in the development of injury caused by mechanical ventilation, as a large individual patient data metaanalysis showed a clear and consistent association between driving pressure and mortality [10–12].' (Page 6; line 182)

We also better explain how this variable is collected, in the Methods as follows:

'Driving pressure will be calculated by subtracting the level of PEEP from the plateau pressure (Pplat in volume–control ventilation) or maximal airway pressure (Pmax in pressure control ventilation). Pplat and Pmax are considered reliable for this calculation if the patient is receiving complete ventilatory assistance without evidence of spontaneous activity, i.e., only when the set respiratory rate equals the measured respiratory rate.' (Page 12; line 316)

2. Because the effects of PEEP and large VT are not the same in passive and spontaneous breathing patients, I suggest collecting the information if the patient is passive or in spontaneous

breath using a clear definition. The ventilation mode is not precise enough for this as we can imagine a patient ventilated in volume assist control mode triggering all the breaths.
We could not agree more. As explained above, and as mentioned in the manuscript on page 10 we collect the set and measured respiratory rate, in order to identify patients with spontaneous breathing activity. This allows us to compare passive and spontaneously breathing patients. We explain this further as follows:
'The presence of spontaneous activity will be identified by any recorded difference between the set and measured respiratory rate.' (Page 12; line 313)

3. Also, it would add a lot to collect the use of sedation and any kind of sedation score.
We discussed this extensively during the planning of the study. While we understand the value of having sedation data as well as sedation levels, collecting these data in a reliable fashion would (a) increase workload tremendously, and (b) mandate a lot of training in scoring sedation levels in places where this is not yet in place – in fact we know the latter is a challenge in the majority of participating centres.
We modified the Discussion to acknowledge this important limitation:
'Second, the case report form used in PRoVENT–iMIC was designed so that it would not induce excessive work loads for the participating centres. Therefore, we decided not to collect data regarding extra–pulmonary complications and hospital–discharge outcomes, neither the amounts of sedation used and sedation levels.' (Page 21; line 520)

4. This study will mix low– and middle–income countries. As stated in the discussion, level of care does not depend only on the country income. Will there be other criteria to assess the type of participating ICU such as nurse/patient ratio, medical staff/patient ratio, specialized medical staff, and overnight coverage.
Indeed, a one–time survey for each participating centre is planned as stated in the Methods. We clarified this in the text as follows:
'Each participating centre is surveyed once regarding the following information: hospital characteristics (private vs. public), ICU characteristics (medical vs. surgical vs. mixed, and open vs. closed, number of ICU beds, annual number of patient admitted, number of ventilators available, and other organ support measures), and staffing (nurse to patient ratio, physician to patient ratio, presence of specialized medical staff, and overnight coverage).' (Page 14; line 363)

5. Is there a minimal duration of MV to include the patients?
No, in order to recruit all patients with invasive ventilation, we capture all patients even if ventilation lasts short. This is explicated once more in the Methods, as follows:
'Consecutive patients intubated for ventilation during a predefined period of 28 days are enrolled. Inclusion is not restricted to patients who are intubated in the ICU: also patients who started invasive ventilation in the emergency room, normal ward, community, or operating room directly preceding the present ICU admission are eligible for participation, without any minimum or maximum hours of ventilation needed for inclusion.' (Page 9; line 239)

6. Will the bedside clinician be aware that their ICU participate in this study? This may be a bias in ventilator settings.
The attending physicians are aware of the service review and this certainly may cause bias. As in other large mechanical ventilation observational studies (JAMA 2016;315:2526 & LRM 2016;4:882) the data collection relies on local investigators that voluntarily collect and record the data. We explicitly ask them not to change their practice because of the service review. We now acknowledge this potential limitation in the Discussion as follows:
'Finally, we cannot exclude that ventilator settings applied by treating physicians might be biased by the participation in the study, a problem that also existed in prior multinational studies [11, 12].' (Page 21; line 535)

Reviewer: 2

1. The authors describe the current state of prospective data collection from high– income countries, but do not discuss any retrospective data. In terms of epidemiology, it may be good for the authors to discuss the benefits of collecting such data prospectively, compared with a retrospective analysis. It may be worthwhile to discuss some of the retrospective work that has been done in high–income countries as well for reference.

