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T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in patients at high-risk of reintubation: the multicentre randomised controlled TIP-EX protocol.

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Contributors

AWT, RC and J-PF, in collaboration with all authors and the REVA network designed the study and wrote the manuscript together. SR provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size with AWT.

AWT, RC, AG, SE, DC, LD, AR, CG, GL, JPQ, BLC, GP, NT, GP, GL, JR, GB, JD, MAN, AR, AD, NS, JPM, JB, AL, LA, QL, JD, EV, MAA, CL, MD, RR, SR, JPF contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Disclaimer

None

Competing interests

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Ethics approval

The study has been approved by the central ethics committee (Ethics Committee Ile de France V, Paris, France) with the registration number 2019-A02151-56 (07 October 2019).

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ABSTRACT (298)

Introduction: In ICU, the decision of extubation is a critical time because mortality is particularly high in case of reintubation. To reduce that risk, guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before extubation in order to mimic the post-extubation physiological conditions. SBT is usually performed with a T-piece disconnecting the patient from the ventilator or with low levels of pressure-support ventilation (PSV). However, work of breathing is lower during PSV than during T-piece. Consequently, while PSV trial may hasten extubation, it may also increase the risk of reintubation. We are hypothesizing that as compared to T-piece, SBT performed using PSV may hasten extubation without increasing the risk of reintubation.

Methods and analysis: This study is an investigator-initiated, multicentre randomised controlled trial comparing T-piece versus PSV for SBTs in patients at high-risk of reintubation in ICUs. Nine-hundred patients will be randomised with a 1:1 ratio in two groups according to the type of SBT. 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 between the initial SBT (day 1) and day 28. Secondary outcomes include the number of days between the initial SBT and the first extubation attempt, weaning difficulty, the number of patients extubated after the initial SBT and not reintubated within the following 72 hours, the number of patients extubated within the 7 days following the initial SBT, the number of patients reintubated within the 7 days following extubation, length of stay in ICU, and mortality in ICU, at day 28 and at day 90.

Ethics and dissemination: The study has been approved by the ethics committee and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04227639

Strengths and limitations of the study

►This large randomised controlled trial may help to establish strong recommendations on daily clinical practice for extubation in ICUs with a high level of evidence.

►Spontaneous breathing trials performed using T-piece or pressure-support ventilation have never been compared in the subset of patients at high-risk of reintubation.

►A large population of patients considered to be at high-risk for reintubation will be included. Patients older than 65 years or those with an underlying chronic cardiac or lung disease are easy to identify in clinical practice and represent nearly half of the patients extubated in ICUs.

►Limitation: The individual study assignments of the patients will not be masked. Given the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

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INTRODUCTION

Background and rationale

In ICU, the decision of extubation is a critical time because mortality is particularly high in case of extubation failure leading to reintubation.[1] The overall rate of reintubation after planned extubation is around 10% but may exceed 20% in patients at high-risk of extubation failure.[1] To reduce that risk, guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before extubation in all patients intubated at least 24h in order to mimic the post-extubation physiological conditions.[2] A standard test for extubation readiness is a SBT with a T-piece disconnecting the patient from the ventilator and providing additional oxygen (T-piece trial). Another widely used trial is performed without disconnecting the patient from the ventilator, using low levels of pressure-support ventilation (PSV trial). In recent large cohort studies these 2 types of SBTs were performed with nearly the same frequency.[3 4] However, these 2 trials are not equivalent in terms of patient breathing effort. Physiological studies have shown that work of breathing measured during T-piece was similar to work of breathing after extubation.[5] In contrast, work of breathing is markedly lower during PSV trial than during T-piece. Consequently, while PSV trial may potentially hasten extubation, it may also increase the risk of reintubation by underestimating the work of breathing needed after extubation.[6]

A large randomised controlled trial recently found that the proportion of patients successfully extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-piece trial for 2 hours.[7] In this study, reintubation rates did not differ using PSV trial or T-piece. These findings confirm that PSV trial is an easier test to pass than T-piece trial, and that it may hasten extubation without an increased risk of reintubation. However, in this study the proportion of patients with simple weaning was particularly high and patients with weaning difficulties were not monitored up until extubation, thereby limiting the application of these findings to simple weaning. Moreover, reintubation rates were particularly low meaning that the population mainly included patients at low-risk of extubation failure.[8] The latest American guidelines suggested an initial SBT using PSV rather than T-piece to hasten extubation.[2] The strength of this recommendation was only conditional given the moderate certainty of evidence. To improve the level of evidence of daily clinical practice, we have decided to assess whether SBTs performed using PSV may hasten extubation without increasing the risk of reintubation in patients at high-risk of extubation failure as compared to T-piece.

Objectives

We aim to conduct a prospective multicentre randomised controlled trial comparing two strategies of extubation performing SBT with T-piece or with PSV in patients at high-risk of extubation failure. Our hypothesis is that SBTs with PSV may hasten extubation without increasing the risk of reintubation.

Primary objective

To compare the number of 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 non-invasive ventilation) within the 28 days following the initial SBT, (2) probability of extubation within the 72 hours and within the 7 days following the initial SBT, (3) proportion of patients with simple (≤ 24h), difficult (> 24 hours and ≤ 7 days) or prolonged (> 7 days) weaning, (4) proportion of patients extubated after the initial SBT and not reintubated within the following 72 hours, (5) weaning duration between the initial SBT and the first extubation attempt among extubated patients, (6) probability of reintubation within the 72 hours and within the 7 days following extubation, (7) proportion of patients with post-extubation respiratory failure within the 7 days following extubation, (8) length of stay in ICU, (9) the mortality in ICU, at day 28 and at day 90.

Trial design

The TIP-EX study is an investigator-initiated, multicentre, randomised, controlled, open-label trial comparing a strategy of extubation in patients at high-risk of reintubation in ICUs. Patients will randomly be assigned to one of the two groups performing SBT with T-piece or with pressure-support, with a 1:1 ratio.

METHODS: PATICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The TIP-EX study is taking place in 31 ICUs in France. Patient flow chart is detailed in the **Figure**.

Eligibility criteria

Inclusion criteria

Adult patients intubated more than 24 hours in ICU and at high-risk of reintubation will be eligible as soon as possible once they meet all weaning criteria for an initial SBT.

Patients will be considered at high-risk of reintubation according to the following criteria[9]: patients older than 65 years, or those having any underlying chronic cardiac or lung disease. Underlying chronic cardiac diseases include left ventricular dysfunction (whatever the cause) defined by left ventricular ejection fraction ≤ 45%, history of cardiogenic pulmonary oedema, documented ischemic heart disease or permanent atrial fibrillation. 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.

According to the international conference consensus on weaning,[10] 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 positive end-expiratory pressure (PEEP) ≤ 8 cmH_2O, hemodynamic stability with no need for vasopressors (or minimal dosis), adequate cough, patient awake with a Richmond Agitation-Sedation Scale between +1 and -2.[11]

Exclusion criteria

Patients fulfilling one of the following criteria will not be included: patients having already undergone an initial SBT since intubation, patients admitted for traumatic brain injury or with pre-existing peripheral neuromuscular disease (underlying myopathy or myasthenia gravis), patients with do-not-reintubate order at time of the initial SBT, patients previously included in the study, patients without health insurance coverage, people under protection (pregnant or breastfeeding women, minor patients, subjects with guardianship or under law protection), or refusal to participate.

Intervention

Spontaneous breathing trials before extubation

Patients included will be randomised before the initial SBT and assigned to one of the following 2 groups: 1) In patients assigned to control group all SBTs will be performed using T-piece; 2) In patients assigned to experimental group all SBTs will be performed using PSV with a PS level of 8 cm H_2O without PEEP.

Control group: T-piece trial

The T-piece trial will be performed with a T-piece connected to the extremity of the endotracheal tube by simply disconnecting the patient from the ventilator and providing additional oxygen (≤ 6 L/min). We will propose to add an oxygen flow rate of 3 L/min 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.

Interventional group: PSV trial

The PSV trial will be performed without disconnecting the patient from the ventilator, by using a low level of pressure-support (PS of 8 cm H2O) with a $FiO_2 \leq 40\%$ without PEEP, and without activation of automatic tube compensation (ATC) mode, while continuously monitoring respiratory rate and tidal volume on the ventilator display.

Duration of treatment and strategy of weaning and extubation

In both groups, the SBT will be performed for around 1 hour according to weaning guidelines.[10] In case of SBT success, patients will be systematically extubated the day of the trial. After a T-piece trial, patients will be reconnected to the ventilator with prior ventilatory settings for at least 1-h rest before extubation to avoid exhaustion.[12]

In case of SBT failure, a once-daily SBT will be performed with the same method according to the assigned group (T-piece or PSV trial) every day as long as weaning criteria are met until SBT success and extubation. SBT failure will be defined according to the usual criteria from the international conference consensus on weaning,[10] as development during the trial of any of the following events: (1) respiratory rate > 35 breaths/min, (2) increased accessory muscle activity, (3) SpO_2 persistently below 90% (or below 88% in case of underlying chronic lung disease) on $FiO_2 \geq 0.4$ or at least 6 L/min of oxygen, (4) hemodynamic instability defined as heart rate persistently above 140 beats / min, or systolic blood pressure < 90 or > 180 mmHg, with signs of hypoperfusion (appearance of cyanosis or mottling), (5) depressed mental status or agitation.

All patients will be followed until day 28 after the initial SBT. In the event of extubation failure and reintubation, weaning will then be performed with the same method according to the assigned group (T-piece or PSV trial). 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.[13 14]

Outcomes

Primary outcome

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.

Secondary outcomes

Secondary outcome variables include the following:

1. The number of days alive and without mechanical ventilation (including intubation and non-invasive ventilation) between the initial SBT (day 1) and day 28.

