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► To cite this version:

Mathieu Capdevila, Audrey de Jong, Yassir Aarab, Aurelie Vonarb, Julie Carr, et al.. Which spontaneous breathing trial to predict effort to breathe after extubation according to five critical illnesses: the cross-over GLOBAL WEAN study protocol. *BMJ Open*, 2023, 13 (7), pp.e070931. 10.1136/bmjopen-2022-070931 . hal-04174589

HAL Id: hal-04174589

<https://hal.science/hal-04174589>

Submitted on 14 Aug 2023

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Which spontaneous breathing trial to predict effort to breathe after extubation according to five critical illnesses: the cross-over GLOBAL WEAN study protocol

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ABSTRACT

Introduction

Readiness to be freed from ventilatory support can be evaluated by spontaneous breathing trial (SBT) assessing the patient's ability to sustain respiratory effort after extubation. Current SBT practices are heterogeneous and there are few physiological studies on the topic. The objective of this study is to assess which SBT best reproduces inspiratory effort to breathe after extubation depending on the patient's illness.

Methods and analysis

This will be a multicentre randomised cross-over physiological study, in a large population, in the era of modern intensive care units using last generation modern ventilators. Each included

patient will perform three 15-minute SBTs in a random order: pressure support ventilation (PSV) level of 7 cmH₂O with positive end expiratory pressure (PEEP) level of 0 cmH₂O, PSV 0 cmH₂O with PEEP 0 cmH₂O and T-piece trial. A rest period of baseline state ventilation will be observed between the SBTs (10 min) and before extubation (30 min). Primary outcome will be the inspiratory muscle effort, reflected by pressure time product per minute (PTPmin). This will be calculated from oesophageal pressure measurements at baseline state, before and after each SBT and 20 min after extubation. Secondary outcomes will be PTPmin at 24 hours and 48 hours after extubation, changes in physiological variables and respiratory parameters at each step, postextubation respiratory management and the rate of successful extubation. One hundred patients with at least 24 hours of invasive mechanical ventilation will be analysed, divided into five categories of critical illness: abdominal surgery, brain injury, chest trauma, chronic obstructive pulmonary disease and miscellaneous (pneumonia, sepsis, heart disease).

Ethics and dissemination

The study project was approved by the appropriate ethics committee (2019-A01063-54, Comité de Protection des Personnes TOURS - Région Centre - Ouest 1, France). Informed consent is required, for all patients or surrogate in case of inability to give consent.

Trial registration number NCT04222569.

STRENGTHS AND LIMITATIONS OF THE STUDY

- ⇒ Robust methodology with a randomised cross-over design.
- ⇒ Three spontaneous breathing trials evaluated.
- ⇒ The largest population for a physiological study on the topic.
- ⇒ Subgroup analysis on specific critical illnesses.
- ⇒ The main limitation is the short 48-hour follow-up.

ADMINISTRATIVE INFORMATION

This manuscript is written in accordance with SPIRIT guidelines.¹ The administrative information is described in table 1.

INTRODUCTION

Background and rationale

Mechanical ventilation is a life-saving intervention and the main organ support in intensive care units (ICUs). After recovery from acute illness, the patient is separated from the ventilator (weaning) and the endotracheal tube is removed (extubation). Predicting whether a critically ill patient can be

successfully extubated is challenging. Readiness to be freed from ventilatory support can be evaluated by a spontaneous breathing trial (SBT)² assessing the patient's ability to sustain respiratory effort after extubation.³

Many SBT methods have been described and are used in ICUs around the world.^{3–7} The most common SBTs are low pressure support ventilation (PSV) with or without positive end expiratory pressure (PEEP) (55%–72%) and T-piece trial (9%–59%).^{4–6} The persistent diversity of practice reflects how controversial this topic is.

A physiological meta-analysis from Sklar *et al* published in 2017,³ including 16 studies and 239 patients, reported that PSV reduces respiratory effort compared with T-piece trial which reflected physiological conditions after extubation more accurately. However, the authors conclude that these results are tempered by the limited number of studies, the small number of patients included in each and by methodological heterogeneity.^{8–23} The authors of this meta-analysis³ stated that further investigations are therefore necessary.