We thank the reviewer for this suggestion and a more specific argument about the advantages of a prospective collection of data was added, with relevant references from retrospective studies performed in high–income countries. We added the following text in Discussion as follows:

'First, its prospective design will allow a higher accuracy of data capturing with regard to exposures, confounders and endpoints compared to studies that used a retrospective design [30]. While a prospective design may cause sources of bias or establish causal effects, it minimizes the chance of residual confounding by unmeasured variables, a common limitation with a retrospective design, as has frequently been used in mechanical ventilation epidemiological studies [31-33].' (Page 18; line 399)

2. The authors do not discuss the diagnosis of pneumothorax imaging modalities that may be used. In particular, the use of ultrasound. This has become a more common technique of late, and may be of real use in low resource areas.

We strongly agree that the use of lung ultrasound is now widely supported to complement or substitute chest radiography in the diagnosis of pneumothorax, as suggested by recent clinical recommendations (e.g. CCM 2015;43:2479). However lung ultrasound is still only sporadically used in the settings of interest of this study. Seen the scattered use we decided not to collect this data.

3. Although the study likely will collect the necessary data, considering the recent interest in driving pressures, it may be reasonable to specifically address this data element and its calculation. In particular, if the plateau pressure is not available, will the peak inspiratory pressure be substituted?

See also our reply to comment 1 by reviewer 1. First of all, driving pressure will only be calculated for those patients in whom we have evidence that there is no spontaneously breathing, based on the set and measured respiratory rate. Second, in patients who are receiving pressure controlled mode ventilation, we will use the maximum airway pressure for calculating the driving pressure. Third, if, in volume controlled ventilation there is no plateau pressure available, we will not calculate the driving pressure in those patients, as the peak airway pressure is not an adequate surrogate for the plateau pressure. This is now better explained in the Methods, as follows:

'Peak airways pressures will not be used to compute driving pressure as these represent a poor surrogate of the plateau pressure.' (Page 12; line 321)

4. There are no specific dates for the potential execution of the trial. Adding such information would be helpful for readers.

We added this to the manuscript:

'Data collection has started in November 2017 in some sites; all sites are expected to initiate the service evaluation within one year after the overall start.' (Page 10; line 260)

VERSION 2 – REVIEW

REVIEWER	Arnal Jean-Michel Hopital Sainte Musse Toulon France
REVIEW RETURNED	11-Feb-2018

GENERAL COMMENTS	The manuscript has been improved after the first review. I just have a comment regarding the measurement of driving pressure in PC mode. Using Pmax is at risk of overestimating driving pressure. Pmax and Palv can be different depending on the resistance and set Ti. Consequently, I would suggest using an end inspiratory occlusion to assess Pplat also in patients ventilated in PC mode.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:
The manuscript has been improved after the first review.
I just have a comment regarding the measurement of driving pressure in PC mode. Using Pmax is at risk of overestimating driving pressure. Pmax and Palv can be different depending on the resistance and set Ti. Consequently, I would suggest using an end inspiratory occlusion to assess Pplat also in patients ventilated in PC mode.
We thank this reviewer for the suggestion. Indeed on pressure control ventilation maximal airway pressure (Pmax) might overestimate alveolar pressure, hence overestimating driving pressure whenever flow does not reach zero during inspiration. The systematic use of end-inspiratory occlusions in pressure control ventilation could alleviate this problem, but is seldom performed in many centres. To clearly acknowledge this limitation we added a sentence in the discussion, as follows:
'Fourth, as in patients on pressure–control modes flow might not reach zero during inspiration, Pmax might overestimate alveolar pressure, hence overestimating driving pressure. An end-inspiratory occlusion could solve this problem, but is almost never performed in many centers. As this study only uses data that is collected as part of standard care, all analysis regarding driving pressure will be done separately for patients on pressure–control modes and volume–control modes.' (Page 22; line 490)

VERSION 3 – REVIEW

REVIEWER	Arnal Jean-Michel Hopital Sainte Musse Toulon France
REVIEW RETURNED	20-Mar-2018

GENERAL COMMENTS	No comments