2. The number of patients extubated within the 72 hours and within the 7 days following the initial SBT.

3. The number of patients extubated after simple (less than 24h), difficult (between 24 hours and 7 days) or prolonged (more than 7 days) weaning.

4. The number of patients extubated after the initial SBT and not reintubated within the following 72 hours.

5. The number of days between the initial SBT and the first extubation attempt.

6. The number of patients reintubated within the 72 hours and within the 7 days following extubation.

7. The number of patients with post-extubation respiratory failure within the 7 days following extubation.

8. Length of stay in ICU.

9. Mortality in ICU, at day 28 and at day 90.

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 pH < 7.35 units and $PaCO_2$ > 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 PaO_2/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 pH < 7.25 units and $PaCO_2$ > 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 (PaO_2/FiO_2) < 100 mm Hg.

Sample size

We determined that enrolment of 900 patients would provide a power of 80% to show an absolute prolonged duration of mechanical ventilation by 2 days (number of ventilator-free days reduced by 2 days) using the T-piece trial as compared to the PSV trial at a two-sided alpha level of 0.05.

Expected number of patients to be included in the study: statistical justification

We calculated the number of patients to include based on results of our previous cohort.[15] In this study, the number of ventilator-free days at day 28 among the 150 patients at high-risk for reintubation was 23 days (± 9) in mean, and all patients were extubated following a strategy of weaning using PSV trials. In the present study, a number of patients will never be extubated, *i.e.* either died or still under mechanical ventilation at day 28, and thus with no ventilator-free days. According to a recent large cohort study,[4] these patients will represent around 2 to 3% of patients. Thus, we calculated that the number of ventilator-free days at day 28 would be 22 days (± 10) days using a PSV trial. In keeping with these results, we determined that enrolment of 786 patients would provide a power of 80% to show absolute prolonged duration of mechanical ventilation by 2 days (number of ventilator-free days reduced by 2 days) using the T-piece trial as compared to the PSV trial at a two-sided alpha level of 0.05. However, given the non-normal distribution of ventilator-free days in this population, the number of patients needed to be included was increased by 1.045 times in each group in order to compare the two groups with non-parametric tests.[16] Therefore, we estimated that 820 patients will be needed. To ensure analysing at least 820 patients for primary and secondary outcomes taking into account of patients with withdrawal of consent or lost to follow-up, we decided to increase the number of inclusions by 10%, *i.e.* 900 patients in total (450 patients per group).

Recruitment

The expected initial duration of patient enrolment is 2 years, starting in January 2020.

► End of 2018: national grant award;

► 2019: approval by an independent ethics committee;

► 2020-2021: inclusion of patients;

► 2021-2022: end of inclusions, monitoring of participating centres and queries to investigators; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database;

► 2022-2023: data analysis, writing of the manuscript and submission for publication.

METHODS: ASSIGNEMENT OF INTERVENTION, DATA COLLECTION, MANAGEMENT AND ANALYSIS

Allocation and sequence intervention

After obtaining consent from the patient or his/her relative, all inclusion/exclusion criteria will be verified by the investigator before randomization. Before the initial SBT the investigator will randomize patients to determine the type of trial allocated (T-piece or PSV trial). Randomization will be stratified on centre and carried out by connecting to the e-CRF website https://chu-poitiers.hugo-online.fr/CSOnline/ after fulfilling the "randomisation" page including all the criteria for eligibility.

Data collection and management

Data will be collected on an e-CRF by a trained investigator or research assistant at each centre. Patient follow-up and data collected are detailed in the study flow chart **(Table).**

Statistical methods

All the analyses will be performed by the study statistician according to a predefined statistical analysis plan and using statistical software (SAS, V.9.4; SAS Institute; USA). A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Descriptive analysis of patient groups at baseline

The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion/exclusion criteria for each patient. The continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges and extreme values or mean and standard deviation), while indicating the number of missing data. The category variables will be presented in the form of absolute frequency and percentage in each modality. Eligibility criteria will be verified on the basis of the data recorded in the case reports. Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the protocol will be described and analysed on a case-by-case basis.

Analysis pertaining to the main criteria of evaluation

The number of ventilator-free days at day 28, defined as the number of days alive and without invasive mechanic ventilation (intubation or tracheostomy) between the initial SBT (day 1) and day 28, will be compared between the 2 groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate. A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Analysis pertaining to the secondary criteria of evaluation

Extubation success and reintubation rates at the various pre-defined times, difficulty of weaning (simple, difficult or prolonged), post-extubation respiratory failure rates, and mortality will be compared between the 2 groups by means of the Chi2 test (or Fisher's exact test).

Weaning duration and lengths of stay will be compared between the two treatment groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate.

Kaplan–Meier curves will be plotted to assess the probability of extubation from the initial SBT to the following 72 hours and to the following 7 days, the probability of reintubation from extubation to the following 72 hours and to the following 7 days, and the probability of death between the initial SBT until day 90, and will be compared by means of the log-rank test.

The variables associated with extubation success and reintubation with a p value <0.20 will be assessed by means of a multivariate logistic regression analysis or Cox proportional-hazard regression analysis using a backward-selection procedure as appropriate.

The final model will include variables significantly associated with intubation with a P value of less than 0.05 and will be expressed using adjusted relative risk and odds ratio or hazard ratio with 95% confident interval.

Predetermined Subgroup Analysis

Patients with prolonged duration of mechanical ventilation may have weaning difficulties and an increased risk of reintubation.[4 15] Therefore, subgroups analyses will be performed for primary and secondary outcomes according to the duration of mechanical ventilation (> 7 versus ≤ 7 days) prior to the initial SBT after an interaction test carried out to detect heterogeneity of treatment effect between patients with a prior duration of mechanical ventilation of more than 7 days and the others.

Data monitoring

The trial will be overseen by a steering committee regarding the progression and monitoring of the study at REVA (Réseau Européen Ventilation Artificielle) Network meetings every 6 months.

Research assistants will regularly monitor all the centres on site to check adherence to the protocol and the accuracy of the data recorded. 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. Although the individual study assignments of the patients cannot be masked, the coordinating centre and all the investigators will remain unaware of the study group outcomes until the data will be locked.

ETHICS AND DISSEMINATION

Consent or assent

The patient will be included after having provided a 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.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years.

Declaration of interest

The TIP-EX study is an investigator-initiated trial supported by the French Ministry of Health with funds obtained in 2018 from a national hospital clinical research program (Programme Hospitalier de Recherche Clinique National 2018). The study is promoted by the University Hospital of Poitiers.

Access to data

All investigators will have access to the final data set. Investigators will make available the documents and individual data strictly required for monitoring, quality control and audit of the study to persons having access to them, in accordance with the statutory and regulatory provisions in place (articles L.1121-3 and R.5121-13 of the French Public Health Code).

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the executive committee. Rules of publication will follow the international recommendations according to *The Uniform Requirements for Manuscripts* (ICMJE, April 2010).

Patient and public Involvement

Patients and public are not involved in the study

DISCUSSION

According to the physiological results,[5] PSV trial is an easier test than T-piece trial and may potentially increase the risk of reintubation by underestimating the work of breathing needed after

extubation.[6] However, no study has demonstrated an increased reintubation rate using PSV trial as compared to T-trial.

Recently, a large randomised controlled trial including 1153 patients found that the proportion of patients successfully extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-piece trial for 2 hours.[7] However, the proportion of patients with simple weaning (*i.e.* patients extubated after the initial SBT) was particularly high in this study (nearly 90%) whereas usual rates in the literature are closer to 60-70%.[3] Moreover, patients with difficult weaning (*i.e.* those who failed the initial SBT) were not monitored up until extubation, thereby limiting application of these findings to simple weaning, and not taking into account patients with weaning difficulties.[3 4] Lastly, reintubation rates were particularly low (around 11%) meaning that the population mainly included patients at low-risk of extubation failure.[8] Although an easy test using PSV trial may hasten extubation, inclusion of patients at low-risk with reintubation rates around 10% or less might not enable to detect an increased risk of extubation failure. Therefore, to avoid underpowering the study and so as be able to detect the risk, we decided to focus on patients at high-risk of extubation failure and to include patients with weaning difficulties. In this population at high-risk of reintubation a recent post-host analysis from a large randomised controlled trial showed that execution of an initial SBT using PSV significantly increased the proportion of patients successfully extubated within the following 72 hours as compared with T-piece.[17] However, a large prospective clinical trial is needed to confirm these findings in this population before being in a position to apply this weaning strategy to all ICU patients.

To assess as primary outcome the duration of weaning on the one the hand and the risk of reintubation on the other hand, we decided to assess the number of ventilator-free days at day 28. This criterion has the advantage of evaluating the 2 end-points (duration of weaning and risk of reintubation) with one and the same criterion. In previous studies, primary outcome was the number of patients extubated after the initial SBT and not reintubated at 48h or 72h.[7 18 19] Although this outcome has weaknesses (too early and focusing only on simple weaning), we will also assess the number of patients extubated after the initial SBT and not reintubated within the following 72h, in order to compare our results to previous studies. Lastly, as performing a T-piece or PSV trial may influence the success of the initial SBT and duration between the initial SBT and successful extubation, we will compare the proportion of patients with simple (less than 24h), difficult (between 24 hours and 7 days) and prolonged (more than 7 days) weaning according to type of SBT.[4]

No risk is expected with these 2 SBTs, as both of them are routinely and daily performed in the clinical practice of participating centers. Type of SBT may modify only the physician's decision of extubation, and no other treatment will be added or modified.

In conclusion, the TIP-EX trial is an investigator-initiated pragmatic randomised controlled trial empowered to test the hypothesis that SBTs performed using PSV may hasten extubation without increasing the risk of reintubation in patients at high-risk of extubation failure as compared to T-piece. These 2 strategies have never been compared in patients at high-risk of reintubation, and therefore, this large trial may help to establish strong recommendations with a high level of evidence on a daily clinical practice for extubation in ICUs.

