

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in patients at high-risk of reintubation: protocol for a multicenter, randomised controlled trial (TIP-EX).
AUTHORS	Thille, Arnaud; Coudroy, Rémi; Gacouin, Arnaud; Ehrmann, Stephan; Contou, Damien; Dangers, Laurence; Romen, Antoine; GUITTON, Christophe; Lacave, Guillaume; Quenot, Jean-Pierre; Lacombe, Béatrice; Pradel, Gael; Terzi, Nicolas; Prat, Gwenael; Labro, Guylaine; Reignier, Jean; Beduneau, Gaetan; Dellamonica, Jean; Nay, Mai-Anh; Rouze, Anahita; Delbove, Agathe; Sedillot, Nicholas; Mira, Jean-Paul; Bourenne, Jeremy; Lautrette, Alexandre; Argaud, Laurent Argaud; Levrat, Quentin; Devaquet, Jérôme; Vivier, Emmanuel; Azais, Marie-Ange; Leroy, Christophe; DRES, Martin; Robert, René; Ragot, Stéphanie; Frat, Jean-Pierre

VERSION 1 – REVIEW

REVIEWER	Karen Brown McGill University, McGill University Health Center, Montreal Canada
REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	<p>This is an ambitious prospective multicenter RCT with an aim to recruit 900 critically ill intubated adults from 31 ICUs in France, in a 2 year time period. The authors wish to evaluate extubation readiness and success with two types of spontaneous breathing trials (SBT): 1) SBT with a T-piece and 2) SBT with low level pressure support ventilation (PSV). Patients will be randomized 1:1 to the SBT type. Patients will be grouped by SBT type and the outcomes will be compared and the probabilities and proportions of each of 9 outcomes (see below), calculated. The authors will use an intention-to-treat analysis.</p> <p>The note from the Editor states that a purpose of publishing the protocol in BMJopen is to make available more information than is currently required by trial registries, to increase transparency and to explain in detail how the study will be conducted. In this regard the manuscript is poorly written and many many explanatory details are missing. Thus I had to read through the citations and to consult Google to sort the issues. For example, I learned from Google that the acronym TIP-EX is for T-piece Versus Pressure-support for the Spontaneous Breathing Trial (TiP-Ex). Please define your acronyms (TiP-Ex, REVA, e-CRF). Please clarify the relationship (consent, data, analysis, investigators) between this RCT and the TiP-Ex.</p> <p>The hypothesis is that compared to the SBT-Tpiece, the SBT-PSV may hasten extubation without increasing the risk of reintubation.</p>
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	<p>The primary outcome is the number of ventilator-free (no ventilator support at all, including NIV) days between the 1st SBT (time zero) and day 28. But the definition of this primary outcome varies throughout the manuscript. Please clarify as different definitions for the primary outcome are given in the abstract, page 10, page 12, page 13 and page 15.</p> <p>There are in addition 8 secondary outcomes:</p> <ol style="list-style-type: none"> 1) Days between the 1st SBT and Extubation. 2) Number of patients extubated within 7 days of the 1st SBT. The authors state they will only study the 1st SBT yet continue to collect data on patients who fail the 1st SBT. If patients fail the 1st SBT, it is not stated if all patients will undergo additional SBTs. If they do, the type of SBT the patient must be identical to the 1st SBT. 3) The weaning profile of patients will be classified by weaning difficulty criteria proposed in Reference 10. 4) Extubation success at 72 hours after the 1st SBT. 5) Extubation success at 7 days after the 1st SBT. 6) Extubation success at 7 days after the day of the actual extubation. 7) Length of stay in the PICU. 8) Mortality in ICU, at day 28 and at day 90. <p>The authors will recruit adult patients intubated >24hours at high risk for extubation failure. Please define the specific measures that will be used to define high risk chronic lung and cardiac disease. A high index of clinical suspicion is not sufficient.</p> <p>Please define the criteria for and objective measures of weaning that define extubation readiness at the time of the 1st SBT.</p> <p>Please report the measure that will be recorded to document compliance with the SBT type. On page 11 and page 12 the authors state the SBT-PSV will be conducted with exactly 8 cmH20 and no PEEP. Across the 31 ICUs, how will this level of pressure support be measured, how will it be documented and what measures to ensure compliance will be implemented?</p> <p>On page 11 Please change to read "The SBT-Tpiece will be performed with a T-piece connected to the patient connection port of the endotracheal tube and an oxygen flow of ≤ 6L/m." Please clarify if this is 100% oxygen or an air/oxygen blend. And then please clarify how you will add an oxygen flow of 3L/m to the patients mechanically ventilated with a FiO2 0.3 prior to the SBT-Tpiece trial and 6 L/m for those mechanically ventilated with a FiO2 0.4. How will you document and report the FiO2 delivered to the patient?</p> <p>Across the 31 ICUs please state how the method to document and report the respiratory rate and tidal volume on the critical care ventilator. Across the 31 ICUs please state the critical care ventilator make and models that will be used to deliver the SBT-PSV.</p> <p>Page 12 the authors state the duration of the SBT will be one hour citing reference 10. But the consensus opinion in reference 10 clearly states that "The initial trial should last 30 min and consist of either T-tube breathing or low levels of pressure support." Please justify the deviation from this practice guideline.</p> <p>Page 12 the SBTs differ. The SBT-Tpiece is followed by a 1 hour period of ventilator support before extubation. The SBT-PSV does not require this period of "rest". Please comment on the impact of this period of ventilator support on the outcomes.</p> <p>Page 12. The authors state they will only study the 1st SBT but in the eventuality of reintubation report that additional SBTs will be the same as the 1st SBT. This seems a constraint on clinical</p>
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practice. Please justify and confirm that these constraints are included in the informed consent form.

