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Study protocol for a single-center randomized controlled trial to investigate the effect of lung recruitment in pediatric patients after cardiac surgery

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Abstract

Introduction

A number of published studies have revealed that lung recruitment can improve oxygenation, shorten the duration of mechanical ventilation (MV), and decrease mortality in adults with acute hypoxemic respiratory failure, especially patients with acute respiratory distress syndrome. However, few articles have assessed lung recruitment in pediatric patients, especially after cardiac surgery. This clinical trial aimed to determine whether lung recruitment can reduce the duration of MV in pediatric patients with hypoxemic respiratory failure after cardiac surgery.

Method and analysis

In this trial, we will randomly assign 234 pediatric patients (aged 28 days to 14 years) within 72 hours after cardiac surgery with an arterial oxygen tension (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2) of ≤300 to either a lung recruitment group or a conventional group. The primary endpoint will be the duration of MV. The secondary endpoints will be ventilator-free days, PaO_2/FiO_2, respiratory system compliance, duration of non-invasive ventilation, reintubation rate, length of ICU stay, length of hospital stay, occurrence of serious adverse events (barotrauma, persistent hypotension and arrhythmia), postoperative pulmonary complications.

Ethics and dissemination

The ethics committee of West China Hospital of Sichuan University granted ethics approval for this study (20/8/2019). The results will be published in peer-reviewed journals and presented at conferences.

Trial registration number: ChiCTR1900025990

Strengths and limitations of this study:

1. The protocol will be a randomized controlled trial, so the reliability of the results will be very high.

2. The incidence of hypoxic respiratory failure in pediatrics with congenital heart disease after surgery is low, and it will take a long time to achieve the expected sample size.

3. Because of lack of sufficient research data on lung recruitment in pediatrics, we do not know whether the methods, parameters of RM and the indications of repeat RM are reasonable, which may affect the outcome of patients.

Introduction

Hypoxemic respiratory failure, especially acute respiratory distress syndrome (ARDS) after cardiac surgery, is the main cause of prolonged mechanical ventilation (MV). General anesthesia, extracorporeal circulation, procedure-related lung injury, and inappropriate ventilation strategies are risk factors for hypoxemic respiratory failure in patients after cardiac surgery [1]. A recent prospective multi-center study diagnosed 10% of patients with ARDS after cardiac surgery [2]. Compared with adults, pediatric patients are more likely to suffer from hypoxemic respiratory failure after cardiac surgery because of their anatomical and physiological characteristics.

Lung recruitment maneuvers(RM) can prevent alveolar collapse, improve oxygenation, and enhance respiratory system compliance by temporarily increasing transpulmonary pressure [3]. Over the past two decades, a number of studies have confirmed the effectiveness of lung recruitment for improving oxygenation, reducing the duration of MV, and decreasing mortality in adults with hypoxemic respiratory failure, especially those diagnosed with ARDS [4-8]. However, studies investigating the clinical use of lung recruitment in pediatric patients are limited. Although several studies have reported that lung recruitment maneuvers combined with positive end-expiratory pressure (PEEP) titration can improve oxygenation and decrease the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) in pediatric patients with hypoxemic respiratory failure, no studies have assessed the effectiveness of lung recruitment in reducing the duration of MV in pediatric patients after cardiac surgery [9-19].

As a result, this single-center study was designed to determine whether lung recruitment maneuvers combined with PEEP titration can reduce the duration of MV and intensive care unit (ICU) stay, as well as all-cause mortality rate, in pediatric patients after cardiac surgery.

Methods

Study setting

This study adopted a prospective, single-center, parallel group, randomized, controlled design and is ongoing at West China Hospital of Sichuan University (January 2020 to December 2022). The ethics committee of West China Hospital of Sichuan University granted ethics approval (20/8/2019).

Eligibility criteria

The inclusion criteria are as follows: 1) pediatric patients after cardiac surgery whose cardiac anatomical deficiency was completely corrected after surgery; 2) pediatric patients aged 28 days to 14 years; 3) partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2) of <300 with PEEP⩾5cm H_2O within 72 hours after surgery.