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Table 1: Study flow chart

Procedures and assessments	From inclusion to the initial SBT	From the initial SBT to extubation	From the initial SBT to day 28	Until ICU discharge and day 90
Inclusion and non-inclusion criteria	X			
Information and consent	X			X
Randomisation	X			
Characteristics of the patient[1]	X			
Characteristics of the initial SBT[2]	X			
Characteristics at time of extubation[3]		X		
Characteristics after extubation[4]			X	
Vital status				X

(1) Characteristics of the patient include age, gender, height, weight, severity score indicated by the Simplified Acute Physiological Score (SAPS) II and the Sepsis-related Organ Failure Assessment (SOFA) score, underlying chronic cardiac or respiratory disease, date and reason for admission/ intubation, duration of intubation prior to the initial SBT, ventilatory settings and blood gases before the initial SBT.

(2) Characteristics of the SBT include duration of the initial SBT, vital parameters during the initial SBT, and criteria for SBT failure.

(3) Characteristics at time of extubation include duration of weaning between the initial SBT and extubation, the number of SBTs attempts before extubation, classification according to the weaning difficulty, administrations of steroids before extubation, qualitative assessment of cough strength and amount of secretions at time of extubation.

(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.

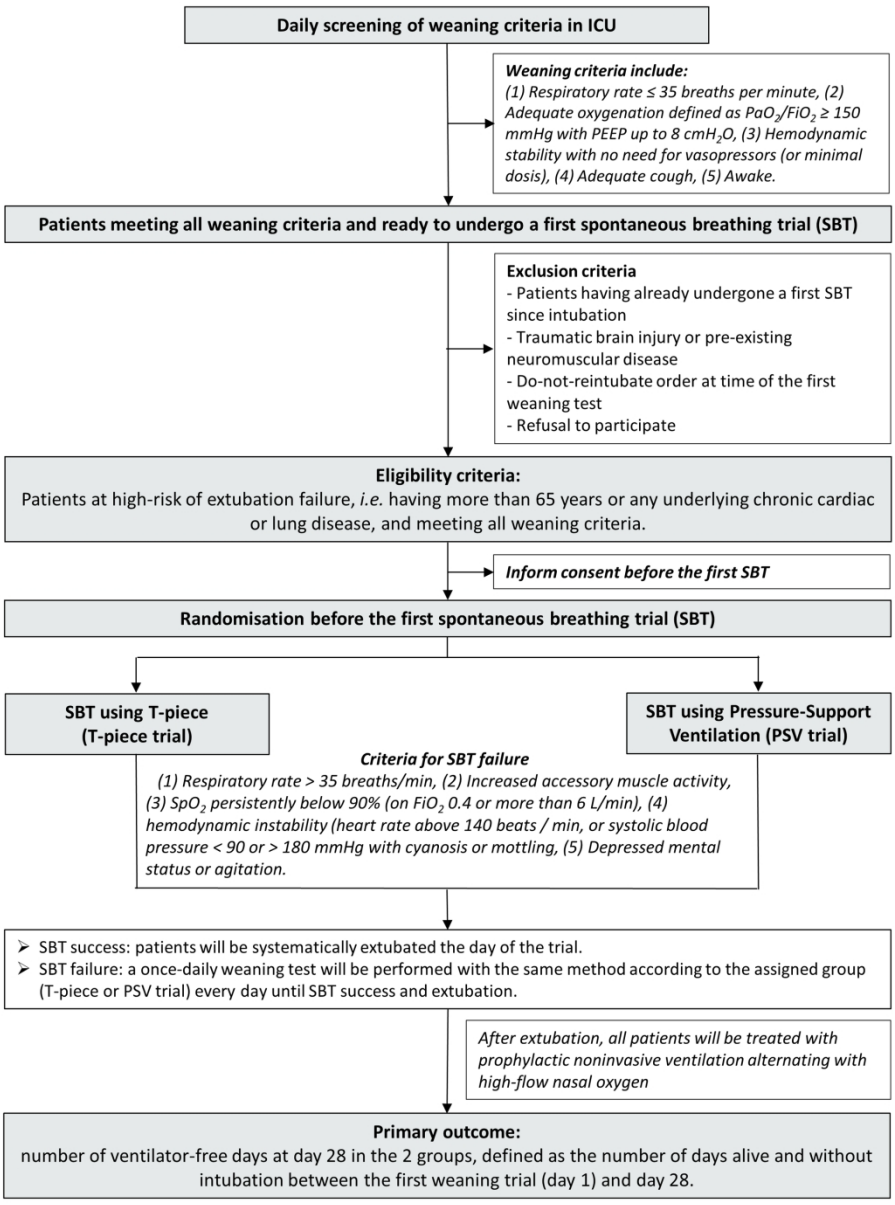

Figure 1: Flow chart of the patients and study design.

190x253mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item; No: Page	Description
Administrative information		
Title	1: **Page 1**	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a: **Page 3**	Trial identifier and registry name. If not yet registered, name of intended registry
	2b: **Page 3**	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4: **Page 3**	Sources and types of financial, material, and other support
Roles and responsibilities	5a: **Page 1-3**	Names, affiliations, and roles of protocol contributors
	5b: **Page 3**	Name and contact information for the trial sponsor
	5c: NA	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d: **Page 14**	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a: **Page 6**	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b: **Page 6**	Explanation for choice of comparators
Objectives	7: **Page 6-7**	Specific objectives or hypotheses

Trial design	8: **Page 7**	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	9: **Page 7**	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10: **Page 7-8**	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a: **Page 8-9**	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b: **Page 9**	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c: **Page 9**	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d: **Page 9**	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12: **Page 9-10**	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13: **Page 9-10**	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14: **Page 11**	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15: **Page 111**	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a: **Page 12**	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b: **Page 12**	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c: **Page 12**	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a: **Page 12**	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b: **Page 12**	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a: **Page 12**	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b: **Page 12**	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19: **Page 12**	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a: **Page 12-13**	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b: **Page 12-13**	Methods for any additional analyses (eg, subgroup and adjusted analyses)

	20c: **Page 12-13**	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a: **Page 13**	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b: **Page 13**	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22: **Page 13**	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23: **Page 13**	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24: **Page 14**	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25: **Page 14**	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a: **Page 14**	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b: **Page 14**	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27: **Page 14**	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28: **Page 14**	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29: **Page 14**	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a: **Page 14**	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33: NA	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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).

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Respiratory medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory physiology < THORACIC MEDICINE

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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).

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Contributors

AWT, RC and J-PF, in collaboration with all authors and the REVA network (Réseau Européen Ventilation Artificielle) designed the study and wrote the manuscript together. SR provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size with AWT.

AWT, RC, AG, SE, DC, LD, AR, CG, GL, JPQ, BLC, GP, NT, GP, GL, JR, GB, JD, MAN, AR, AD, NS, JPM, JB, AL, LA, QL, JD, EV, MAA, CL, MD, RR, SR, JPF contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Disclaimer

None

Competing interests

AWT reports financial support (payment for lectures and travel expenses coverage to attend scientific meetings) by Fisher & Paykel, Covidien, Maquet – Getinge, GE Healthcare.

J-PF reports consulting fees from Fisher & Paykel and SOS oxygène.

Ethics approval

The study has been approved by the central ethics committee (Ethics Committee Ile de France V, Paris, France) with the registration number 2019-A02151-56 (07 October 2019).

Data sharing

Data will be made available after reasonable request has been discussed among the steering committee.

Provenance and peer review

Not commissioned; externally peer reviewed.

ABSTRACT (300 words)

Introduction: In ICU, the decision of extubation is a critical time because mortality is particularly high in case of reintubation. To reduce that risk, guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before extubation in order to mimic the post-extubation physiological conditions. SBT is usually performed with a T-piece disconnecting the patient from the ventilator or with low levels of pressure-support ventilation (PSV). However, work of breathing is lower during PSV than during T-piece. Consequently, while PSV trial may hasten extubation, it may also increase the risk of reintubation. We are hypothesizing that as compared to T-piece, SBT performed using PSV may hasten extubation without increasing the risk of reintubation.

Methods and analysis: This study is an investigator-initiated, multicentre randomised controlled trial comparing T-piece versus PSV for SBTs in patients at high-risk of reintubation in ICUs. Nine-hundred patients will be randomised with a 1:1 ratio in two groups according to the type of SBT. 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 between the initial SBT (day 1) and day 28. Secondary outcomes include the number of days between the initial SBT and the first extubation attempt, weaning difficulty, the number of patients extubated after the initial SBT and not reintubated within the following 72 hours, the number of patients extubated within the 7 days following the initial SBT, the number of patients reintubated within the 7 days following extubation, length of stay in ICU, and mortality in ICU, at day 28 and at day 90.

Ethics and dissemination: The study has been approved by the central ethics committee "Ile de France V" (2019-A02151-56) and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04227639

Strengths and limitations of the study

►This large randomised controlled trial may help to establish strong recommendations on daily clinical practice for extubation in ICUs with a high level of evidence.

►Spontaneous breathing trials performed using T-piece or pressure-support ventilation have never been compared in the subset of patients at high-risk of reintubation.

►A large population of patients considered to be at high-risk for reintubation will be included. Patients older than 65 years or those with an underlying chronic cardiac or lung disease are easy to identify in clinical practice and represent nearly half of the patients extubated in ICUs.