To the best of our knowledge, there is no randomised cross-over trial evaluating which SBT most closely mimics postextubation effort to breathe, in a large population, in the era of modern ICU using last generation ventilators (online supplemental table S1) according to specific profiles of respiratory mechanics and critical illness.^{10 17 21}

Objectives

We hypothesise that non-assisted breathing trials (PSV 0 cmH₂O PEEP 0 cmH₂O and T-piece trial) will most closely mimic effort to breathe after extubation.

Primary objective.

To determine which SBT will best reproduce postextubation effort to breathe for overall patients.

Secondary objectives.

To determine which SBT will best reproduce post-extubation effort to breathe for five specific critical illnesses: abdominal surgery, brain injury, chest trauma, chronic obstructive pulmonary disease (COPD) and miscellaneous.

To compare inspiratory effort at 20 min, 24 hours and 48 hours after extubation.

To compare three SBTs for effort to breath, respiratory variables and lung aeration. We will also describe the respiratory management (physiotherapy, oxygen therapy, non-invasive ventilation) following extubation, and the rate of extubation failure.

Trial design

The GLOBAL WEAN trial is an investigator initiated multicentric prospective randomised cross-over study.

Each patient, serving as their own control, will perform three SBTs in a randomly assigned order. The expected duration of subject participation is 48 hours after inclusion in the study.

CONSORT diagram

Figure 1 shows the Consolidated Standards of Reporting Trial (CONSORT) diagram of the GLOBAL WEAN study.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The GLOBAL WEAN study is currently taking place in three mixed medical and surgical ICUs for a total of 52 beds, in France.

Eligibility criteria

Inclusion criteria

All consecutive ICU patients under invasive mechanical ventilation for at least 24 hours and considered by the clinician in charge to be ready for extubation according to guidelines²⁴ are eligible for inclusion in the study. All criteria for ventilatory weaning must be present²⁴: conscious patient (Richmond Agitation-Sedation Scale ≥ 0) or VISAGE (VISual pursuit, Swallowing, Age, Glasgow for Extubation) score ≥ 3 ²⁵ (visual pursuit, good swallowing, Glasgow Coma Scale >10) if severe brain injury, no sedation, good coughing effort, good swallowing, positive leak test when required (leaks $\geq 12\%$ of tidal volume (VT)), no significant secretions, no respiratory acidosis, adequate oxygenation (arterial oxygen tension to inspiratory oxygen fraction ratio (PaO₂)/FiO₂ ≥ 150 mm Hg and continuous positive airway pressure ≤ 8), adequate pulmonary function (respiratory rate (RR) ≤ 35 , negative inspiratory force > -20 cmH₂O, RR/VT < 105), stable cardiovascular status (heart rate (HR) < 140 bpm, systolic blood pressure > 90 mm Hg, no or minimal vasopressors), resolution of acute phase of disease for which the patient was intubated.

Patients must be over 18 years old, have health insurance coverage and provide written consent.

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: body mass index (BMI) (total body weight in kg/height in m²) higher than 35 kg/m², any contraindication to the insertion of an oesophageal catheter, age < 18 years, pregnant or breastfeeding woman, protected person or under curatorship.

Critical illnesses

Five critical illnesses with specific features are defined a priori: (1) postoperative abdominal surgery with laparotomy²⁶ within 15 days after surgery, (2) brain injured patients,²⁷ (3) patients with chest trauma,^{28 29} (4) COPD exacerbation according to the 2018 international guidelines,³⁰ (5) miscellaneous patients other than the four critical illnesses described above which could include pneumoniae, sepsis or heart failure. An ancillary study will be performed on patients with COVID-19-associated acute respiratory distress syndrome.