The exclusion criteria are as follows: 1) pediatric patients deemed unsuitable for lung recruitment by the attending intensivist; 2) presence of an uncuffed endotracheal tube; 3) pneumothorax; 4) severe hemodynamic instability (requiring norepinephrine >0.2 μg/kg/min or epinephrine >0.2 μg/kg/min); 5) lack of consent from the next of kin; 6) diaphragmatic paralysis; 7) central nervous system complications; 8) raised intracranial pressure (>20 mmHg); 9) bronchopleural fistula;10)intracardiac shunt.

Participant selection and recruitment

Before identifying and screening patients for eligibility, all patients will be initially ventilated with synchronized intermittent mandatory ventilation-pressure control (SIMV-PC) using a Puritan Bennett™ 840 Ventilator (Covidien, Medtronic Inc., Minneapolis, MN) for 30 minutes (Figure 1). Then the first arterial blood gas analysis will be obtained. Specific ventilator settings are described in Table 1. $PetCO_2$, an index of $PaCO_2$, will be monitored using a carbon dioxide (CO_2) analyzer. Informed consent will be obtained by the doctor in charge. All information will be transferred into an electronic database so that the trial office can monitor recruitment and refusal rates.

Table 1. Ventilator mode and initial settings.

Age	Mode	F	Ti	Pi	Ps	FiO_2	PEEP	vsens
4 weeks < age ≤ 1 year	SIMV-PC	30	0.67	12	10	50%	5	1
1 year < age ≤ 3 years	SIMV-PC	25	0.80	12	10	50%	5	1
3 years < age ≤ 12 years	SIMV-PC	20	0.86	12	10	50%	5	1
Age > 12 years	SIMV-PC	15	1.0	12	10	50%	5	1

Intervention

The intervention group comprises patients who have undergone lung recruitment and PEEP titration. The control group comprises patients who have undergone conventional MV. Patients will be prospectively followed from the day of enrollment for at least 28 days or until discharge, whichever comes first.

In both groups, the ventilation and oxygenation goals are as follows: 1) arterial pH, 7.35~7.45; $PaCO_2$, 35–45 mm Hg; 2) SpO_2, 92%–97% for patients with a PEEP <10 cm H_2O and 88%–92% for patients with a PEEP >10 cm H_2O. To prevent ventilator-induced lung injury, the general principle of ventilator setting includes limiting driving pressure to 15cm H_2O, plateau pressure to 28cm H_2O (allowing for slightly higher plateau pressures (29–32 cm H_2O) for patients with increased chest wall elastance), PEEP to 20 cm H_2O. In patients with severe hypoxemia, FiO_2 can be more than 60%.[20] High-frequency oscillatory ventilation (HFOV) should be considered as an alternative ventilatory mode in patients in whom plateau airway pressures exceed 28 cm H_2O in the absence of clinical evidence of reduced chest wall compliance. ECMO may be considered in patients whose ventilation parameters have been maximized but still cannot achieve adequate gas exchange.[13]

In the conventional group, PEEP and FiO_2 will be adjusted according to the PEEP-FiO_2 table (Table 2) to achieve the target SpO_2 described above. In the lung recruitment group, RM and decremental PEEP

titration will be performed immediately after enrollment and applied at least twice a day until extubation. RM will also be repeated if patients meet any of the following three conditions: 1) $PaO_2 \leq 60$ mmHg; 2) $SpO_2 \leq 88\%$; 3) $PaCO_2 > 45$ mmHg. Additionally, physicians will apply routine care interventions for the general management of critically ill patients, according to current guideline standards.