Page 12 The authors state that following extubation all patients will receive two types of NIV; alternating NIV (possibly by mask) and HFNC. The authors cite references 13 and 14. Ref 14 is the HIGH-WEAN protocol. Ref 13 is original work by Dr Thille. I learned from this reference that the NIV modality was “Noninvasive ventilation (NIV) was carried out with an ICU ventilator with noninvasive ventilation mode or dedicated bilevel ventilator in pressure-support mode with a minimal pressure-support level of 5 cmH₂O targeting a tidal volume around 6 to 8 mL/kg of predicted body weight, a positive end-expiratory pressure level between 5 and 10 cm H₂O, and a FIO₂ adjusted to obtain adequate oxygenation (SpO₂ ≥92%).” Please define the parameters for NIV and HFNC following extubation. This requirement for ventilator support for 48 hours after extubation impacts on the primary outcome: The primary outcome is the number of ventilator-free (no ventilator support at all, including NIV) days between the 1st SBT (time zero) and day 28. Thus no patient can have more that 26 ventilator free days by day 28 post 1st SBT. In addition it introduces additional variable(s) that may affect the outcome. Please specify and standardize the duration of the NIV support and HFNC delivered to each patient, the means to measure and record efficacy and the means to determine the order of each.

Page 13 The patients will be classified by their weaning process. This will be a post hoc classification will be based on the actual performance of the patient. I learned from ref 10 that there are 3 classes for the weaning process. Please define the criteria for classification of the weaning performance in the current study.

Please define the objective measures defining extubation failure and how, across the 31 ICUs, the specific steps that will be taken to record all data.

Page 14 2021-22. The authors state that they will conduct a review of protocol violation and cleaning and closure of the database. On page 16 the authors mention REVA. Please explain the relationship and reporting structure between steering committee for the current study, REVA, and TIP-EX. Please explain the relationship between the research assistants and REVA.

Page 15 Please state at what point in time informed written consent will be obtained. How can an intubated adult in the ICU give informed consent that includes the SBT type to be used throughout the weaning process?

Page 15 Please describe the e-CRF to be used for data collection. I learned from Google that an e-CRF may be “...an electronic form for collecting relevant information in a clinical trial to achieve the objective of this trial. Its content is described by the protocol. Its access is nominative and protected by a password.” Please report how data will be transferred to the central database. Please describe how will the data be anonymized and stored. Please detail the training of the investigators and research assistants across the 31 ICUs.

Page 16 The authors plan to perform a multivariate logistic regression analysis with variables associated with 1) extubation success and 2) reintubation that will be selected by their p values (<0.2). The final model will include variables associated with reintubation that have a p value <0.05.

	<p>Page 16 We learn that patients will also be grouped by the duration of mechanical ventilation prior to the 1st SBT. The authors do not discuss the data that will be collected to conduct this analysis. From figure 1 it seems that this data will be collected prior to obtaining informed consent. Please report in the methods, and clarify.</p> <p>Page 16 Please provide more detail as to how the data will be collected and stored and what is meant by the phrase data will be locked.</p> <p>Page 17. A next of kin does not have signing authority for a RCT. This authority is reserved for legal guardians. In addition, please clarify the statement: After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.</p>
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REVIEWER	Paolo Navalesi Anesthesia and Intensive Care Department of Medicine-DIMED University of Padua
REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	<p>GENERAL COMMENTS</p> <p>The study protocol proposed by Thille et al. is undoubtedly of relevant interest for ICU physicians. The protocol is overall properly designed and clearly written, except for a few points that can be easily clarified (see below). The sample size is adequate to avert the risk of insufficient power.</p> <p>I cannot see whether or not the enrollment has already begun. In the following specific comments, I will provide the Authors with a few (minor) comments and some additional criticisms/suggestions that they may or may not consider and do not preclude, in my intention, acceptance of the manuscript</p> <p>SPECIFIC COMMENTS</p> <p>Minor Comments</p> <p>1) Page 8, end of first paragraph: "hemodynamic stability with no need for vasopressors (or minimal doses), adequate cough". I suggest a) defining criteria for hemodynamic stability, b) indicate the minimal doses, c) provide some sort of criteria for considering cough adequate.</p> <p>2) Page 7, Primary objective: please clarify whether the term "ventilator-free" considers here only invasive ventilation or also noninvasive ventilation. Reading "Primary outcome" later on and the first secondary objective in the next paragraph I understand the first option is correct. Nonetheless, I suggest clarifying.</p> <p>3) Page 7, Secondary objectives: "the number of ventilator-free days (including non-invasive ventilation) within the 28 days following the initial SBT". The hours (up to 48") of prophylactic noninvasive ventilation are included?</p> <p>4) Page 8, first row: I suggest replacing "high-risk of reintubation" with "high-risk of extubation failure"</p> <p>5) Page 8, Exclusion criteria: "patients having already undergone an initial SBT since intubation". I guess the Author refer to patients who underwent a SBT in the first 24 hours after intubation, when the eligibility criteria was not met yet. If this holds true, I suggest replacing "initial SBT" with "SBT in the first 24 hours". Otherwise, I wonder if the Authors refer to conditions of protocol violation.</p> <p>6) Page 9, second paragraph: "SBT will be performed for around 1 hour according to weaning guidelines (Ref 10)". Ref 10 (Boles et al) suggests SBT duration of 30 minutes.</p>
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	<p>7) Page 9, same paragraph “for at least 1-h rest”. At least or 1 hour? “At least” can be up to 10 hours. I suggest being precise at this regard.</p> <p>Additional comments</p> <p>1) I understand the threshold of 65 years has been widely used in most (if not all) previous studies to consider a patient at high-risk of extubation failure. That said, is this threshold reasonable nowadays? This means the vast majority of our patients are at increased risk.</p> <p>2) Control group: T-piece trial. I have 3 comments: a) providing additional oxygen does not allow precise FiO₂; b) Deciding to provide 6 L/min for patients ventilated with FiO₂ 0.4, and 3 L/min for those with FiO₂ 0.3 is arbitrary and lacks of physiologic meaning; c) What does it mean “We will propose”? Do you expect varying behaviors in different centers?</p> <p>I wonder why the Authors preferred this approach rather than maintain the patient connected to the ventilator with a flow trigger and zero PEEP and zero support. In addition, this would allow maintaining adequate humidification throughout SBT.</p> <p>I understand it is hard to change the protocol of an ongoing trial. If recruitment has not begun yet, however, I would suggest considering this option.</p> <p>3) Just a suggestion unrelated to the present manuscript. Two “old” studies having rather similar protocols (Esteban et al. NEJM and Brochard et al. AJRCCM) ended up in quite conflicting results. I heard many times explaining that this may have depended on the different usual practice of the recruiting centers of the two studies. I would suggest considering this aspect when reporting and discussing data.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Karen Brown