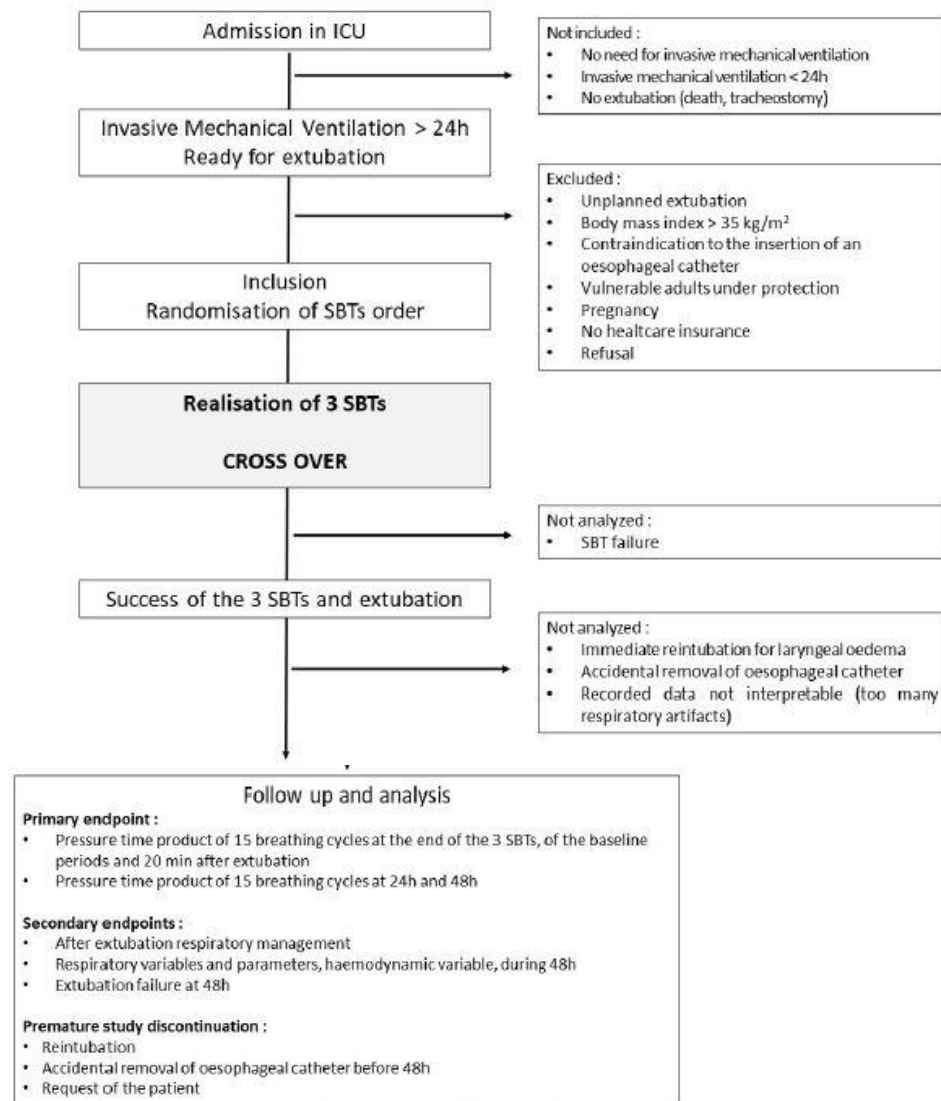


Figure 1 Consolidated Standards of Reporting Trial (CONSORT) diagram of the GLOBAL WEAN study. ICU, intensive care unit; SBT, spontaneous breathing trial.

Outcomes

Primary outcome measure

Primary outcome will be the inspiratory effort to breathe of all inspiratory muscles evaluated by oesophageal pressure time product per minute (PTPmin). This is a reliable assessment of the patient's inspiratory effort, calculated by integration of oesophageal pressure over time.^{31 32}