►Limitation: The individual study assignments of the patients will not be masked. Given the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

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INTRODUCTION

Background and rationale

In ICU, the decision of extubation is a critical time because mortality is particularly high in case of extubation failure leading to reintubation.[1] The overall rate of reintubation after planned extubation is around 10% but may exceed 20% in patients at high-risk of extubation failure.[1] To reduce that risk, guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before extubation in all patients intubated at least 24h in order to mimic the post-extubation physiological conditions.[2] A standard test for extubation readiness is a SBT with a T-piece disconnecting the patient from the ventilator and providing additional oxygen (T-piece trial). Another widely used trial is performed without disconnecting the patient from the ventilator, using low levels of pressure-support ventilation (PSV trial). In recent large cohort studies these 2 types of SBTs were performed with nearly the same frequency.[3 4] However, these 2 trials are not equivalent in terms of patient breathing effort. Physiological studies have shown that work of breathing measured during T-piece was similar to work of breathing after extubation.[5] In contrast, work of breathing is markedly lower during PSV trial than during T-piece. Consequently, while PSV trial may potentially hasten extubation, it may also increase the risk of reintubation by underestimating the work of breathing needed after extubation.[6]

A large randomised controlled trial recently found that the proportion of patients successfully extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-piece trial for 2 hours.[7] In this study, reintubation rates did not differ using PSV trial or T-piece. These findings confirm that PSV trial is an easier test to pass than T-piece trial, and that it may hasten extubation without an increased risk of reintubation. However, in this study the proportion of patients with simple weaning was particularly high and patients with weaning difficulties were not monitored up until extubation, thereby limiting the application of these findings to simple weaning. Moreover, reintubation rates were particularly low meaning that the population mainly included patients at low-risk of extubation failure.[8] The latest American guidelines suggested an initial SBT using PSV rather than T-piece to hasten extubation.[2] The strength of this recommendation was only conditional given the moderate certainty of evidence. To improve the level of evidence of daily clinical practice, we have decided to assess whether SBTs performed using PSV may hasten extubation without increasing the risk of reintubation in patients at high-risk of extubation failure as compared to T-piece.

Objectives

We aim to conduct a prospective multicentre randomised controlled trial comparing two strategies of extubation performing SBT with T-piece or with PSV in patients at high-risk of extubation failure. Our hypothesis is that SBTs with PSV may hasten extubation without increasing the risk of reintubation.

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, (2) probability of extubation within the 72 hours and within the 7 days following the initial SBT, (3) proportion of patients with simple (≤ 24h), difficult (> 24 hours and ≤ 7 days) or prolonged (> 7 days) weaning, (4) proportion of patients extubated after the initial SBT and not reintubated within the following 72 hours, (5) weaning duration between the initial SBT and the first extubation attempt among extubated patients, (6) probability of reintubation within the 72 hours and within the 7 days following extubation, (7) proportion of patients with post-extubation respiratory failure within the 7 days following extubation, (8) length of stay in ICU, (9) the mortality in ICU, at day 28 and at day 90.

Trial design

The TIP-EX study is an investigator-initiated, multicentre, randomised, controlled, open-label trial comparing a strategy of extubation in patients at high-risk of reintubation in ICUs. Patients will randomly be assigned to one of the two groups performing SBT with T-piece or with pressure-support, with a 1:1 ratio.

METHODS: PATICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The TIP-EX study is taking place in 31 ICUs in France. Patient flow chart is detailed in the **Figure**.

Eligibility criteria

Inclusion criteria

Adult patients intubated more than 24 hours in ICU and at high-risk of reintubation will be eligible as soon as possible once they meet all weaning criteria for an initial SBT.

Patients will be considered at high-risk of extubation failure according to the following criteria[9]: patients older than 65 years, or those having any underlying chronic cardiac or lung disease. Underlying chronic cardiac diseases include left ventricular dysfunction (whatever the cause) defined by left ventricular ejection fraction ≤ 45%, history of cardiogenic pulmonary oedema, documented ischemic heart disease or permanent atrial fibrillation. 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 ($PaCO_2$ > 45 mm Hg) suggesting obesity-hypoventilation syndrome, or 3) rib cage deformation suggesting restrictive pulmonary disease.

According to the international conference consensus on weaning,[10] 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 positive end-expiratory pressure (PEEP) ≤ 8 cmH_2O, hemodynamic stability with no need for vasopressors (or minimal dosis ≤ 0.3 μg/kg/min), adequate cough, patient awake with a Richmond Agitation-Sedation Scale between +1 and -2.[11]

Exclusion criteria

Patients fulfilling one of the following criteria will not be included: patients having already undergone an initial SBT at any time since intubation, patients admitted for traumatic brain injury or with pre-existing peripheral neuromuscular disease (underlying myopathy or myasthenia gravis), patients with do-not-reintubate order at time of the initial SBT, patients previously included in the study, patients without health insurance coverage, people under protection (pregnant or breastfeeding women, minor patients, subjects with guardianship or under law protection), or refusal to participate.

Intervention

Spontaneous breathing trials before extubation

Patients included will be randomised before the initial SBT and assigned to one of the following 2 groups: 1) In patients assigned to control group all SBTs will be performed using T-piece; 2) In patients assigned to experimental group all SBTs will be performed using PSV with a PS level of 8 cm H_2O without PEEP.

Control group: T-piece trial

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.

Interventional group: PSV trial

The PSV trial will be performed without disconnecting the patient from the ventilator, by using a low level of pressure-support (PS of 8 cm H_2O) with a $FiO_2 \leq 40\%$ without PEEP, and without activation of automatic tube compensation (ATC) mode, while continuously monitoring respiratory rate and tidal volume on the ventilator display.

Duration of treatment and strategy of weaning and extubation

In both groups, the SBT will be performed for around 1 hour according to weaning guidelines.[10] In case of SBT success, patients will be systematically extubated the day of the trial. After a T-piece trial, patients will be reconnected to the ventilator with prior ventilatory settings for around 1-h rest before extubation to avoid exhaustion.[12]

In case of SBT failure, a once-daily SBT will be performed with the same method according to the assigned group (T-piece or PSV trial) every day as long as weaning criteria are met until SBT success and extubation. SBT failure will be defined according to the usual criteria from the international conference consensus on weaning,[10] as development during the trial of any of the following events: (1) respiratory rate > 35 breaths/min, (2) increased accessory muscle activity, (3) SpO_2 persistently below 90% (or below 88% in case of underlying chronic lung disease) on $FiO_2 \geq 0.4$ or at least 6 L/min of oxygen, (4) hemodynamic instability defined as heart rate persistently above 140 beats / min, or systolic blood pressure < 90 or > 180 mmHg, with signs of hypoperfusion (appearance of cyanosis or mottling), (5) depressed mental status or agitation.

All patients will be followed until day 28 after the initial SBT. In the event of extubation failure and reintubation, weaning will then be performed with the same method according to the assigned group (T-piece or PSV trial). 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.[13 14]

Outcomes

Primary outcome

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.

Secondary outcomes

Secondary outcome variables include the following:

1. The number of days alive and without mechanical ventilation (including intubation and non-invasive ventilation) between the initial SBT (day 1) and day 28.
2. The number of patients extubated within the 72 hours and within the 7 days following the initial SBT.
3. The number of patients extubated after simple (less than 24h), difficult (between 24 hours and 7 days) or prolonged (more than 7 days) weaning.
4. The number of patients extubated after the initial SBT and not reintubated within the following 72 hours.
5. The number of days between the initial SBT and the first extubation attempt.
6. The number of patients reintubated within the 72 hours and within the 7 days following extubation.
7. The number of patients with post-extubation respiratory failure within the 7 days following extubation.
8. Length of stay in ICU.
9. Mortality in ICU, at day 28 and at day 90.

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 pH < 7.35 units and $PaCO_2$ > 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 PaO_2/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 pH < 7.25 units and $PaCO_2$ > 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 (PaO_2/FiO_2) < 100 mm Hg.

Sample size

We determined that enrolment of 900 patients would provide a power of 80% to show an absolute prolonged duration of mechanical ventilation by 2 days (number of ventilator-free days reduced by 2 days) using the T-piece trial as compared to the PSV trial at a two-sided alpha level of 0.05.

Expected number of patients to be included in the study: statistical justification

We calculated the number of patients to include based on results of our previous cohort.[15] In this study, the number of ventilator-free days at day 28 among the 150 patients at high-risk for reintubation was 23 days (± 9) in mean, and all patients were extubated following a strategy of weaning using PSV trials. In the present study, a number of patients will never be extubated, *i.e.* either died or still under mechanical ventilation at day 28, and thus with no ventilator-free days. According to a recent large cohort study,[4] these patients will represent around 2 to 3% of patients. Thus, we calculated that the number of ventilator-free days at day 28 would be 22 days (± 10) days using a PSV trial. In keeping with these results, we determined that enrolment of 786 patients would provide a power of 80% to show absolute prolonged duration of mechanical ventilation by 2 days (number of ventilator-free days reduced by 2 days) using the T-piece trial as compared to the PSV trial at a two-sided alpha level of 0.05. However, given the non-normal distribution of ventilator-free days in this population, the number of patients needed to be included was increased by 1.045 times in each group in order to compare the two groups with non-parametric tests.[16] Therefore, we estimated that 820 patients will be needed. To ensure analysing at least 820 patients for primary and secondary outcomes taking into account of patients with withdrawal of consent or lost to follow-up, we decided to increase the number of inclusions by 10%, *i.e.* 900 patients in total (450 patients per group).

Recruitment

The expected initial duration of patient enrolment is 2 years, starting in January 2020.

► End of 2018: national grant award;

► 2019: approval by an independent ethics committee;

► 2020-2021: inclusion of patients (the first participant was enrolled the 31st January 2020)

► 2021-2022: end of inclusions, monitoring of participating centres and queries to investigators; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database;

► 2022-2023: data analysis, writing of the manuscript and submission for publication.

METHODS: ASSIGNEMENT OF INTERVENTION, DATA COLLECTION, MANAGEMENT AND ANALYSIS

Allocation and sequence intervention

After obtaining consent from the patient or his/her relative, all inclusion/exclusion criteria will be verified by the investigator before randomization. Before the initial SBT the investigator will randomize patients to determine the type of trial allocated (T-piece or PSV trial). Randomization will be stratified on centre and carried out by connecting to the electronic case report form (e-CRF) website https://chu-poitiers.hugo-online.fr/CSOnline/ after fulfilling the "randomisation" page including all the criteria for eligibility.