Institution and Country: McGill University, McGill University Health Center, Montreal, Canada

Please state any competing interests or state ‘None declared’: None declared

This is an ambitious prospective multicenter RCT with an aim to recruit 900 critically ill intubated adults from 31 ICUs in France, in a 2 year time period. The authors wish to evaluate extubation readiness and success with two types of spontaneous breathing trials (SBT): 1) SBT with a T-piece and 2) SBT with low level pressure support ventilation (PSV). Patients will be randomized 1:1 to the SBT type. Patients will be grouped by SBT type and the outcomes will be compared and the probabilities and proportions of each of 9 outcomes (see below), calculated. The authors will use an intention-to-treat analysis.

The note from the Editor states that a purpose of publishing the protocol in BMJopen is to make available more information than is currently required by trial registries, to increase transparency and to explain in detail how the study will be conducted. In this regard the manuscript is poorly written and many many explanatory details are missing. Thus I had to read through the citations and to consult Google to sort the issues. For example, I learned from Google that the acronym TIP-EX is for T-piece Versus Pressure-support for the Spontaneous Breathing Trial (TiP-Ex). Please define your acronyms (TiP-Ex, REVA, e-CRF). Please clarify the relationship (consent, data, analysis, investigators) between this RCT and the TiP-Ex.

Response: We now define all acronyms throughout the manuscript.

Concerning TIP-EX, this is the acronym for “T-piece versus Pressure-support ventilation for spontaneous breathing trials before EXTubation in patients at high-risk of reintubation” indicated in the title.

The hypothesis is that compared to the SBT-Piece, the SBT-PSV may hasten extubation without increasing the risk of reintubation.

The primary outcome is the number of ventilator-free (no ventilator support at all, including NIV) days between the 1st SBT (time zero) and day 28. But the definition of this primary outcome varies throughout the manuscript. Please clarify as different definitions for the primary outcome are given in the abstract, page 10, page 12, page 13 and page 15.

Response: I am very sorry but the primary outcome of our study is not what you mentioned above. Maybe the reviewer misread the manuscript.

The primary outcome is indicated in the manuscript, as follows: “The primary outcome is the number of ventilator-free days at day 28, defined as the number of days alive and without invasive mechanical ventilation (intubation or tracheostomy) between the initial SBT (day 1) and day 28”.

Therefore, as you can see, the primary outcome does not include days free of NIV, but only invasive mechanical ventilation (intubation or tracheostomy). The primary outcome is expressed with the same definition in the abstract, and in the manuscript section “primary outcome”, and section “Analysis pertaining to the main criteria of evaluation”. Maybe the reviewer made a mistake and was referring to one of the secondary outcomes, which indeed include invasive and noninvasive ventilation, as indicated in the “secondary outcomes” section.

There are in addition 8 secondary outcomes:

- 1) Days between the 1st SBT and Extubation.
- 2) Number of patients extubated within 7 days of the 1st SBT. The authors state they will only study the 1st SBT yet continue to collect data on patients who fail the 1st SBT. If patients fail the 1st SBT, it is not stated if all patients will undergo additional SBTs. If they do, the type of SBT the patient must be identical to the 1st SBT.
- 3) The weaning profile of patients will be classified by weaning difficulty criteria proposed in Reference 10.
- 4) Extubation success at 72 hours after the 1st SBT.
- 5) Extubation success at 7 days after the 1st SBT.
- 6) Extubation success at 7 days after the day of the actual extubation.
- 7) Length of stay in the PICU.
- 8) Mortality in ICU, at day 28 and at day 90.

The authors will recruit adult patients intubated >24hours at high risk for extubation failure. Please define the specific measures that will be used to define high risk chronic lung and cardiac disease. A high index of clinical suspicion is not sufficient.