Measurement of oesophageal swing pressures will be performed with a second-generation balloon oesophageal catheter: Nutrivent (SIDAM, Italy), oesophageal catheter C76U (Marquat, France) and oesophageal catheter 47-9005 (CooperSurgical, Trumbull, Connecticut, USA). After insertion, the initial filling volume of inflation will be within the range defined by Mojoli *et al*³³ depending on the catheter used: 4 mL for Nutrivent and Marquat catheter, 1 mL for Cooper. Then the volume will be titrated to obtain the largest tidal oesophageal pressure (Pes).³⁴ We will confirm the appropriate position in the lower third of the oesophagus by an inspiratory effort manoeuvre performed by the patient against an end-expiratory occlusion. Slope of linear regression between changes in airway pressure (Paw)

and P_{es} should be 1 ± 0.2 for validation of the position.^{35 36} Pressures P_{aw} , P_{es} and flow will be measured with a FluxMed GrT device (L3Medical, France). Fifteen consecutive constant breathing cycles (eg, no coughing, no shallow breathing, no maximal inspiratory effort, no oesophageal spasm, no artefacts) will be assessed during the last 3 min of each period. The PTP_{min} will be calculated by FluxReview software (L3Medical, France). To determine the contribution of resistive or elastic workload, the oesophageal pressure time product will be also partitioned into three parts: resistive, elastic and related to the intrinsic PEEP (PEEP_i) (online supplemental figure S1). Theoretical chest wall compliance required for the PTP_{min} is calculated using a theoretical value (4% of the predicted value for the vital capacity per cm of water) according to the manufacturers' recommendation. Even if using this theoretical value may result in approximation, this is expected to be identical for all periods and not to affect the validity of comparisons. We will use a tight-fitting facemask for the postextubation PTP_{min} measurements as previously described.^{17 37 38}

Secondary outcome measures

Secondary outcomes will be PTP_{min} at 24 hours and 48 hours after extubation, changes in physiological variables and respiratory parameters at each step, postextubation respiratory management and the rate of successful extubation.

Standard three-lead monitoring electrodes will continuously record HR and rhythm. Oxygen saturation (SpO_2) will be continuously monitored using pulse oximetry. Systolic and diastolic arterial blood pressures will be continuously monitored with a non-invasive blood pressure cuff or through a 20-gauge catheter inserted in a radial or femoral artery. Arterial Blood Gases analysis (GEM Premier 3000 analyzer; Instrumentation Laboratory, Lexington, MA, USA) will be obtained at baseline and just before extubation. Central venous oxygen saturation will be collected whenever possible, when venous blood gases have been performed from a central venous catheter within 4 hours before SBT period, during SBT period and after extubation. The ventilatory variables and parameters will be collected in real time on the ventilator: inspired oxygen fraction (FiO_2), VT, RR, inspiratory flow, baseline PSV and PEEP values. After extubation, outcomes data will be collected: extubation success or failure (defined as reintubation within 48 hours) and postextubation respiratory management (physiotherapy, oxygen therapy, non-invasive ventilation).

Interventions

The experimental protocol with timeline is summarised in [figure 2](#). A 10-minute period corresponding to a baseline state will be recorded first (using PSV and PEEP set by the clinician in charge of the patient before inclusion). Patients will be then assessed with the three SBTs: (1) PSV 7 cmH₂O and PEEP 0 cmH₂O (PSV 7 PEEP 0), (2) PSV 0 cmH₂O and PEEP 0 cmH₂O (PSV 0 PEEP 0) and (3) T-piece trial. Each patient, serving as their own control, will perform the three SBTs in a randomised order. Each SBT lasts 15 min, with a 10-minute washout period of return to baseline state between trials. Data will be recorded before (guarantee of real return to baseline) and after each SBT. In case of clinical success of the different SBTs, extubation will be decided by clinician in charge, in accordance with guidelines²⁴ and our local protocol described in detail in a previous review.³⁹ The patient will be reconnected to the ventilator with baseline parameters for 30 min before planned extubation.⁴⁰ Data will be recorded just before extubation and then 20 min, 24 hours and 48 hours after. Respiratory management after extubation is left to the discretion of attending teams and will be notified.

