Study Protocol

Weaning critically ill patients from mechanical ventilation: a protocol from a multicenter retrospective cohort study

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Background: Mechanical ventilation (MV) is an important lifesaving method in intensive care unit (ICU). Prolonged MV is associated with ventilator associated pneumonia (VAP) and other complications. However, premature weaning from MV may lead to higher risk of reintubation or mortality. Therefore, timely and safe weaning from MV is important. In addition, identification of the right patient and performing a suitable weaning process is necessary. Although several guidelines about weaning have been reported, compliance with these guidelines is unknown. Therefore, the aim of this study is to explore the variation of weaning in China, associations between initial MV reason and clinical outcomes, and factors associated with weaning strategies using a multicenter cohort.

Methods: This multicenter retrospective cohort study will be conducted at 17 adult ICUs in China, that included patients who were admitted in this 17 ICUs between October 2020 and February 2021. Patients under 18 years of age and patients without the possibility for weaning will be excluded. The questionnaire information will be registered by a specific clinician in each center who has been evaluated and qualified to carry out the study.

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Discussion: In a previous observational study of weaning in 17 ICUs in China, weaning practices varies nationally. Therefore, a multicenter retrospective cohort study is necessary to be conducted to explore the present weaning methods used in China.

Trial Registration: Chinese Clinical Trial Registry (ChiCTR) (No. ChiCTR2100044634).

Keywords: Mechanical ventilation (MV); weaning; prolong weaning; epidemiology

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Introduction

Mechanical ventilation (MV) is an important lifesaving method in intensive care unit (ICU). It improves ventilation function and gas exchange of patients. However, prolonged MV is associated with several complications such as ventilator associated pneumonia (VAP) (1,2). These complications worsen the prognosis of patients, as time spent in the weaning process accounts for approximately 40–50% of the total duration of MV (3,4). Several studies have explored methods to shorten the weaning process thus minimizing the MV duration. However, premature weaning from MV may increase reintubation rate or mortality (5-7). Therefore, it is important to identify the "right patients" at the "right time" through a reasonable strategy to ensure safe and timely discontinuation from the ventilator (8,9).

Protocol-directed weaning is recommended as a routine process to improve the patient's prognosis compared with physician-directed weaning (10). The protocol includes several aspects such as identifying the patients who are ready for spontaneous breathing trials (SBTs), methods to conduct SBTs and sequential respiratory support after weaning. However, despite demonstration of large-scale implementation, studies have not achieved an optimal strategy, which means "optimal protocol", to wean the critical patients from MV. Moreover, although several guidelines on protocol-directed weaning have been reported, rate of compliance to present guidelines is unknown (11-13).

Therefore, this multicenter retrospective cohort study is necessary to be conducted to explore the epidemiology of weaning in China. The aim of this study is to explore the actual variation of weaning strategies in clinical practice from each center, and to determine which variation is associated with MV duration and patient's outcome.

We present the following article in accordance with the SPIRIT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1217/rc).

Methods

Study design

This will be a multicenter retrospective cohort study that included patients who were admitted to 17 adult ICUs in China (Table S1 and Figure S1), between October 2020 and February 2021. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval for the trial was obtained only from the main center - Institutional Review Board of the First Affiliated Hospital of Guangzhou Medical University (Medical Research Ethics Review 2021. No. 1). The Institutional Review Board waived the need for written informed consent from the patients due to the retrospective nature of the study. In addition, patients' information will be anonymized and deidentified prior to analysis. This study was registered at Chinese Clinical Trial Registry (ChiCTR) (No. ChiCTR2100044634).

A meeting was held with all centers to discuss the study items. Electronic medical record system or other electronic medical care systems of each center was explored before the study. All systems from each center met the study requirements.

Patient screening

This study will include patients who received invasive ventilation in ICU. The exclusion criteria will be (I) patients under 18 years of age; (II) dyscrasia caused by advanced malignancy diagnosed by specialists; (III) patients with neuromuscular disease leading to spontaneous ventilation damage (e.g., motor neuron disease); (IV) COVID-19 patients were excluded from the study.

Data collection

A specific clinician (not the accessing clinician) in each

Table 1 Screening before weaning

Weaning screening items
(I) Partial or complete reversal of the cause of respiratory failure
(II) Oxygenation index improvement, $SpO_2 \geq 90\%$ on a $FiO_2 \leq 0.4$ (or at a baseline level in chronically hypoxemic patients) and PEEP ≤ 5 cmH_2O
(III) Hemodynamic stability (off vasopressors or on low levels of vasopressors)
(IV) Spontaneous breathing existence. Frequency of screening, Glasgow Coma Scale

PEEP, positive end-expiratory pressure.

center who had been evaluated and was qualified recorded information from the center. The assessing clinicians will be each center ICU doctors who will be qualified by their own center, not for certain. The recording clinician will not participate or give advice in the weaning process. The requested data will be acquired in an electronic medical record system or other electronic medical care systems of each center. Data will be entered in an online questionnaire through scanning a QR code with the mobile phone.