Table 2. PEEP-FiO_2 table

FiO_2	PEEP	Adjustment
$FiO_2 \leq 40\%$	PEEP $\leq$ 8 cm H_2O	Increase in PEEP or FiO_2
	PEEP > 8 cm H_2O	Increase in FiO_2
FiO_2 ＞40%	PEEP $\leq$ 8 cm H_2O	Increase in PEEP
	PEEP > 8 cm H_2O	Increase in FiO_2

RM Procedure

Patients will be placed in SIMV-PC mode with a fixed driving pressure of 15 cm H_2O above PEEP. Respiratory rate (RR), inspiratory time (Ti), and FiO_2 will remain unchanged from baseline. Sequential RM will be performed, increasing PEEP by 5 cm H_2O every 2 minutes until a maximum PEEP of 20 cm H_2O. Then, PEEP will be decreased by 2 cm H_2O every 2 minutes when PEEP is >10 cm H_2O or by 1 cm H_2O every 2 minutes when PEEP is <10 cm H_2O. During the decremental phase of the maneuver, PEEP will be optimized to achieve better dynamic compliance (Cdyn) (decremental PEEP trial). Then, PEEP will be increased to 20 cm H_2O and maintained for 2 minutes. After RM, optimal PEEP will be set at the PEEP with the best Cdyn plus 2 cm H_2O, and the other parameters will be returned back to the previous level. Maneuvers will be manually performed using the Puritan Bennett™ 840 Ventilator (Covidien, Medtronic Inc., Minneapolis, MN) （Figure 2）. In our trial, RM will be performed by two respiratory therapists, one performing the procedure and the other monitoring the process.

Weaning from MV

All patients will follow the same analgesia and sedation protocols and treatment principles. Additionally, physicians will apply the same care interventions for general management of patients according to current guideline standards. Physicians will interrupt sedation once daily, and respiratory therapists will manage patients with the Spontaneous Breathing Trials (SBT) safety screen every morning. Patients who pass the SBT safety screen will undergo a 30-minute SBT with a pressure support ventilation of 5–7 cm H_2O, PEEP of 5 cm H_2O, and FiO_2 of ≤40%. When the SBT safety screen is successful, physicians and respiratory therapists will extubate patients [21].

Management of nasal continuous positive airway pressure (NCPAP)

Patients considered high-risk for failed extubation will receive preventative NCPAP in the immediate post-extubation period. Risk factors for extubation failure are as follows: 1) decreased left ventricular systolic function; 2) refractory atelectasis; 3) O-shaped tracheal cartilage and airway stenosis caused by cardiac expansion; 4) >20% decrease in PaO_2 after SBT. Patients without these risk factors will receive conventional oxygen therapy, shifting to NIV if any of the following five indications appear: 1) mild-to-moderate dyspnea, retraction or accessory muscle use, grunting, nasal flaring, head bobbing; 2) abnormal outcomes on arterial blood gas analysis (pH < 7.35, $PaCO_2$ > 45 mmHg [1 mmHg = 0.133 kPa], or PaO_2/FiO_2 < 250 mmHg); 3) SpO_2 < 92% with supplemental O_2; 4) requiring an oxygen flow of >2 L/min; 5) tachypnea, RR of >50 breaths per min (<1 year old) or RR >40 breaths per min (1–4 years old) [22-24].

In the initial stage of NCPAP, patients will receive CPAP at 4–6 cm H_2O and a total flow of either 6–12 L/min (infants) or 8–20 L/min (pediatrics) depending on their age. CPAP, FiO_2, and total flow will be adjusted to achieve target oxygenation and ventilation goals, as described above. If SpO_2 is <92%,

CPAP will be increased by 1–2 cm H_2O (maximum, 10 cm H_2O) and FiO_2 by 0.05–0.10 per increment. For patients with a SpO_2 of >97%, FiO_2 will be decreased first by 0.05 per decrement until FiO_2 is <0.35. If SpO_2 is still >97%, CPAP will be decreased by 1 cm H_2O per decrement. When a CPAP of 2–3 cm H_2O combined with a FiO_2 <0.35 is sufficient to maintain target oxygenation and ventilation goals, patients will be switched to conventional oxygen therapy.

Indications for reintubation are as follows: 1) respiratory acidosis (pH < 7.35 and $PaCO_2$ > 45 mmHg, or an increase in $PaCO_2$ of >15% compared with pre-extubation level); 2) hypoxemia (FiO_2 > 50%, PaO_2 < 60 mmHg, or SpO_2 < 90%); 3) rapid RR as defined in Table 3; 4) respiratory fatigue and severe dyspnea; 5) inability to maintain the natural airway；6）persistent respiratory acidosis, hypoxemia, dyspnea even on NCPAP/NIV [25].