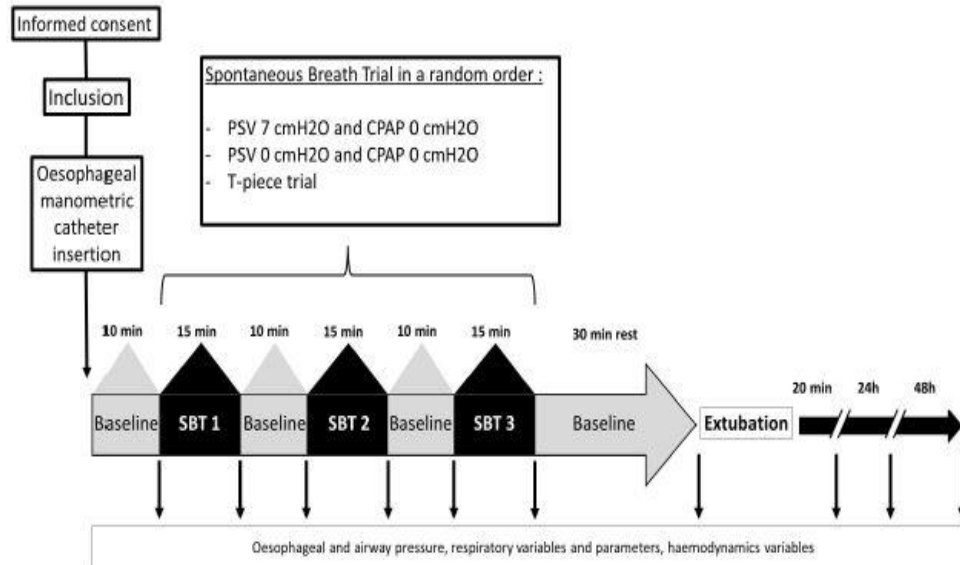


Figure 2 Study design and timeline of data collection. CPAP, continuous positive airway pressure; PSV, pressure support ventilation; SBT, spontaneous breathing trial.

All patients will be studied in a semi-recumbent position with the head of the bed elevated to an angle between 30° and 45°, according to patient comfort.³⁷ The humidification device is a heated humidifier, linked to a last generation ventilator from the same company (Dräger, Germany). The T-piece will be connected to the inspiratory line of the ventilator and thus directly connected to the heated humidifier. The moistened air will be supplied at a flow rate of 30 L/min, with a suitable FiO₂ for SpO₂ within the targets defined by the clinician in charge.

Criteria for discontinuing or modifying allocated interventions

Patients who do not tolerate an SBT will be reconnected to the ventilator, discontinue the intervention, and therefore not be included in the data analysis. The clinician in charge will be free to perform another SBT of his choice, to extubate the patient or not.

Criteria of non-tolerance of an SBT will be:

- ▶ Excessive agitation or anxiety.
- ▶ Loss of consciousness, severe sweating and excessive end tidal carbon dioxide.
- ▶ Acute respiratory failure with RR >35 cycles per min or RR/VT >105.
- ▶ Cyanosis, dyspnoea, SpO₂ <90% with FiO₂ >50%.
- ▶ Haemodynamic instability, HR >140 bpm, systolic blood pressure <80 mm Hg, high dose of vasopressors.

Strategies to improve adherence to intervention protocols

The entire procedure will be performed by the research staff, and the clinician will have no additional workload. The patient will be followed closely for 48 hours after extubation.

Relevant concomitant care and interventions that are permitted or prohibited during the trial

All care will be permitted during the procedure except for that involving additional effort for the patient: nursing, physiotherapy and painful procedure. Changes in respiratory parameters will be allowed if they are necessary for the patient (eg, FiO₂ in case of desaturation). Any changes in respiratory parameters or treatment during the procedure will be recorded.

Participant timeline

The participant timeline is described in [table 2](#).

Sample size

To validate our hypothesis that postextubation effort to breathe will be similar to non-assisted breathing trials (PSV 0 PEEP 0 and T-piece), we plan to include up to 100 analysable patients (convenience sample according to previous physiological studies and planned subgroup analyses). We expect that we will need 120 inclusions, estimating the non-exploitable data and failed SBTs between 10% and 20% with regard to previous similar studies.^{21 24} After accounting for the number of multiple comparisons, using the Bonferroni correction, significance was fixed at $p < 0.01$.