Please define the criteria for and objective measures of weaning that define extubation readiness at the time of the 1st SBT.

Response: You are right. The number of words is limited and therefore we did not detail what exactly we mean by suspected “underlying chronic disease”. We used exactly the same definition as in our previous study,¹ and as requested, we now detail criteria for suspicion of chronic lung disease.

“Chronic lung diseases include any underlying chronic obstructive pulmonary disease, obesity-hypoventilation syndrome (OHS) or restrictive pulmonary disease. The underlying lung disease will be either documented or highly suspected by the physician in a patient intubated for acute hypercapnic respiratory failure and having 1) a history of smoking with intrinsic positive end-expiratory pressure (PEEP) during mechanical ventilation and/or emphysema on chest X-ray or scanner suggesting underlying chronic obstructive pulmonary disease, 2) obesity (body-mass index > 30 kg/m²) with alveolar hypoventilation (PaCO₂ > 45 mm Hg) suggesting obesity-hypoventilation syndrome, or 3) rib cage deformation suggesting restrictive pulmonary disease”.

Concerning the criteria for extubation, all criteria were mentioned in the inclusion criteria section: According to the international conference consensus on weaning,² patients will be considered as ready for an initial SBT as soon as they meet all the following criteria: a respiratory rate ≤ 35 breaths per minute, adequate oxygenation defined as $SpO_2 \geq 90\%$ with $FiO_2 \leq 0.4$ or $PaO_2/FiO_2 \geq 150$ mm Hg with $PEEP \leq 8$ cmH₂O, hemodynamic stability with no need for vasopressors (or minimal dosis), adequate cough, patient awake with a Richmond Agitation-Sedation Scale between +1 and -2.³

Please report the measure that will be recorded to document compliance with the SBT type. On page 11 and page 12 the authors state the SBT-PSV will be conducted with exactly 8 cmH₂O and no PEEP. Across the 31 ICUs, how will this level of pressure support be measured, how will it be documented and what measures to ensure compliance will be implemented?

Response: We chose the 2 trials that are the most widely used in the world, and we decided to choose a pressure-support level of 8 cm H₂O as applied in the previous study by Subirà and colleagues.⁴ Before starting the study, we organized an opening meeting with all centers and all of them agreed on the protocol. The pressure-support level is not measured as mentioned by the reviewer but simply set on the ventilator and corresponds to the usual level of pressure support adjusted in clinical practice. After consent and inclusion into the protocol the main investigator in each centre will set the pressure-support level mentioned in the protocol, i.e. 8 cm H₂O. If the level is for any reason different from that required, the actual level set by the clinician will be collected in the e-CRF, and we will therefore be able to provide the actual pressure-support level used in the protocol. As indicated in the "data monitoring" section: Research assistants will regularly monitor all the centres on site to check adherence to the protocol and the accuracy of the recorded data.

At the bottom of table 1, we also added collected data (2) Characteristics of the SBT include duration, type and settings of the initial SBT, vital parameters at the end of the initial SBT, and criteria for SBT failure.

On page 11 Please change to read "The SBT-T piece will be performed with a T-piece connected to the patient connection port of the endotracheal tube and an oxygen flow of ≤ 6 L/m. " Please clarify if this is 100% oxygen or an air/oxygen blend. And then please clarify how you will add an oxygen flow of 3 L/m to the patients mechanically ventilated with a FiO_2 0.3 prior to the SBT-Tpiece trial and 6 L/m for those mechanically ventilated with a FiO_2 0.4. How will you document and report the FiO_2 delivered to the patient?

Response: These proposals for oxygen flow are based on the publication of our group,⁵ in which we determined that the best method to assess FiO_2 during standard oxygen therapy was the following: $21\% + \text{oxygen flow rate (in L/min)} \times 3$. Therefore, a flow rate of 3 L/min of oxygen corresponds to FiO_2 around 30% and a flow of 6 L/min to FiO_2 of 40%. The flow of oxygen is one of the settings collected during the initial SBT.

We changed the sentence as suggested by the reviewer and specified that it is oxygen blend. The new sentence is "The T-piece trial will be performed with a T-piece connected to the patient connection port of the endotracheal tube and providing additional oxygen (≤ 6 L/min). We will propose to add an oxygen flow rate of 3 L/min (oxygen blend) during the T-piece trial in patients mechanically ventilated with a FiO_2 0.3 prior to the T-piece trial and 6 L/min for those mechanically ventilated with a FiO_2 0.4".

Across the 31 ICUs please state how the method to document and report the respiratory rate and tidal volume on the critical care ventilator. Across the 31 ICUs please state the critical care ventilator make and models that will be used to deliver the SBT-PSV.

Response: Respiratory rate at the end of the SBT will be collected in a CRF-file at bedside by the nurse as usually done. We detailed this point at the bottom of table 1 indicating study flow chart and data collected. (2) Characteristics of the SBT include duration, type and settings of the initial SBT, vital parameters at the end of the initial SBT, and criteria for SBT failure.

Numerous ventilators (GE, Dräger, Hamilton, Maquet, Lowenstein....) can be used. As performance

in terms of pressure-support ventilation is very similar for ICU ventilators⁶, this information will not be collected.

Page 12 the authors state the duration of the SBT will be one hour citing reference 10. But the consensus opinion in reference 10 clearly states that “The initial trial should last 30 min and consist of either T-tube breathing or low levels of pressure support.” Please justify the deviation from this practice guideline.