Data collection and management

Data will be collected on an e-CRF by a trained investigator or research assistant at each centre. Patient follow-up and data collected are detailed in the study flow chart **(Table 1).**

Statistical methods

All the analyses will be performed by the study statistician according to a predefined statistical analysis plan and using statistical software (SAS, V.9.4; SAS Institute; USA). A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Descriptive analysis of patient groups at baseline

The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion/exclusion criteria for each patient. The continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges and extreme values or mean and standard deviation), while indicating the number of missing data. The category variables will be presented in the form of absolute frequency and percentage in each modality. Eligibility criteria will be verified on the basis of the data recorded in the case reports. Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the protocol will be described and analysed on a case-by-case basis.

Analysis pertaining to the main criteria of evaluation

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, will be compared between the 2 groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate. A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Analysis pertaining to the secondary criteria of evaluation

Extubation success and reintubation rates at the various pre-defined times, difficulty of weaning (simple, difficult or prolonged), post-extubation respiratory failure rates, and mortality will be compared between the 2 groups by means of the Chi2 test (or Fisher's exact test).

Weaning duration and lengths of stay will be compared between the two treatment groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate.

Kaplan–Meier curves will be plotted to assess the probability of extubation from the initial SBT to the following 72 hours and to the following 7 days, the probability of reintubation from extubation to the following 72 hours and to the following 7 days, and the probability of death between the initial SBT until day 90, and will be compared by means of the log-rank test.

The variables associated with extubation success and reintubation with a p value <0.20 will be assessed by means of a multivariate logistic regression analysis or Cox proportional-hazard regression analysis using a backward-selection procedure as appropriate.

The final model will include variables significantly associated with intubation with a P value of less than 0.05 and will be expressed using adjusted relative risk and odds ratio or hazard ratio with 95% confident interval.

Predetermined Subgroup Analysis

Patients with prolonged duration of mechanical ventilation may have weaning difficulties and an increased risk of reintubation.[4 15] Therefore, subgroups analyses will be performed for primary and secondary outcomes according to the duration of mechanical ventilation (> 7 versus ≤ 7 days) prior to the initial SBT after an interaction test carried out to detect heterogeneity of treatment effect between patients with a prior duration of mechanical ventilation of more than 7 days and the others.

Data monitoring

The trial will be overseen by a steering committee regarding the progression and monitoring of the study at REVA (Réseau Européen Ventilation Artificielle) Network meetings every 6 months.

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. 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. Although the individual study assignments of the patients cannot be masked, the coordinating centre and all the investigators will remain unaware of the study group outcomes until the database will be locked.

ETHICS AND DISSEMINATION

The study has been approved by the central ethics committee (Ethics Committee Ile de France V, Paris, France) with the registration number 2019-A02151-56 (07 October 2019).

Consent or assent

The patient will be included after having provided a 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.

Confidentiality

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

Declaration of interest

The TIP-EX study is an investigator-initiated trial supported by the French Ministry of Health with funds obtained in 2018 from a national hospital clinical research program (Programme Hospitalier de Recherche Clinique National 2018). The study is promoted by the University Hospital of Poitiers.

Access to data

All investigators will have access to the final data set. Investigators will make available the documents and individual data strictly required for monitoring, quality control and audit of the study to persons having access to them, in accordance with the statutory and regulatory provisions in place (articles L.1121-3 and R.5121-13 of the French Public Health Code).

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the executive committee. Rules of publication will follow the international recommendations according to *The Uniform Requirements for Manuscripts* (ICMJE, April 2010).

Patient and public Involvement

Patients and public are not involved in the study

DISCUSSION

According to the physiological results,[5] PSV trial is an easier test than T-piece trial and may potentially increase the risk of reintubation by underestimating the work of breathing needed after extubation.[6] However, no study has demonstrated an increased reintubation rate using PSV trial as compared to T-trial.

Recently, a large randomised controlled trial including 1153 patients found that the proportion of patients successfully extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-piece trial for 2 hours.[7] However, the proportion of patients with simple weaning (*i.e.* patients extubated after the initial SBT) was particularly high in this study (nearly 90%) whereas usual rates in the literature are closer to 60-70%.[3] Moreover, patients with difficult weaning (*i.e.* those who failed the initial SBT) were not monitored up until extubation, thereby limiting application of these findings to simple weaning, and not taking into account patients with weaning difficulties.[3] [4] Lastly, reintubation rates were particularly low (around 11%) meaning that the population mainly included patients at low-risk of extubation failure.[8] Although an easy test using PSV trial may hasten extubation, inclusion of patients at low-risk with reintubation rates around 10% or less might not enable to detect an increased risk of extubation failure. Therefore, to avoid underpowering the study and so as be able to detect the risk, we decided to focus on patients at high-risk of extubation failure and to include patients with weaning difficulties. In this population at high-risk of reintubation a recent post-host analysis from a large randomised controlled trial showed that execution of an initial SBT using PSV significantly increased the proportion of patients successfully extubated within the following 72 hours as compared with T-piece.[17] However, a large prospective clinical trial is needed to confirm these findings in this population before being in a position to apply this weaning strategy to all ICU patients.

To assess as primary outcome the duration of weaning on the one the hand and the risk of reintubation on the other hand, we decided to assess the number of ventilator-free days at day 28.

This criterion has the advantage of evaluating the 2 end-points (duration of weaning and risk of reintubation) with one and the same criterion. In previous studies, primary outcome was the number of patients extubated after the initial SBT and not reintubated at 48h or 72h.[7 18 19] Although this outcome has weaknesses (too early and focusing only on simple weaning), we will also assess the number of patients extubated after the initial SBT and not reintubated within the following 72h, in order to compare our results to previous studies. Lastly, as performing a T-piece or PSV trial may influence the success of the initial SBT and duration between the initial SBT and successful extubation, we will compare the proportion of patients with simple, difficult and prolonged weaning according to type of SBT. 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.[4]

No risk is expected with these 2 SBTs, as both of them are routinely and daily performed in the clinical practice of participating centers. Type of SBT may modify only the physician's decision of extubation, and no other treatment will be added or modified.

In conclusion, the TIP-EX trial is an investigator-initiated pragmatic randomised controlled trial empowered to test the hypothesis that SBTs performed using PSV may hasten extubation without increasing the risk of reintubation in patients at high-risk of extubation failure as compared to T-piece. These 2 strategies have never been compared in patients at high-risk of reintubation, and therefore, this large trial may help to establish strong recommendations with a high level of evidence on a daily clinical practice for extubation in ICUs.

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Table 1: Study flow chart

Procedures and assessments	From inclusion to the initial SBT	From the initial SBT to extubation	From the initial SBT to day 28	Until ICU discharge and day 90
Inclusion and non-inclusion criteria	X			
Information and consent	X			X
Randomisation	X			
Characteristics of the patient[1]	X			
Characteristics of the initial SBT[2]	X			
Characteristics at time of extubation[3]		X		
Characteristics after extubation[4]			X	
Vital status				X

(1) Characteristics of the patient include age, gender, height, weight, severity score indicated by the Simplified Acute Physiological Score (SAPS) II and the Sepsis-related Organ Failure Assessment (SOFA) score, underlying chronic cardiac or respiratory disease, date and reason for admission/ intubation, duration of intubation prior to the initial SBT, ventilatory settings and blood gases before the initial SBT.

(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.

(3) Characteristics at time of extubation include duration of weaning between the initial SBT and extubation, the number of SBTs attempts before extubation, classification according to the weaning difficulty, administrations of steroids before extubation, qualitative assessment of cough strength and amount of secretions at time of extubation.

(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), 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.

FIGURE LEGEND

Figure 1: Flow chart of the patients and study design.