Item	Screening/ baseline		Final visit
	Visit 1	Visit 2	Visit 3
Date	H0	H24	H48
Eligibility: check inclusion and exclusion criteria	X		
Informed consent	X		
Inclusion and randomisation	X		
Demography	X		
Medical history	X		
Clinical evaluation*	X	X	X
Arterial blood gases†	X	X	X
Endpoint evaluation/ physiological measures	X	X	X
Status of extubation success	X	X	X
Adverse events recording	X	X	X
*Includes haemodynamic, respiratory and ventilatory parameters. †As usually performed for the daily patient care if an arterial catheter was in place. Supplementary blood gases could be done according to the clinical state of the patient.			

Recruitment

Patients are expected to be included during a 3-year inclusion period starting June 2020. 2019: Protocol, approvals from ethics committee and trial tool development (case report form, randomisation system).

Planned start for the study: June 2020.

2020–2023: Inclusion of patients.

Planned end for the study: June 2023.

2023: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

Consecutive inclusions will be carried out in each centre. A computer-generated randomisation will be used for SBTs' order, generated by a statistician who is not involved in determining patient eligibility or outcome assessment. Randomisation will be stratified for each critical illness. Opaque sealed envelopes containing the allocation group will be then created by the statistician and addressed to the research staff. At bedside, the allocation of SBTs' order will be done by using these envelopes. The research staff will enrol participants and will assign participants to interventions.

Blinding

Patients, clinical staff (physicians, nurses, physiotherapists) and statisticians will be blind to group allocation. The blinding will not be possible for the research staff involved in the intervention. In case of non-tolerance of an SBT, the intervention will be discontinued, and the clinical staff will be informed. The clinician in charge will be free to perform another SBT of his choice, to extubate the patient or not.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on paper case report forms by trained local research coordinators or physicians, the day of extubation, 24 and 48 hours after extubation.

Patient's characteristics will be collected and registered before intervention: age, gender, severity score quantified by Simplified Severity Index and Sequential Organ Failure Assessment Score at admission in ICU, height, weight and BMI, comorbidities (ie, pre-existing chronic respiratory disease, cardiac, renal or hepatic disease, immunosuppression) and medical or surgical ICU hospitalisation.

All original records will be kept on file for 15 years, archived in a locked room at the Intensive Care Unit & Anesthesiology Department B in University of Montpellier Saint-Eloi Hospital. The clean database file will be retained for 15 years and anonymised.

Plans to promote participant retention and complete follow-up

Not applicable. Patients will complete their intervention during their stay in the hospital.

Statistical methods

Statistical analysis

A predefined statistical analysis plan will be followed (online supplemental file 3). All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, V.9.4; SAS Institute; Cary, NC, USA, and R, V.3.6.2). The baseline characteristics of the overall population and of each group will be

described. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with IQRs. To assess differences between SBTs and after extubation effort to breathe, we will use the Friedman test and then pairwise comparisons with the Wilcoxon test if a significant difference appears. To assess changes in physiological variables and respiratory parameters along the intervention, we will use a paired t-test. A two-sided p value of less than 0.01 will be considered to indicate statistical significance, after Bonferroni correction.

Additional analysis

A subgroup analysis will be performed to assess differences between SBTs and after extubation effort to breathe according to five illnesses: (1) abdominal surgery, (2) brain injury, (3) chest trauma, (4) COPD and (5) miscellaneous. No interim analysis will be conducted.

Analysis of non-adherence to the protocol

A per protocol analysis will be used. Patients who did not complete all three SBTs or were not extubated will not be included in the data analysis.

METHODS: MONITORING

Data monitoring

The daily patient screening and inclusion, protocol compliance, data collection and assessment are all handled by trained physicians in collaboration with a clinical research nurse and/or clinical research assistant.

Harms

The use of second-generation balloon oesophageal catheters does not appear likely to produce a significant danger during this protocol. They are already marketed and used in current clinical practice.

Concerning the project's safety, the duties of the investigator and sponsor, the reporting of major adverse events (AEs) and annual safety reports will be monitored and carried out in accordance with regulations.