Response: You are right that clinical practice guidelines recommend SBT duration of 30 minutes. However, SBT lasted between 30 min to 2 hours in previous large-scale RCTs comparing spontaneous breathing trials.^{4 6-9} Although a RCT found no difference in terms of outcome between 30 min and 2 hours,⁷ it has been shown that some patients may fail beyond the first 30 min, and that a 30-min period could be too short to assess extubation readiness, especially in patients at high-risk of extubation failure.⁹ In the most recent RCT on spontaneous breathing trials, the authors compared an easy trial lasting 30-min with PSV vs. a difficult trial lasting 2-h with T-piece,⁴ showing that usual SBT duration ranges from 30 min to 2 hours. Therefore, SBT duration may vary from one centre to another. In our previous study on weaning including the same centers, the median duration of SBT was 60 [30-60] minutes. Therefore, we specified “around” one hour to avoid confusion and constrain only the type and not the duration of SBT. Obviously, SBT duration is specified in the e-CRF.

Page 12 the SBTs differ. The SBT-T piece is followed by a 1 hour period of ventilator support before extubation. The SBT-PSV does not require this period of “rest”. Please comment on the impact of this period of ventilator support on the outcomes.

Page 12. The authors state they will only study the 1st SBT but in the eventuality of reintubation report that additional SBTs will be the same as the 1st SBT. This seems a constraint on clinical practice. Please justify and confirm that these constraints are included in the informed consent form.
Response: A previous study showed that a one-hour period at rest under mechanical ventilation after SBT trial with T-piece may improve outcome¹⁰. We therefore decided to apply this protocol in our interventions. In this previous study, this period at rest was only applied in patients with SBT trial using T-piece. As patients with SBT using PSV are not disconnected, it is not justified proceed likewise.

I am very sorry but I don't think that applying the arm of the protocol is a constraint. The main objective is to compare T-piece vs. PSV and therefore weaning should be performed using T-piece or PSV during the entire ICU stay. It is not a constraint on clinical practice since there is no type of SBT recommended and since the two types of SBT can be performed.

Page 12 The authors state that following extubation all patients will receive two types of NIV; alternating NIV (possibly by mask) and HFNC. The authors cite references 13 and 14. Ref 14 is the HIGH-WEAN protocol. Ref 13 is original work by Dr Thille. I learned from this reference that the NIV modality was “Noninvasive ventilation (NIV) was carried out with an ICU ventilator with noninvasive ventilation mode or dedicated bi-level ventilator in pressure-support mode with a minimal pressure-support level of 5 cmH₂O targeting a tidal volume around 6 to 8 mL/kg of predicted body weight, a positive end-expiratory pressure level between 5 and 10 cm H₂O, and a FIO₂ adjusted to obtain adequate oxygenation (SpO₂ ≥92%).” Please define the parameters for NIV and HFNC following extubation. This requirement for ventilator support for 48 hours after extubation impacts on the primary outcome: The primary outcome is the number of ventilator-free (no ventilator support at all, including NIV) days between the 1st SBT (time zero) and day 28. Thus no patient can have more than 26 ventilator free days by day 28 post 1st SBT. In addition it introduces additional variable(s) that may affect the outcome. Please specify and standardize the duration of the NIV support and HFNC delivered to each patient, the means to measure and record efficacy and the means to determine the order of each.

Response: Once again, the reviewer may have misread the manuscript as NIV duration is not included in the primary outcome and therefore does not impact the outcome. NIV and high-flow will be

applied exactly as in our previous study and we therefore did not provide the protocol: After extubation, prophylactic use of non-invasive ventilation alternating with high-flow nasal oxygen between non-invasive ventilation sessions will be recommended in all patients for at least 48 hours according to the results of the HIGH-WEAN study.^{1 11}

Page 13: The patients will be classified by their weaning process. This will be a post hoc classification will be based on the actual performance of the patient. I learned from ref 10 that there are 3 classes for the weaning process. Please define the criteria for classification of the weaning performance in the current study.

Response: We added the definition in the discussion. Simple weaning includes patients extubated within the first 24 hours after the initial SBT, difficult weaning includes patients extubated between 24 hours and 7 days after the initial SBT, and prolonged weaning includes patients extubated more than 7 days after the initial SBT.¹²

Please define the objective measures defining extubation failure and how, across the 31 ICUs, the specific steps that will be taken to record all data.

Response: We accurately defined

- 1) post-extubation respiratory failure and
- 2) Reintubation (which actually refers to extubation failure).

Criteria for post-extubation respiratory failure

An episode of post-extubation respiratory failure will be defined by the presence of at least two criteria among the following: a respiratory rate above 25 breaths per minute, clinical signs suggesting respiratory distress with increased accessory muscle activity, respiratory acidosis defined as $\text{pH} < 7.35$ units and $\text{PaCO}_2 > 45$ mm Hg, hypoxemia defined as a need for FiO_2 at 50% or more to maintain SpO_2 level at least 92% or a $\text{PaO}_2/\text{FiO}_2$ ratio < 150 mm Hg.

Criteria for reintubation

To ensure the consistency of indications across sites and reduce the risk of delayed intubation, patients will be immediately reintubated if at least one of the following criteria is fulfilled: severe respiratory failure, hemodynamic failure defined by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg with signs of hypoperfusion and serum lactate level greater than 2 mmol/L, neurological failure (altered consciousness with Glasgow coma scale below 12), cardiac or respiratory arrest.