Data collection of the assess clinician

Recorded information includes, present working institute, type of institute, type of ICU, number of beds in each ICU, the total number of invasive MV patients each year in each ICU, length of time working in ICU, length of time working, the major, the highest qualification, the position title and the length of time in that position.

In addition, information of the previous working institute, type of institute, whether the former workplace is ICU and the type of ICU.

Data collection of registered patients

- ❖ Part 1-Basic information: primary reasons for hospitalization, primary reasons for ICU admission, primary reasons for MV (indications for MV), the method for intubation, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) (14) at before or within 24 hours after ICU admission, medical history (including smoking, time of MV) and complications (15,16).
- ❖ Part 2-Weaning information (requirements for filling the form included):
  - (I) Fill the index with the ward round result in the weaning day morning.
  - (II) Fill in the best data of biochemical experiment or examinationperformed24-48 hours before or after weaning.
- ❖ Part 3-Before weaning (17): Weaning screening or not (18,19)? We consider either of the following screening item has been done by assess clinician. The answer is "yes", otherwise is "no". The details see *Table 1*.
- ❖ Part 4-The following items may be screened (details in https://cdn.amegroups.cn/static/public/10.21037jtd-21-1217-1.docx):
  - (I) The situation of circulation system (including heart rate, mean arterial pressure, Electrocardiograph and Pro-BNP).
  - (II) Respiratory mechanics index, perfusion related index (including arterial blood gas analysis, central venous blood gas analysis and blood lactic acid level).
  - (III) Blood routine (20).
  - (IV) PCT.
  - (V) Biochemical experiment data.
  - (VI) Cuff-leak test (21).
  - (VII) Cough strength assessment (*Table 2*).
  - (VIII) Characteristic of secretion of endotracheal or oral.
  - (IX) Use of vasopressors/sedatives/analgesics (27).
  - (X) Psychological situations (28).
  - (XI) Blood glucose, serum cortisol.
  - (XII) Abdominal situation (girth and pressure).
  - (XIII) Four limbs muscle strength.
- ❖ Part 5-Weaning processing (details in https://cdn.amegroups.cn/static/public/10.21037jtd-21-1217-1.docx):
  - (I) Weaning method (SBT or not) (18,19).
  - (II) The first SBT method, the first SBT postprocessing.
  - (III) The total duration of SBT.
  - (IV) Ventilatory support methods after weaning at day 1 and day 2 (29).
- ❖ Part 6-Post-weaning situation (details in https://cdn.amegroups.cn/static/public/10.21037jtd-21-1217-1.docx):
  - (I) The time from initiating MV to first weaning.
  - (II) Reintubation situation (reintubation within 48 hours after extubation or not).
  - (III) Total MV time, length of stay in hospital before or after ICU.

Table 2 Cough strength assessment

No.	Details
Method 1	Spirometry—A spirometer (specifically designed for mechanical ventilators) was inserted into the ventilator circuit and the patient was then instructed to cough. PEF during the cough was measured. Most experts use a cutoff of PEF ≤60 L/min since this indicates a high likelihood of failure. Patients with a PEF ≤60 L/min are five times more likely to require reintubation compared with patients with a PEF >60 L/min (22,23)
Method 2	Index card—The ETT was detached from the ventilator circuit and a card (e.g., an index card) was held approximately 1 to 2 cm from the proximal end of the ETT. The patient was then instructed to cough. A patient who is unable to moisten the card with 3 to 4 coughs was three times more likely to fail extubation compared with a patient who can moisten the card (24,25)
Method 3	Cough strength was assessed informally during deep (endotracheal) suctioning at the bedside depending on clinicians' experience (26)

ETT, endotracheal tube.

(IV) Total length of stay in ICU and hospital.
(V) Complications of MV.
(VI) Prognosis.
(VII) The cost in ICU and hospital.

Study endpoints

Primary outcomes

The weaning success rate in different centers and overall will be determined through analysis of data from each center. In addition, the variate related to successful weaning, and steps most clinicians will take before or after weaning will be explored. A weaning model will be established to provide an appropriate strategy and provide information on the duration of weaning.

Weaning Success and Failure Definitions: According to the definition provided by the 2007 International Task Force, weaning success is established when a patient who has just been extubated does not require ventilatory support for at least 48 h after the extubation procedure. Accordingly, weaning failure is characterized by: (I) an unsuccessful SBT, (II) reintubation/recannulation and/or the resumption of MV, or (III) death within 48 hours of extubation (30,31).