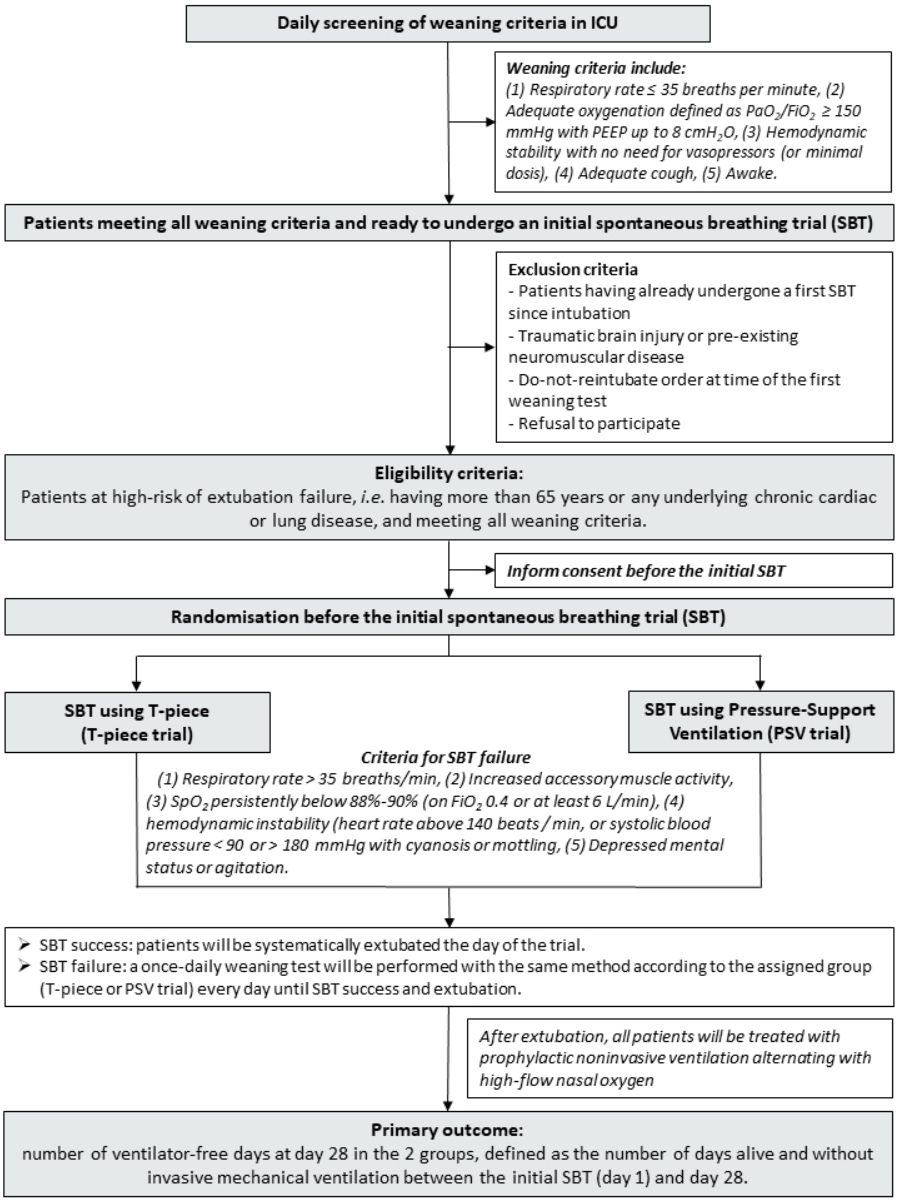

Figure 1: Flow chart of the patients and study design.

190x254mm (96 x 96 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item; No: Page	Description
Administrative information		
Title	1: **Page 1**	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a: **Page 3**	Trial identifier and registry name. If not yet registered, name of intended registry
	2b: **Page 3**	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4: **Page 3**	Sources and types of financial, material, and other support
Roles and responsibilities	5a: **Page 1-3**	Names, affiliations, and roles of protocol contributors
	5b: **Page 3**	Name and contact information for the trial sponsor
	5c: NA	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d: **Page 14**	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a: **Page 6**	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b: **Page 6**	Explanation for choice of comparators
Objectives	7: **Page 6-7**	Specific objectives or hypotheses

Trial design	8: **Page 7**	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	9: **Page 7**	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10: **Page 7-8**	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a: **Page 8-9**	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b: **Page 9**	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c: **Page 9**	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d: **Page 9**	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12: **Page 9-10**	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13: **Page 9-10**	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14: **Page 11**	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15: **Page 111**	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a: **Page 12**	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b: **Page 12**	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c: **Page 12**	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a: **Page 12**	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b: **Page 12**	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a: **Page 12**	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b: **Page 12**	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19: **Page 12**	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a: **Page 12-13**	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b: **Page 12-13**	Methods for any additional analyses (eg, subgroup and adjusted analyses)

	20c: **Page 12-13**	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a: **Page 13**	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b: **Page 13**	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22: **Page 13**	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23: **Page 13**	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24: **Page 14**	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25: **Page 14**	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a: **Page 14**	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b: **Page 14**	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27: **Page 14**	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28: **Page 14**	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29: **Page 14**	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a: **Page 14**	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32: model consent form available in supplementary files	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33: NA	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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).

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Secondary Subject Heading:	Respiratory medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory physiology < THORACIC MEDICINE

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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).

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Contributors

AWT, RC and J-PF, in collaboration with all authors and the REVA network (Réseau Européen Ventilation Artificielle) designed the study and wrote the manuscript together. SR provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size with AWT.

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Disclaimer

None

Competing interests

AWT reports financial support (payment for lectures and travel expenses coverage to attend scientific meetings) by Fisher & Paykel, Covidien, Maquet – Getinge, GE Healthcare.

J-PF reports consulting fees from Fisher & Paykel and SOS oxygène.

Ethics approval

The study has been approved by the central ethics committee (Ethics Committee Ile de France V, Paris, France) with the registration number 2019-A02151-56 (07 October 2019).

Data sharing

Data will be made available after reasonable request and it has been discussed among the steering committee.

Provenance and peer review

Not commissioned; externally peer reviewed.

ABSTRACT (300 words)

Introduction: In intensive care unit (ICU), the decision of extubation is a critical time because mortality is particularly high in case of reintubation. To reduce that risk, guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before extubation in order to mimic the post-extubation physiological conditions. SBT is usually performed with a T-piece disconnecting the patient from the ventilator or with low levels of pressure-support ventilation (PSV). However, work of breathing is lower during PSV than during T-piece. Consequently, while PSV trial may hasten extubation, it may also increase the risk of reintubation. We hypothesize that, compared to T-piece, SBT performed using PSV may hasten extubation without increasing the risk of reintubation.

Methods and analysis: This study is an investigator-initiated, multicentre randomised controlled trial comparing T-piece versus PSV for SBTs in patients at high-risk of reintubation in ICUs. Nine-hundred patients will be randomised with a 1:1 ratio in two groups according to the type of SBT. 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 between the initial SBT (day 1) and day 28. Secondary outcomes include the number of days between the initial SBT and the first extubation attempt, weaning difficulty, the number of patients extubated after the initial SBT and not reintubated within the following 72 hours, the number of patients extubated within the 7 days following the initial SBT, the number of patients reintubated within the 7 days following extubation, in-ICU length of stay, and mortality in ICU, at day 28 and at day 90.

Ethics and dissemination: The study has been approved by the central ethics committee “Ile de France V” (2019-A02151-56) and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04227639

Strengths and limitations of the study

►This large randomised controlled trial may help to establish strong recommendations on daily clinical practice for extubation in intensive care units with a high level of evidence.

►Spontaneous breathing trials performed using T-piece or pressure-support ventilation have never been compared in the subset of patients at high-risk of reintubation.

►A large population of patients considered to be at high-risk for reintubation will be included. Patients older than 65 years or those with an underlying chronic cardiac or lung disease are easy to identify in clinical practice and represent nearly half of the patients extubated in intensive care units.

►Limitation: The individual study assignments of the patients will not be masked. Given the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

Words count: 4236

INTRODUCTION

Background and rationale

In intensive care unit (ICU), the decision of extubation is a critical time because mortality is particularly high in case of extubation failure leading to reintubation.[1] The overall rate of reintubation after planned extubation is around 10% but may exceed 20% in patients at high-risk of extubation failure.[1] To reduce that risk, guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before extubation in all patients intubated at least 24h in order to mimic the post-extubation physiological conditions.[2] A standard test for extubation readiness is a SBT with a T-piece disconnecting the patient from the ventilator and providing additional oxygen (T-piece trial). Another widely used trial is performed without disconnecting the patient from the ventilator, using low levels of pressure-support ventilation (PSV trial). In recent large cohort studies these 2 types of SBTs were performed with nearly the same frequency.[3 4] However, these 2 trials are not equivalent in terms of patient breathing effort. Physiological studies have shown that work of breathing measured during T-piece was similar to work of breathing after extubation.[5] In contrast, work of breathing is markedly lower during PSV trial than during T-piece. Consequently, while PSV trial may potentially hasten extubation, it may also increase the risk of reintubation by underestimating the work of breathing needed after extubation.[6]

A large randomised controlled trial recently found that the proportion of patients successfully extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-piece trial for 2 hours.[7] In this study, reintubation rates did not differ using PSV trial or T-piece. These findings confirm that PSV trial is an easier test to pass than T-piece trial, and that it may hasten extubation without an increased risk of reintubation. However, in this study the proportion of patients with simple weaning was particularly high and patients with weaning difficulties were not monitored up until extubation, thereby limiting the application of these findings to simple weaning. Moreover, reintubation rates were particularly low meaning that the population mainly included patients at low-risk of extubation failure.[8] The latest American guidelines suggested an initial SBT using PSV rather than T-piece to hasten extubation.[2] The strength of this recommendation was only conditional given the moderate certainty of evidence. To improve the level of evidence of daily clinical practice, we have decided to assess whether SBTs performed using PSV may hasten extubation without increasing the risk of reintubation in patients at high-risk of extubation failure as compared to T-piece.

Objectives

We aim to conduct a prospective multicentre randomised controlled trial comparing two strategies of extubation performing SBT with T-piece or with PSV in patients at high-risk of extubation failure. Our hypothesis is that SBTs with PSV may hasten extubation without increasing the risk of reintubation.

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, (2) probability of extubation within the 72 hours and within the 7 days following the initial SBT, (3) proportion of patients with simple (≤ 24h), difficult (> 24 hours and ≤ 7 days) or prolonged (> 7 days) weaning, (4) proportion of patients extubated after the initial SBT and not reintubated within the following 72 hours, (5) weaning duration between the initial SBT and the first extubation attempt among extubated patients, (6) probability of reintubation within the 72 hours and within the 7 days following extubation, (7) proportion of patients with post-extubation respiratory failure within the 7 days following extubation, (8) length of stay in ICU, (9) the mortality in ICU, at day 28 and at day 90.

Trial design

The TIP-EX study is an investigator-initiated, multicentre, randomised, controlled, open-label trial comparing a strategy of extubation in patients at high-risk of reintubation in ICUs. Patients will randomly be assigned to one of the two groups performing SBT with T-piece or with pressure-support, with a 1:1 ratio.

METHODS: PATICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The TIP-EX study is taking place in 31 ICUs in France. Patient flow chart is detailed in the **Figure**.

Eligibility criteria

Inclusion criteria

Adult patients intubated more than 24 hours in ICU and at high-risk of reintubation will be eligible as soon as possible once they meet all weaning criteria for an initial SBT.