Patients with occurrence of the first indication, the second indication, or any other two indications will be reintubated.

Table 3. Rapid RR based on ages

Age (years)	Respiratory rate (breaths per min)
<1	>60
1–2	>45
2–5	>40
>5	>35

Patient termination and withdrawal criteria

At any time, the next of kin can retreat patients from the study. Patients may be withdrawn from the study because of: (1)severe adverse events(barotrauma ， arrhythmia and cardiac arrest); or (2) violating or

deviating from the protocol；or（3）severe hypoxemia who meet the indication of ECMO or HFOV. If a patient is withdrawn for one of the three reasons mentioned, security analysis will be implemented.

Outcomes

The primary outcome is the duration of MV. The duration of MV refers to the time between admission to the ICU and extubation(hours). The secondary endpoints include PaO_2/FiO_2 (mmHg), respiratory system compliance, duration of non-invasive ventilation（from the initiation to the weaning ,hours）, reintubation rate in 48 hours after extubation, length of ICU stay(from the admission the ICU to discharge from ICU, days), length of hospital stay(from the admission the hospital to discharge from hospital ,days), occurrence of serious adverse event(barotrauma, arrhythmia and cardiac arrest) , postoperative pulmonary complications(respiratory infection, respiratory failure, pleural effusion, pneumothorax, atelectasis, bronchospasm, etc.). Before recruiting subjects, ventilator-free days through day 28 was added as a secondary outcome measure based on the lung recruitment studies in adults with ARDS and reviewers' opinions (If the patient dies before 28 days, ventilator-free days equals 0; If the patient is successfully weaned from mechanical ventilation within 28 days, ventilator-free days equals (28-x) ; If the patient requires mechanical ventilation for 28 days or more; ventilator-free days equals 0) .

Sample size

The duration of mechanical ventilation following cardiac surgery vary substantially across hospitals.[26] At the same time, no previous studies can be used as a reference.According to the information system data of health care before and after the implementation of RM in our PICU（2019 vs 2020）, the average duration of mechanical ventilation in pediatrics after cardiac surgery was 16 hours and 11 hours, respectively. The study sample size was calculated on the basis of an expected 11 hours of MV in the lung recruitment group and 16 hours in the conventional group. Allowing for a 10% dropout rate, 117

patients are required for each group. After reviewing multiple adult lung recruitment studies, we conclude that the sample size of 234 cases will be sufficient[5 27 28] .

Randomization

Patients will be randomized in a 1:1 ratio to a conventional group or to a lung recruitment group. The random allocation list was generated by a statistician with no clinical involvement in the trial using a computer-generated random number list. Then the statistician will use sequentially numbered containers to implement the random allocation sequence, and the treatment allocation group will be hidden beyond the coated card in the container. For patients who meet the required criteria, the investigator will open a randomized card that records the treatment allocation group. Hence, treatment allocation will be concealed.

Patient and Public Involvement

No patient and public involved.

Data collection and inspection

The principal investigators will centralize all data weekly and examine the accuracy of these data to promote data quality. Data collection for each patient will begin on the day that informed consent was received from the patient and will continue until the patient is discharged or transferred to another hospital. Data will be collected using a paper-based case report form (see Online Supplementary files 1-3) and an electronic database. Investigators will follow a schedule for data collection, including: (1) screening data, informed consent, demographic data, inclusion and exclusion criteria, and enrollment data; (2) baseline information (age, sex, ID, height, weight, diagnosis, type of surgery, pulmonary infection, airway stenosis, pulmonary hypertension, duration of cardiopulmonary bypass, Pediatric Risk of Mortality score, Risk Adjustment in Congenital Heart Surgery score(RACHS score), vasoactive-

inotropic score(VIS score), antibiotic therapy); (3) daily information on cardiovascular system (heart rate, blood pressure, central venous pressure, urine output, dosage of vasoactive agents), respiratory system (ventilator settings, PaO_2, $PaCO_2$, lung compliance), infection (white blood count, procalcitonin, C-reactive protein, interleukin-6), liver function (bilirubin, alanine aminotransferase, aspartate aminotransferase, albumin), renal function (urea nitrogen, creatinine); 4)prognosis: time of admission to ICU , extubation, initiation of NIV and reintubation , date of transferring out of the intensive care unit and date of discharge/death, whichever comes first**.**