Severe respiratory failure leading to reintubation will be defined by the presence of at least two criteria among the following: a respiratory rate above 35 breaths per minute, clinical signs suggesting respiratory distress with increased accessory muscle activity, respiratory acidosis defined as $\text{pH} < 7.25$ units and $\text{PaCO}_2 > 45$ mm Hg, hypoxemia defined as a need for FiO_2 at 80% or to maintain SpO_2 level at least 92% or a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 100 mm Hg.

All criteria will be collected by the investigator of each centre as specified at the bottom of table 1: (4) Characteristics after extubation include the use and duration of non-invasive ventilation and high-flow nasal oxygen after extubation, criteria for post-extubation respiratory failure, criteria for reintubation, need for reintubation, number of days of mechanical ventilation (invasive and non-invasive), tracheostomy, and death.

Page 14 2021-22. The authors state that they will conduct a review of protocol violation and cleaning and closure of the database. On page 16 the authors mention REVA. Please explain the relationship and reporting structure between steering committee for the current study, REVA, and TIP-EX. Please explain the relationship between the research assistants and REVA.

Response: TIP-EX is the acronym of the trial and does not mean anything else. REVA is a research network. The protocol was presented, modified and discussed with the committee. As indicated in the manuscript, progression of the study is presented and discussed regularly at the REVA meeting, where all investigators are present. There is no relationship between research assistant and REVA as

they belong to the coordinating centre the University hospital of Poitiers. We added: Research assistants from the coordinating centre will regularly monitor all the centres on site to check adherence to the protocol and the accuracy of the recorded data.

Page 15 Please state at what point in time informed written consent will be obtained. How can an intubated adult in the ICU give informed consent that includes the SBT type to be used throughout the weaning process?

Response: Informed consent will be obtained according to two modalities. In a patient conscious and able to perfectly understand and communicate, informed consent is obtained directly from the patient. Otherwise, informed consent will be obtained from the next of kin while continuation of the trial and use of data collected will be approved by the patient him/herself.

This is clearly mentioned in the appropriate section:

Consent or assent

The patient will be included after having provided written informed consent to the investigator according to the decision of the central ethics committee. If the patient is not able to understand the information given, he/she can be included if the same procedure is completed with a next of kin. After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.

Page 15 Please describe the e-CRF to be used for data collection. I learned from Google that an e-CRF may be "...an electronic form for collecting relevant information in a clinical trial to achieve the objective of this trial. Its content is described by the protocol. Its access is nominative and protected by a password." Please report how data will be transferred to the central database. Please describe how will the data be anonymized and stored. Please detail the training of the investigators and research assistants across the 31 ICUs.

Response: We modified the confidentiality section as follows "Data will be handled according to French law. Coding subjects will be done by recording the first letter of the name and forename, accompanied by a single study identifier indicating the order of subject inclusion, in order to store anonymized data in the e-CRF. The sponsor will ensure that each study participant has given his/her consent for access to his/her personal data that is strictly required for quality control of the study. All original records will be archived at trial sites for 15 years". And we added in the data monitoring section: After being trained to conduct the protocol and to fulfil the e-CRF, an investigator at each centre will be responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the electronic case-report form.

Page 16 The authors plan to perform a multivariate logistic regression analysis with variables associated with 1) extubation success and 2) reintubation that will be selected by their p values (<0.2). The final model will include variables associated with reintubation that have a p value <0.05.

Page 16 We learn that patients will also be grouped by the duration of mechanical ventilation prior to the 1st SBT. The authors do not discuss the data that will be collected to conduct this analysis. From figure 1 it seems that this data will be collected prior to obtaining informed consent. Please report in the methods, and clarify.

Response: We will collect duration of mechanical ventilation prior to the initial SBT and in the multivariable analysis variables, among the planned collected values associated with outcome a p value <0.2 will be entered in the maximal model. Therefore, these data cannot be determined before final statistical analysis. Obviously, all data concerning the patient will be collected after obtaining the consent and at no time in the manuscript is it mentioned that data will be collected before consent. All data collected are indicated in the Table 1.

Page 16 Please provide more detail as to how the data will be collected and stored and what is meant by the phrase data will be locked.

Response: We committed a typo e. It is not data but database that will be locked.

Page 17. A next of kin does not have signing authority for a RCT. This authority is reserved for legal guardians. In addition, please clarify the statement: After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.

Response: According to French law next of kin is considered as legal guardian for clinical research. Therefore we have to apply the law of the country in which a trial is performed.

Reviewer: 2

Reviewer Name: Paolo Navalesi

Institution and Country: Anesthesia and Intensive Care, Department of Medicine-DIMED, University of Padua, Italy

Please state any competing interests or state 'None declared': None declared

GENERAL COMMENTS

The study protocol proposed by Thille et al. is undoubtedly of relevant interest for ICU physicians. The protocol is overall properly designed and clearly written, except for a few points that can be easily clarified (see below). The sample size is adequate to avert the risk of insufficient power.

I cannot see whether or not the enrolment has already begun.

In the following specific comments, I will provide the Authors with a few (minor) comments and some additional criticisms/suggestions that they may or may not consider and do not preclude, in my intention, acceptance of the manuscript

Response: Thank you very much for your comment. We specified the date of enrolment of the first patient in the recruitment section: (the first participant was enrolled the 31st January 2020)

SPECIFIC COMMENTS

Minor Comments

1) Page 8, end of first paragraph: "hemodynamic stability with no need for vasopressors (or minimal doses), adequate cough". I suggest a) defining criteria for hemodynamic stability, b) indicate the minimal doses, c) provide some sort of criteria for considering cough adequate.