Secondary outcomes

The following data and events will be assessed as clinical outcomes: ventilator-free days within 28 days, reintubation within 48 hours after extubation (32), need for tracheostomy during weaning process after first SBT, length of stay in ICU and hospital, mortality in ICU and hospital, mortalities in ICU, post-ICU, and hospital, and type of hospital discharge.

Potential predictors

Based on the previous studies and our clinical experience, we will select the following potential predictors in the current study.

(I) Respiratory (such as Bronchospasm, pneumonia) (20,26).
(II) Circulation (such as BNP, CVP, CI, urinary output, fluid balance) (33).

Statistical analysis

After determination of normality of data, continuous variables will be presented as means and standardized deviations (SDs), or median and interquartile range (IQR), whereas categorical variables will be presented as frequencies and proportion. For univariate analysis, *t* tests (or Wilcoxon rank sum test) and ANNOVA (or Kruskal-Wallis test) will be performed for comparisons for continuous variables, and χ^2 tests will be used for comparisons for categorical variables among groups. According to the results of univariate analysis, we will preliminarily select the potential predictors for the multiple analysis. Then, multiple regression models will be used to estimate the association between potential predictors and the outcomes of interest. For continuous dependent variables such as length of stay in ICU and hospital, multiple linear regression models will be used. For categorical dependent variables such as the success of weaning, logistic regression or Cox regression models will be used (31-35). Given that patients in different centers may have different clinical characteristics, random effects term are added in models to control the related bias (36).

Based on the above models, we can identify the significant predictors and construct the predicted models. The predictors in models will be further refined based on the R^2, root mean square error (RMSE), Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC). In addition, half participants will be randomly selected as trained samples and used to reconstruct the refined model with the same predictors. Another half participants will be used to test the accuracy of our model, which will be measured by sensitivity and specificity.

All analyses will be conducted using R software (V3.6.1, R Development Core Team). All testes are 2-tailed, and $P<0.05$ is considered statistically significant.

Discussion

Weaning from MV is important however, studies on weaning report contradicting findings. Burns *et al.* conducted an international prospective observational study, and reported that use of specific strategies to discontinue MV in critically ill patients is important. However, studies methods for weaning and discontinuing MV in practice or the association between different discontinuation strategies and outcomes are few (37). Therefore, studies should explore weaning from MV to identify the most effective and efficient methods and for quality improvement. As we knew, the rapid shallow breathing index (RSBI) was widely used by clinicians to support decision-making during weaning and to predict the likelihood of successful weaning from invasive mechanical ventilation (IMV) (38). The earliest study conducted by Yang and Tobin proposed that an RSBI of <105 (rounded <100 in some studies) measured using a Wright's spirometer and without ventilator support was identified as a threshold less than which extubation was more likely to be successful (sensitivity, 0.97; specificity, 0.64) for most patients (39). This threshold of RSBI is still accepted by most clinicians in nowadays. Recently, another major meta-analysis has pointed that across 48 studies (10,946 patients), the RSBI showed not perfect enough for predicting extubation success (sensitivity, 0.83; specificity, 0.58), with no credible subgroup effects based on thresholds, measurement techniques, or patient characteristics (40). The writer considers RSBI is a simple measure of respiratory mechanics. Patients in different ICUs (e.g., medical, surgical, cardiovascular, and neurologic) may have variable respiratory drive and clinical indications for ongoing IMV. These differences may preclude clinicians from using the RSBI in directing weaning from IMV.

Several studies on P0.1 are available. In a study by Delisle, the findings showed that P0.1 has significantly high sensitivity and specificity to better guide invasive MV weaning and was used to develop the CORE index (41). A recent systematic review and meta-analysis conducted by Baptistella *et al.* (15) reported that each study on P0.1 included in meta-analysis has shortcomings. Although this analysis showed the potential ability of P0.1 to predict successful weaning, the true sensitivity and specificity of P0.1 still are not clear. In Mallat *et al.* (42), central venous-to-arterial pCo_2difference and central venous oxygen saturation during SBT, were independent predictors of weaning outcomes. Combination analysis of both parameters enhanced their diagnostic performance and provided excellent predictability in extubation failure detection in critically ill patients. A study by Teixeira *et al.* (43) reported that central venous saturation was an early and independent predictor of extubation failure in difficult-to-wean patient. However, the central venous gas blood test may not be detected before extubation, therefore, studies should explore it further.