Patients will be considered at high-risk of extubation failure according to the following criteria[9]: patients older than 65 years, or those having any underlying chronic cardiac or lung disease. Underlying chronic cardiac diseases include left ventricular dysfunction (whatever the cause) defined by left ventricular ejection fraction ≤ 45%, history of cardiogenic pulmonary oedema, documented ischemic heart disease or permanent atrial fibrillation. 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 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 ($PaCO_2$ > 45 mm Hg) suggesting obesity-hypoventilation syndrome, or 3) rib cage deformation suggesting restrictive pulmonary disease.

According to the international conference consensus on weaning,[10] 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 positive end-expiratory pressure ≤ 8 cmH_2O, hemodynamic stability with no need for vasopressors (or minimal dosis ≤ 0.3 μg/kg/min), adequate cough, patient awake with a Richmond Agitation-Sedation Scale between +1 and -2.[11]

Exclusion criteria

Patients fulfilling one of the following criteria will not be included: patients having already undergone an initial SBT at any time since intubation, patients admitted for traumatic brain injury or with pre-existing peripheral neuromuscular disease (underlying myopathy or myasthenia gravis), patients with do-not-reintubate order at time of the initial SBT, patients previously included in the study, patients without health insurance coverage, people under protection (pregnant or breastfeeding women, minor patients, subjects with guardianship or under law protection), or refusal to participate.

Intervention

Spontaneous breathing trials before extubation

Patients included will be randomised before the initial SBT and assigned to one of the following 2 groups: 1) In patients assigned to control group all SBTs will be performed using T-piece; 2) In patients assigned to experimental group all SBTs will be performed using PSV with a PS level of 8 cm H_2O without positive end-expiratory pressure.

Control group: T-piece trial

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.

Interventional group: PSV trial

The PSV trial will be performed without disconnecting the patient from the ventilator, by using a low level of pressure-support (PS of 8 cm H_2O) with a FiO_2 ≤ 40% without positive end-expiratory pressure, and without activation of automatic tube compensation (ATC) mode, while continuously monitoring respiratory rate and tidal volume on the ventilator display.

Duration of treatment and strategy of weaning and extubation

In both groups, the SBT will be performed for around 1 hour according to weaning guidelines.[10] In case of SBT success, patients will be systematically extubated the day of the trial. After a successful T-piece trial, patients will be reconnected to the ventilator with prior ventilatory settings for around 1-hour before extubation to avoid exhaustion. A previous study showed that a 1-hour period at rest under mechanical ventilation after SBT trial with T-piece may improve outcome.[12] We therefore decided to apply this protocol in our interventions.

In case of SBT failure, a once-daily SBT will be performed with the same method according to the assigned group (T-piece or PSV trial) every day as long as weaning criteria are met until SBT success and extubation. SBT failure will be defined according to the usual criteria from the international conference consensus on weaning,[10] as development during the trial of any of the following events: (1) respiratory rate > 35 breaths/min, (2) increased accessory muscle activity, (3) SpO_2 persistently below 90% (or below 88% in case of underlying chronic lung disease) on $FiO_2 \geq 0.4$ or at least 6 L/min of oxygen, (4) hemodynamic instability defined as heart rate persistently above 140 beats / min, or systolic blood pressure < 90 or > 180 mmHg, with signs of hypoperfusion (appearance of cyanosis or mottling), (5) depressed mental status or agitation.

All patients will be followed until day 28 after the initial SBT. In the event of extubation failure and reintubation, weaning will then be performed with the same method according to the assigned group (T-piece or PSV trial). 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.[13 14]

Outcomes

Primary outcome

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.

Secondary outcomes

Secondary outcome variables include the following:

1. The number of days alive and without mechanical ventilation (including intubation and non-invasive ventilation) between the initial SBT (day 1) and day 28.
2. The number of patients extubated within the 72 hours and within the 7 days following the initial SBT.
3. The number of patients extubated after simple (less than 24h), difficult (between 24 hours and 7 days) or prolonged (more than 7 days) weaning.
4. The number of patients extubated after the initial SBT and not reintubated within the following 72 hours.
5. The number of days between the initial SBT and the first extubation attempt.
6. The number of patients reintubated within the 72 hours and within the 7 days following extubation.
7. The number of patients with post-extubation respiratory failure within the 7 days following extubation.
8. Length of stay in ICU.
9. Mortality in ICU, at day 28 and at day 90.

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 pH < 7.35 units and $PaCO_2$ > 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 PaO_2/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 pH < 7.25 units and $PaCO_2$ > 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 (PaO_2/FiO_2) < 100 mm Hg.

Sample size

We determined that enrolment of 900 patients would provide a power of 80% to show an absolute prolonged duration of mechanical ventilation by 2 days (number of ventilator-free days reduced by 2 days) using the T-piece trial as compared to the PSV trial at a two-sided alpha level of 0.05.

Expected number of patients to be included in the study: statistical justification

We calculated the number of patients to include based on results of our previous cohort.[15] In this study, the number of ventilator-free days at day 28 among the 150 patients at high-risk for reintubation was 23 days (± 9) in mean, and all patients were extubated following a strategy of weaning using PSV trials. In the present study, a number of patients will never be extubated, *i.e.* either died or still under mechanical ventilation at day 28, and thus with no ventilator-free days. According to a recent large cohort study,[4] these patients will represent around 2 to 3% of patients. Thus, we calculated that the number of ventilator-free days at day 28 would be 22 days (± 10) days using a PSV trial. In keeping with these results, we determined that enrolment of 786 patients would provide a power of 80% to show absolute prolonged duration of mechanical ventilation by 2 days (number of ventilator-free days reduced by 2 days) using the T-piece trial as compared to the PSV trial at a two-sided alpha level of 0.05. However, given the non-normal distribution of ventilator-free days in this population, the number of patients needed to be included was increased by 1.045 times in each group in order to compare the two groups with non-parametric tests.[16] Therefore, we estimated that 820 patients will be needed. To ensure analysing at least 820 patients for primary and secondary outcomes taking into account of patients with withdrawal of consent or lost to follow-up, we decided to increase the number of inclusions by 10%, *i.e.* 900 patients in total (450 patients per group).

Recruitment

The expected initial duration of patient enrolment is 2 years, starting in January 2020.

► End of 2018: national grant award;

► 2019: approval by an independent ethics committee;

► 2020-2021: inclusion of patients (the first participant was enrolled the 31st January 2020)

► 2021-2022: end of inclusions, monitoring of participating centres and queries to investigators; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database;

► 2022-2023: data analysis, writing of the manuscript and submission for publication.

METHODS: ASSIGNEMENT OF INTERVENTION, DATA COLLECTION, MANAGEMENT AND ANALYSIS

Allocation and sequence intervention

After obtaining consent from the patient or his/her relative, all inclusion/exclusion criteria will be verified by the investigator before randomization. Before the initial SBT the investigator will randomize patients to determine the type of trial allocated (T-piece or PSV trial). Randomization will be stratified on centre and carried out by connecting to the electronic case report form (e-CRF) website https://chu-poitiers.hugo-online.fr/CSOnline/ after fulfilling the "randomisation" page including all the criteria for eligibility.

Data collection and management

Data will be collected on an e-CRF by a trained investigator or research assistant at each centre. Patient follow-up and data collected are detailed in the study flow chart **(Table 1).**

Statistical methods

All the analyses will be performed by the study statistician according to a predefined statistical analysis plan and using statistical software (SAS, V.9.4; SAS Institute; USA). A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Descriptive analysis of patient groups at baseline

The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion/exclusion criteria for each patient. The continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges and extreme values or mean and standard deviation), while indicating the number of missing data. The category variables will be presented in the form of absolute frequency and percentage in each modality. Eligibility criteria will be verified on the basis of the data recorded in the case reports. Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the protocol will be described and analysed on a case-by-case basis.

Analysis pertaining to the main criteria of evaluation

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, will be compared between the 2 groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate. A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Analysis pertaining to the secondary criteria of evaluation

Extubation success and reintubation rates at the various pre-defined times, difficulty of weaning (simple, difficult or prolonged), post-extubation respiratory failure rates, and mortality will be compared between the 2 groups by means of the Chi2 test (or Fisher's exact test).

Weaning duration and lengths of stay will be compared between the two treatment groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate.

Kaplan–Meier curves will be plotted to assess the probability of extubation from the initial SBT to the following 72 hours and to the following 7 days, the probability of reintubation from extubation to the following 72 hours and to the following 7 days, and the probability of death between the initial SBT until day 90, and will be compared by means of the log-rank test.

The variables associated with extubation success and reintubation with a p value <0.20 will be assessed by means of a multivariate logistic regression analysis or Cox proportional-hazard regression analysis using a backward-selection procedure as appropriate.

The final model will include variables significantly associated with intubation with a P value of less than 0.05 and will be expressed using adjusted relative risk and odds ratio or hazard ratio with 95% confident interval.

Predetermined Subgroup Analysis

Patients with prolonged duration of mechanical ventilation may have weaning difficulties and an increased risk of reintubation.[4 15] Therefore, subgroups analyses will be performed for primary and secondary outcomes according to the duration of mechanical ventilation (> 7 versus ≤ 7 days) prior to the initial SBT after an interaction test carried out to detect heterogeneity of treatment effect between patients with a prior duration of mechanical ventilation of more than 7 days and the others.

Data monitoring

The trial will be overseen by a steering committee regarding the progression and monitoring of the study at REVA (Réseau Européen Ventilation Artificielle) Network meetings every 6 months.

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. 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. Although the individual study assignments of the patients cannot be masked, the coordinating centre and all the investigators will remain unaware of the study group outcomes until the database will be locked.

ETHICS AND DISSEMINATION

The study has been approved by the central ethics committee (Ethics Committee Ile de France V, Paris, France) with the registration number 2019-A02151-56 (07 October 2019).

Consent or assent

The patient will be included after having provided a 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.

Confidentiality

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

Declaration of interest

The TIP-EX study is an investigator-initiated trial supported by the French Ministry of Health with funds obtained in 2018 from a national hospital clinical research program (Programme Hospitalier de Recherche Clinique National 2018). The study is promoted by the University Hospital of Poitiers.