Throughout the course of the study, all AEs encountered during the clinical trial will be reported continually and accurately on the AE form of the case report file. A description of the event, an evaluation of its seriousness based on the aforementioned criteria, an assessment of its duration, intensity, relationship to the study treatment, any additional causality factors (if any), any concurrent medications prescribed, actions taken with the study device or other therapeutic interventions and the outcome at the conclusion of the observation period must all be included in an AE report. A unique AE form will be filled out for each AE.

In case of major serious AEs suspected to be related to the type of SBT performed, the trial may be temporarily stopped for an individual patient, at the discretion of the attending physician.

Auditing

A midterm audit will be conducted after inclusion of 50 analysable patients. The Clinical Research and Innovation Department of the Montpellier University Hospital will be involved in this procedure independently from investigators.

Patient and public involvement statement

- ▶ Patients and public involved in the research question or the outcome measures: none.
- ▶ Patients and public involved in study design and planning: none.
- ▶ Patients and public involved in study recruitment or execution: none.
- ▶ Patients won't be the ones to judge the intervention's burden.
- ▶ Study participants will have access to results at their convenience. The results will not be systematically distributed to research participants.

ETHICS AND DISSEMINATION

Research ethics approval

The Institutional Review Board of the University Hospital of Montpellier (France) approved the trial. By 28 May 2019, the study has been approved the Ethics Committee of the Tours University Hospital (Comité de Protection des Personnes TOURS - Région Centre - Ouest 1, France) with the registration number 2019-A01063-54. The GLOBAL WEAN study is conducted in accordance with the Declaration of Helsinki and was registered at <http://www.clinicaltrials.gov> with trial identification number NCT04222569 (registered on 10 January 2020).

Plans for communicating important protocol modifications

In case of possible future protocol modifications, the Ethics Committee of the Tours University Hospital will be informed.

Consent or assent

As needed by the institutional review board in accordance with the 2013 Declaration of Helsinki, three different types of consent will be obtained (online supplemental files 4–6). The research staff will take informed consent before inclusion. After receiving written informed consent, the patient will be included. However, he may not understand given information because of brain injury. These patients will be enrolled following the next of kin's written informed consent. All patients will be retroactively prompted for written agreement to continue the trial following recovery, if possible.

Additional consent provisions for collection and use of participant data and biological specimens

Participants or their caregivers will provide further consent if related data from participants are required in future research.

Confidentiality

French legislation will be followed in the handling of data. At trial sites, all original records will be kept on file for 15 years. The clean database file will be retained for 15 years and anonymised.

Declaration of interest

The study is an investigator-initiated trial. The study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Access to data

Only the research staff and statisticians will have access to the full trial dataset during the enrolment period. The complete data collection will be available to all researchers at the end of inclusions. Controlled access will be granted to participant-level data sets. Data will be available for the corresponding author on reasonable request.

Post-trial care

We will assess, document, and treat any patients who will be harmed as a result of their involvement in the project.

Authorship eligibility, professional writers

We will not use the assistance of a professional writer.

Dissemination policy

To disseminate information and explain the research to clinicians, commissioners and service users, findings will be published in peer-reviewed journals and presented at regional, national, and worldwide meetings and conferences.

Biological specimens

Not applicable, no biological specimens will be collected.

DISCUSSION

To the best of our knowledge, GLOBAL WEAN trial will be the first pragmatic multicentric randomised physiological cross-over study with a large population, evaluating effort to breathe of three SBTs and after extubation, using the last generation of modern ICU ventilators, with a focus on specific critical illnesses (online supplemental table S1).

Online supplemental table S1 which summarises the main characteristics of 17 physiological studies evaluating different SBTs, suggests that mechanical ventilation allows to unload the respiratory muscles.^{3 8–14 17 19 21} As the amount of support provided by the given SBTs' modality increases (assisted trials), the workload of patient's respiratory muscles decreases. However, there are differences in the comparison with effort to breathe after extubation. Although the landmark study by Brochard *et al*⁸ showed that unassisted trials (T-piece and PSV 0) increased effort to breathe compared with postextubation, Straus *et al*¹⁵ and Mahul *et al*²¹ recorded similar respiratory effort, while Nathan *et al*,¹¹ Ishaaya *et al*¹³ and Mehta *et al*¹⁷ showed less effort to breathe compared with postextubation. This difference could be explained by the heterogeneity of patients, of ventilators or interfaces for postextubation assessment (mouthpiece or facemask). Performing an assisted trial helps the patient provide overall inspiratory muscle effort (resistive and elastic workload) and adds pressure needed to overcome the PEEPi. In unassisted trial, the global inspiratory muscle effort is provided by the patient. The difference that might be observed between PSV 0 PEEP 0 trial and T-piece trial could be explained by additional resistive work in PSV 0 PEEP 0 trial because, despite advances in respiratory engineering and pressurization performance,^{41–43} ventilator and circuit overload could still be significant. We might speculate that respiratory mechanism specificities and respiratory drive could be different between critical illnesses.