Previous studies showed that simple, difficult and prolonged weaning could occur in 58%, 29% and 13% patients, respectively (44). ICU clinicians attend to several MV patients every day, and weaning is an important consideration for clinicians. Notably, timely weaning from MV is important. A recent meta-analysis by Blackwood *et al.* (45), reported that in most trials, protocol-based weaning reduces the duration of MV, weaning, and ICU length of stay. However, approximately 15% of patients receiving MV required a prolonged process of weaning and experience higher mortality (46,47). An international consensus conference on weaning from MV in 2005 proposed that weaning should be categorized into three groups (simple, difficult, and prolonged) based on the difficulty and duration of the weaning process (30). However, this classification was based on expert opinion and not rigorous analysis of a cohort of ventilated patients. A study by Jeong *et al.* (11) categorized patients into three groups (simple, difficult, and prolonged), however, the classification in this research was based on patients' weaning process. The findings of the study showed that weaning classification based on difficulty and duration of the weaning process may provide prognostic information for patients under MV who undergo the weaning process, especially in patients with prolonged weaning.

Several factors are associated with clinical outcomes in mechanically ventilated patients who are subsequently

weaned from MV, however, the effective factor for clinical use is not known. Therefore, there is a need to establish a clinical weaning prediction model. The weaning practices may vary nationally as shown by varying findings from studies conducted in other countries (48). In addition, the initial MV reason especially factors related to pneumonia may lead to a poor clinical outcome. Therefore, a multicenter retrospective cohort study will be conducted to explore the present weaning methods used in China.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1217/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1217/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1217/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval for the trial was obtained only from the main center - Institutional Review Board of the First Affiliated Hospital of Guangzhou Medical University (Medical Research Ethics Review 2021. No. 1). The Institutional Review Board waived the need for written informed consent from the patients due to the retrospective nature of the study.

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Supplementary

Table S1 The complete list of 17 hospitals included

Number	Hospital name	City
1	The First Affiliated Hospital of Guangzhou Medical University	Guangzhou
2	Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital	Guangzhou
3	Guangdong Hospital of Traditional Chinese Medicine	Zhuhai
4	Huizhou First Hospital	Huizhou
5	The First Affiliated Hospital of Shantou University Medical College	Shantou
6	The First Affiliated Hospital of Guangdong Pharmaceutical University	Guangzhou
7	The First Affiliated Hospital of Sun Yat-sen University	Guangzhou
8	Shunde Hospital of Southern Medical University	Foshan
9	Shunde Hospital Guangzhou University of Chinese Medicine (Shunde District Hospital of Chinese Medicine of Foshan City)	Foshan
10	The Third Affiliated Hospital of Sun Yat-sen University-Lingnan hospital	Guangzhou
11	Zhongshan People's Hospital	Zhongshan
12	Foresea Life Insurance Guangzhou General Hospital	Guangzhou
13	Guangzhou Panyu Central Hospital	Guangzhou
14	The Third Affiliated Hospital of Southern Medical University	Guangzhou
15	The Third Affiliated Hospital of Sun Yat-sen University	Guangzhou
16	The First Affiliated Hospital of Guangzhou University of Chinese Medicine	Guangzhou
17	The First Affiliated Hospital of Jinan University	Guangzhou

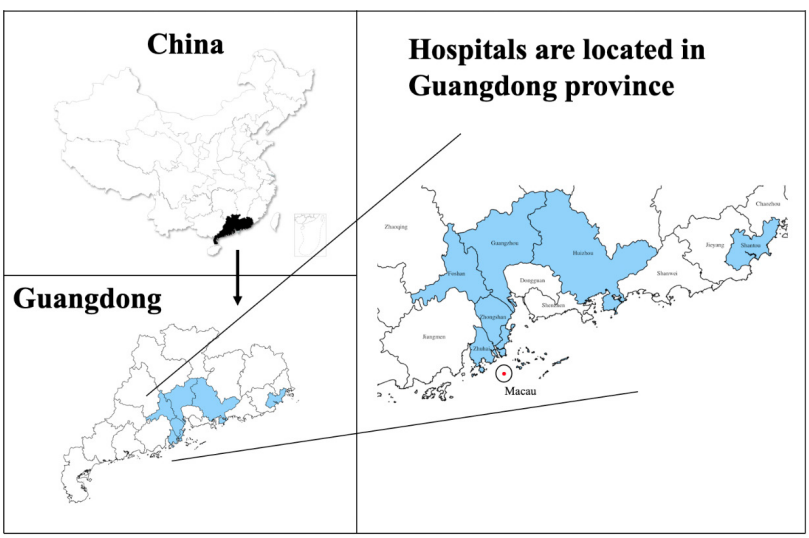

Figure S1 The geographic location of the hospitals included.

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