Response: We fully agree with you on this very difficult point. In fact, we used exactly the terms employed in the clinical practice guidelines, i.e. "adequate cough" and "no or minimal vasopressors", although I agree it seems not accurate enough. On the other hand, I admit that it's a bit touchy to modify inclusion criteria because inclusions are already in progress.

Concerning hemodynamics we can change and specify, particularly the doses of vasopressors and we thereby propose: hemodynamic stability with no need for vasopressors (or minimal dosis ≤ 0.3 $\mu\text{g}/\text{kg}/\text{min}$). This threshold has been previously used as severity criterion in patients with respiratory failure.¹³

Concerning cough, we recently published several articles on the relation between cough strength and extubation,^{14 15} and we found that semi-qualitative assessment had better predictive accuracy than measurement of peak cough expiratory flow to predict extubation failure. We used a Likert-scale to classify cough strength as absent, weak, moderate, effective or very effective, and we then defined ineffective cough as weak or absent. In these previous studies, ineffective cough, although not frequent at time of extubation, was a strong predictor of reintubation in the 2 studies. As it appeared difficult to include a supplementary cough assessment scale before starting the initial SBT, we decided to keep the vague definition from practice guidelines. However, patients may have succeeded in the initial SBT and not be extubated by the clinician considering that cough is not effective enough (data collected in the CRF), and second, cough strength is systematically assessed at time of extubation according to our semi-qualitative assessment. Therefore, we will be able to perform post-hoc analysis in patients with effective or ineffective cough.

2) Page 7, Primary objective: please clarify whether the term "ventilator-free" considers here only

invasive ventilation or also noninvasive ventilation. Reading “Primary outcome” later on and the first secondary objective in the next paragraph I understand the first option is correct. Nonetheless, I suggest clarifying.

Response: We clarified the objectives to avoid confusion.

Primary objective: To compare the number of invasive ventilator-free days within the 28 days following the initial SBT between a strategy of extubation performing SBT with T-piece or with PSV.

Secondary objectives: To compare between the 2 groups: (1) the number of ventilator-free days (including intubation and non-invasive ventilation) within the 28 days following the initial SBT,

3) Page 7, Secondary objectives: “the number of ventilator-free days (including non-invasive ventilation) within the 28 days following the initial SBT”. The hours (up to 48”) of prophylactic noninvasive ventilation are included?

Response: Yes, the duration of prophylactic NIV will be included in this outcome and it is now indicated at the bottom of table 1 among the collected data in the e-CRF: (4) Characteristics after extubation include the use and duration of non-invasive ventilation and high-flow nasal oxygen after extubation (as well prophylactic use as rescue therapy to treat post-extubation respiratory failure). In our previous trial on prophylactic NIV after extubation,¹¹ we planned to apply around 48 hours of NIV after extubation. However, NIV may be prolonged according to patient respiratory status. Consequently, NIV was stopped early (before 48 hours) in 25% of cases, and by contrast, it was prolonged beyond the first 48 hours in 25% of cases. In this case, prolongation of NIV may be a sign of severity to take into account.

4) Page 8, first row: I suggest replacing “high-risk of reintubation” with “high-risk of extubation failure”

Response: we changed as requested

5) Page 8, Exclusion criteria: “patients having already undergone an initial SBT since intubation”. I guess the Author refer to patients who underwent a SBT in the first 24 hours after intubation, when the eligibility criteria was not met yet. If this holds true, I suggest replacing “initial SBT” with “SBT in the first 24 hours”. Otherwise, I wonder if the Authors refer to conditions of protocol violation.

Response: We did not refer only to patients who underwent a SBT in the first 24 hours but rather to patients having already undergone an initial SBT at any time since intubation (screening failure, for example). In cases of previous SBT, it is no longer possible to assess weaning difficulty, and therefore, to avoid this major bias, all patients must be included before the initial SBT. We changed the sentence to “patients having already undergone an initial SBT at any time since intubation”,

6) Page 9, second paragraph: “SBT will be performed for around 1 hour according to weaning guidelines (Ref 10)”. Ref 10 (Boles et al) suggests SBT duration of 30 minutes.

Response: You are right that clinical practice guidelines recommend SBT duration of 30 minutes. However, SBT lasted between 30 min to 2 hours in previous large-scale RCTs comparing spontaneous breathing trials.^{4 6-9} Although a RCT found no difference in terms of outcome between 30 min and 2 hours,⁷ it has been shown that some patients may fail beyond the first 30 min, and that a 30-min period could be too short to assess extubation readiness, especially in patients at high-risk of extubation failure.⁹ In the most recent RCT on spontaneous breathing trials, the authors compared an easy trial lasting 30-min with PSV vs. a difficult trial lasting 2-h with T-piece,⁴ showing that usual SBT duration ranges from 30 min to 2 hours. Therefore, SBT duration may vary from one centre to another. In our previous study on weaning including the same centers, the median duration of SBT was 60 [30-60] minutes. Therefore, we specified “around” one hour to avoid confusion and constrain only the type and not the duration of SBT. Obviously, SBT duration is specified in the e-CRF.

7) Page 9, same paragraph “for at least 1-h rest”. At least or 1 hour? “At least” can be up to 10 hours. I suggest being precise at this regard.