Access to data

All investigators will have access to the final data set. Investigators will make available the documents and individual data strictly required for monitoring, quality control and audit of the study to persons having access to them, in accordance with the statutory and regulatory provisions in place (articles L.1121-3 and R.5121-13 of the French Public Health Code).

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the executive committee. Rules of publication will follow the international recommendations according to *The Uniform Requirements for Manuscripts* (ICMJE, April 2010).

Patient and public Involvement

Patients and public are not involved in the study

DISCUSSION

According to the physiological results,[5] PSV trial is an easier test than T-piece trial and may potentially increase the risk of reintubation by underestimating the work of breathing needed after extubation.[6] However, no study has demonstrated an increased reintubation rate using PSV trial as compared to T-trial.

Recently, a large randomised controlled trial including 1153 patients found that the proportion of patients successfully extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-piece trial for 2 hours.[7] However, the proportion of patients with simple weaning (*i.e.* patients extubated after the initial SBT) was particularly high in this study (nearly 90%) whereas usual rates in the literature are closer to 60-70%.[3] Moreover, patients with difficult weaning (*i.e.* those who failed the initial SBT) were not monitored up until extubation, thereby limiting application of these findings to simple weaning, and not taking into account patients with weaning difficulties.[3] [4] Lastly, reintubation rates were particularly low (around 11%) meaning that the population mainly included patients at low-risk of extubation failure.[8] Although an easy test using PSV trial may hasten extubation, inclusion of patients at low-risk with reintubation rates around 10% or less might not enable to detect an increased risk of extubation failure. Therefore, to avoid underpowering the study and so as be able to detect the risk, we decided to focus on patients at high-risk of extubation failure and to include patients with weaning difficulties. In this population at high-risk of reintubation a recent post-host analysis from a large randomised controlled trial showed that execution of an initial SBT using PSV significantly increased the proportion of patients successfully extubated within the following 72 hours as compared with T-piece.[17] However, a large prospective clinical trial is needed to confirm these findings in this population before being in a position to apply this weaning strategy to all ICU patients.

To assess as primary outcome the duration of weaning on the one the hand and the risk of reintubation on the other hand, we decided to assess the number of ventilator-free days at day 28.

This criterion has the advantage of evaluating the 2 end-points (duration of weaning and risk of reintubation) with one and the same criterion. In previous studies, primary outcome was the number of patients extubated after the initial SBT and not reintubated at 48h or 72h.[7 18 19] Although this outcome has weaknesses (too early and focusing only on simple weaning), we will also assess the number of patients extubated after the initial SBT and not reintubated within the following 72h, in order to compare our results to previous studies. Lastly, as performing a T-piece or PSV trial may influence the success of the initial SBT and duration between the initial SBT and successful extubation, we will compare the proportion of patients with simple, difficult and prolonged weaning according to type of SBT. 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.[4]

No risk is expected with these 2 SBTs, as both of them are routinely and daily performed in the clinical practice of participating centers. Type of SBT may modify only the physician's decision of extubation, and no other treatment will be added or modified.

In conclusion, the TIP-EX trial is an investigator-initiated pragmatic randomised controlled trial empowered to test the hypothesis that SBTs performed using PSV may hasten extubation without increasing the risk of reintubation in patients at high-risk of extubation failure as compared to T-piece. These 2 strategies have never been compared in patients at high-risk of reintubation, and therefore, this large trial may help to establish strong recommendations with a high level of evidence on a daily clinical practice for extubation in ICUs.

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Table 1: Study flow chart

Procedures and assessments	From inclusion to the initial SBT	From the initial SBT to extubation	From the initial SBT to day 28	Until ICU discharge and day 90
Inclusion and non-inclusion criteria	X			
Information and consent	X			X
Randomisation	X			
Characteristics of the patient[1]	X			
Characteristics of the initial SBT[2]	X			
Characteristics at time of extubation[3]		X		
Characteristics after extubation[4]			X	
Vital status				X

(1) Characteristics of the patient include age, gender, height, weight, severity score indicated by the Simplified Acute Physiological Score (SAPS) II and the Sepsis-related Organ Failure Assessment (SOFA) score, underlying chronic cardiac or respiratory disease, date and reason for admission/ intubation, duration of intubation prior to the initial SBT, ventilatory settings and blood gases before the initial SBT.

(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.

(3) Characteristics at time of extubation include duration of weaning between the initial SBT and extubation, the number of SBTs attempts before extubation, classification according to the weaning difficulty, administrations of steroids before extubation, qualitative assessment of cough strength and amount of secretions at time of extubation.

(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), 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.

FIGURE LEGEND

Figure 1: Flow chart of the patients and study design.

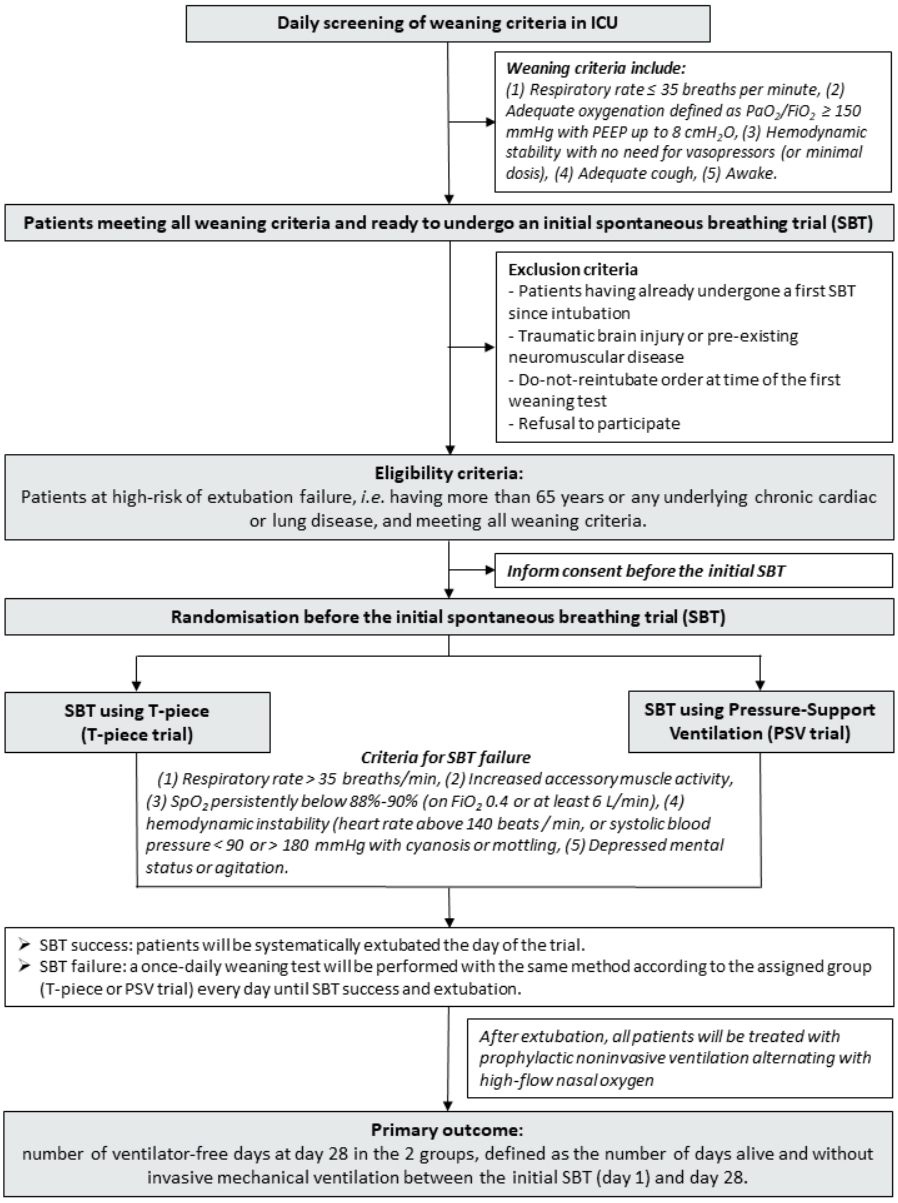

Figure 1: Flow chart of the patients and study design.

190x254mm (96 x 96 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item; No: Page	Description
Administrative information		
Title	1: **Page 1**	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a: **Page 3**	Trial identifier and registry name. If not yet registered, name of intended registry
	2b: **Page 3**	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4: **Page 3**	Sources and types of financial, material, and other support
Roles and responsibilities	5a: **Page 1-3**	Names, affiliations, and roles of protocol contributors
	5b: **Page 3**	Name and contact information for the trial sponsor
	5c: NA	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d: **Page 14**	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a: **Page 6**	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b: **Page 6**	Explanation for choice of comparators
Objectives	7: **Page 6-7**	Specific objectives or hypotheses

Trial design	8: **Page 7**	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	9: **Page 7**	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10: **Page 7-8**	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a: **Page 8-9**	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b: **Page 9**	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c: **Page 9**	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d: **Page 9**	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12: **Page 9-10**	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13: **Page 9-10**	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14: **Page 11**	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15: **Page 111**	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a: **Page 12**	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b: **Page 12**	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c: **Page 12**	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a: **Page 12**	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b: **Page 12**	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a: **Page 12**	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b: **Page 12**	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19: **Page 12**	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a: **Page 12-13**	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b: **Page 12-13**	Methods for any additional analyses (eg, subgroup and adjusted analyses)

	20c: **Page 12-13**	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a: **Page 13**	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b: **Page 13**	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22: **Page 13**	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23: **Page 13**	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24: **Page 14**	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25: **Page 14**	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a: **Page 14**	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b: **Page 14**	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27: **Page 14**	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28: **Page 14**	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29: **Page 14**	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a: **Page 14**	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32: model consent form available in supplementary files	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33: NA	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.