Strengths of the GLOBAL WEAN study are the large population comparing to other similar physiological trials, the use of last generation modern ICU ventilators and the focus on specific critical illnesses. One other strength is that the team has extensive experience in performing physiological studies about weaning, SBTs and effort to breathe evaluation, such as the WEANOBESE study²¹ and others.^{44–46} No industry will be involved.

Our study does present some limitations. First, the 48-hour follow-up is probably short to allow proper interpretation of extubation success. Second, we assumed the absence of gastric pressure measurement as previous studies did.^{8 11 13 17} These missing data blind us to the participation of abdominal expiratory muscle relaxation in the initiation of the inspiratory effort. As included patients will be recovered from acute illness and ready for extubation, we considered the measurement of abdominal expiratory effort irrelevant. Third, we will not calculate the work of breathing (WOB). WOB is strongly correlated with the PTP in most physiological studies.⁶ The choice of PTP as primary outcome is justified by the fact that unlike WOB, the PTP allows the assessment of non-volume-generating effort, such as the isometric load imposed by the respiratory support initiation process. Fourth, another limitation of this study is the duration of the SBT, 15 min. The standard of care is a 30-minute duration for an SBT.⁴⁷ Choosing 15 min was a deliberate decision as in previous studies,²¹ in agreement with the ethics committee, in order to prevent patients' discomfort. Despite all, patient fatigue and discomfort could persist and influence performance during the trial. Random order will mitigate this, but a potential bias remains. Fifth, the total duration of the intervention will be quite long, changes in the patient's condition may appear and require care. Any changes in respiratory parameters or treatment during the procedure will be

recorded. Sixth, the intervention is technical and requires a trained research staff to be available, which could be an enrolment bias and could slow down the recruitment. Seventh, the recruitment period coincides with the COVID-19 outbreak which could generate a recruitment bias. For example, the significant decrease in trauma admissions due to governments restrictions.^{48 49} Eighth, some elements that may affect inspiratory effort and extubation success will not be recorded such as amount of airway secretions, percentage of leak during the cuff leak test or coughing effort (peak expiratory flow).

In conclusion, the GLOBAL WEAN study will be the first pragmatic multicentric randomised physiological cross-over study evaluating which SBT closely mimics the postextubation effort to breath, in a large population, an adequate statistical power and a considered study design, in modern era with the last generation ICU ventilators, focusing on specific critical illnesses in order to develop personalised weaning protocols as the final aim of this work.

Trial status

The trial is ongoing and is actively enrolling since June 2020.

Contributors

MC drafted the manuscript together with ADJ and SJ. SJ designed the study together with MC and ADJ. NM and ADJ wrote the statistical analysis plan, estimated the sample size and are involved in data analysis. MC, YA and AV are involved in the intervention and data acquisition. All authors MC, ADJ, YA, AV, JC, NM, XC, LB and SJ revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding

The study is an investigator-initiated trial. Study promoter is Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Competing interests

SJ reports receiving consulting fees from Drager, Mindray, Medtronic, Baxter, Fresenius-Xenios and Fisher & Paykel. ADJ reports receiving consulting fees from Drager, Medtronic and Fisher & Paykel. LB's lab has received research grants from Medtronic, Drager and Stimit and equipment from Sentec, Fisher & Paykel and Philips and lecture fees from Fisher & Paykel. No potential conflict of interest relevant to this article was reported for other authors.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

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