Response: You are right. We changed to “around” one hour

Additional comments

1) I understand the threshold of 65 years has been widely used in most (if not all) previous studies to consider a patient at high-risk of extubation failure. That said, is this threshold reasonable nowadays? This means the vast majority of our patients are at increased risk.

Response: You are right. Probably this threshold fails to identify old patients (>65) but rather helps to identify young patients (<65) at low-risk. Effectively, 65 is the threshold most often used in previous studies and remains a determining factor for health according to the criteria of the World Health Organization. In our previous study, patients at high-risk of extubation using our criteria (age or underlying disease) based on the flow chart of the study represented around half of patients extubated, given that a majority of centers were medical ICUs. This proportion is probably a little bit lower in centers admitting predominantly surgical and trauma patients. However, our main objective (as when we used prophylactic NIV) is to propose an efficient treatment not for a small subset of patients but, by contrast, for a large population of patients.

2) Control group: T-piece trial. I have 3 comments: a) providing additional oxygen does not allow precise FiO₂; b) Deciding to provide 6 L/min for patients ventilated with FiO₂ 0.4, and 3 L/min for those with FiO₂ 0.3 is arbitrary and lacks of physiologic meaning; c) What does it mean “We will propose”? Do you expect varying behaviors in different centers?

Response: These proposals for oxygen flow are based on the publication of our group,⁵ in which we determined that the best method to assess FiO₂ during standard oxygen therapy was the following: 21 % + oxygen flow rate (in L/min) x 3. Therefore, a flow rate of 3L/min of oxygen corresponds to FiO₂ around 30% and a flow of 6 L/min to FiO₂ of 40%. The flow of oxygen is one of the settings collected during the initial SBT.

We changed the sentence as suggested by the reviewer 1 and specified that it is oxygen blend. The new sentence is “The T-piece trial will be performed with a T-piece connected to the patient connection port of the endotracheal tube and providing additional oxygen (\leq 6 L/min). We will propose to add an oxygen flow rate of 3 L/min (oxygen blend) during the T-piece trial in patients mechanically ventilated with a FiO₂ 0.3 prior to the T-piece trial and 6 L/min for those mechanically ventilated with a FiO₂ 0.4”.

I wonder why the Authors preferred this approach rather than maintain the patient connected to the ventilator with a flow trigger and zero PEEP and zero support. In addition, this would allow maintaining adequate humidification throughout SBT.

I understand it is hard to change the protocol of an on-going trial. If recruitment has not begun yet, however, I would suggest considering this option.

Response: This is a very interesting remark that has been discussed with all centers before starting the trial. Our conclusions are the following: It is true that work of breathing with T-piece is similar to that with PSV0/PEEP0 as recently shown in a meta-analysis of physiological studies.¹⁶ However, few patients (around 50) have been assessed while breathing with PSV0/PEEP0. Moreover, all clinical trials on spontaneous breathing trials have used T-piece (and not PSV0/PEEP0) as control or interventional group.^{4 6 7} Our objective is to prove findings applicable everywhere concerning a test routinely used regardless of the country. Probably that PSV0/PEEP0 is similar but it is probably not the same for centers always performing T-piece and without experience to perform PSV0. In my opinion, but maybe I am wrong, PSV0 is only used in expert centres, in centers working on respiratory physiology as in Italy, in France or in Canada, but is not widely used in other countries. When we organized our meeting before starting the trial, only 2 centers of the 31 centers regularly used PSV0. Therefore, and although we agree that PSV0 enables continuous monitoring of respiratory rate, tidal volume and provides humidification, we decided to use THE test routinely applied around the world, and which is applicable in the greatest number of units. I think results from our trial could be extrapolated to centers performing PSV0, while the opposite is not certain.

3) Just a suggestion unrelated to the present manuscript. Two “old” studies having rather similar protocols (Esteban et al. NEJM and Brochard et al. AJRCCM) ended up in quite conflicting results. I heard many times explaining that this may have depended on the different usual practice of the recruiting centers of the two studies. I would suggest considering this aspect when reporting and discussing data.

Response: It is interesting. I think contradictory results are mainly due to the fact that these 2 studies compared two strategies of weaning and not two strategies of extubation. These studies did not compare SBTs but how to get to SBT as quickly as possible and therefore compared T-piece (strategy of extubation) and gradual reduction of PSV until extubation (strategy of weaning before extubation). A strategy of gradual reduction can indeed be very different according to a centre's experience. It can be rapid in France where it was routinely used in 90s and not in Spain where it was not used. Since 2000s the paradigm has changed and it is now recommended to perform SBT as soon as possible when the weaning criteria are met. However, the level of pressure-support is never included among weaning criteria, meaning that gradual reduction of PS may possibly delay weaning, as in the Spanish study.

I think that results of our trial could improve clinical practice and contribute to the establishment of a strong recommendation on weaning strategy. If the results were positive in favor of PSV (after the study by Subirà et al.), this strategy might be applied as a standard treatment for weaning procedure in all ICU patients(at risk or not). If effective, it could help to reduce the duration of mechanical ventilation and ICU stay in a population of severely ill patients.

If the results were negative, the results by Subirà et al would be attenuated in the subset of patients at high-risk of extubation failure and would not really be conflicting.

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VERSION 2 – REVIEW

REVIEWER	Paolo Navalesi University of Padua
REVIEW RETURNED	17-Sep-2020

GENERAL COMMENTS	No additional comment. I am satisfied by the Authors' response
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