Adverse events

RM related adverse events include transient hypotension (4weeks-1year SBP < 65mmHg, 1year-4years SBP < 70mmHg, 5years-12 years SBP < 80mmHg, >12 years SBP < 90mmHg), hypoxemia (SpO_2 < 84%) for more than 1 minute, and heart rate decreased or increased by more than 20% of the base value. RM won't be continued in those patients with adverse events and will be started again at another time. Severe adverse events include barotrauma (such as, pneumothorax, subcutaneous emphysema, mediastinal emphysema, interstitial emphysema), arrhythmias and cardiac arrest, etc. If severe adverse events happen, patient will be retreated from RM group. All patients who will receive RM will be monitored for blood pressure, SpO_2, and ECG, and will receive physical examination to assess barotrauma in real time. If necessary, lung ultrasound or chest imaging can be performed during or after the RM. Researchers will record and report adverse events and severe adverse events timely, at the same time, appropriate treatment for those adverse events will be prescribed to patients.

Data analysis

Descriptive statistics will be expressed as mean ± SD or median and interquartile range depending on the nature and distribution of the variables. Inferential statistics will use estimates of the mean of the

differences and their 95 % confidence intervals (CI). Variables normally distributed will be compared with the Student's t test. For variables without a normal distribution, the Mann-Whitney U rank test will be used for comparison. Categorical variables will be compared using Fisher's exact test. The primary outcome variable (total duration of MV) and ventilator-free days through day 28 will be assessed with the Student's t test or the Mann-Whitney U rank test dependent on the distribution of the data. The relative risks and their 95 % CIs will be estimated. For all these comparisons, we will consider a difference to be statistically significant if $p < 0.05$.

Safety and quality control

Recent studies have demonstrated the efficacy and safety of lung recruitment performed by incremental and decremental PEEP [8 10 11]. The study applicants and other primary investigators performed detailed and rigorous lung recruitment, which was applied to more than 200 patients at our pediatric ICU. Each patient demonstrated an increase in PaO_2, improved lung compliance, and a decrease in PaO_2, while none of them showed pneumothorax, subcutaneous emphysema, or other complications.

Ethics and dissemination

The protocol has been registered at the Chinese Clinical Trial registry (registration number: ChiCTR1900025990). Any revisions to the protocol will be documented in the ClinicalTrials.gov registry. Written informed consent has and will be obtained from all patients. All included patients will be able to access and correct the data. In the event of additional studies from the database, all investigators will keep the results confidential until publicly available, and they will not publish any data related to the database without approval of the principal investigator. We will publish the results of this trial in peer reviewed clinical journals and present the findings at conferences for widespread dissemination.

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Author Contributions

LJD and GPL together designed the study. ND and MMG drafted the manuscript. LJD and ND critically revised the manuscript. ND, MMG and WXX contributed to the study development. ND and MMG contributed equally to this paper.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The study has been approved by the ethics committee of West China Hospital, Sichuan University.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional unpublished data are available.

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Figure 1. Enrollment and Study Protocol.

Figure 2. Recruitment maneuver (RM) procedure. The RM will be performed in synchronized intermittent mandatory ventilation-pressure control (SIMV-PC) mode with a fixed driving pressure (DP) of 15 cmH_2O above positive end-expiratory pressure (PEEP). PEEP will be increased by 5 cmH_2O every 2 minutes to a maximum of 25 cmH_2O. During the decremental phase of the RM, PEEP will be optimized to achieve better dynamic compliance (Cdyn; decremental PEEP trial). The PEEP with the best Cdyn is called the closing pressure. After the decremental PEEP trial, the RM will be repeated with a PEEP of 20 cmH_2O and a DP of 15 cmH_2O. The optimal PEEP will be the closing pressure plus

2 cmH_2O. For example, Figure 2 shows that the PEEP with the best Cdyn is 9 cmH_2O. Thus, PEEP will be set to 11 cmH_2O.

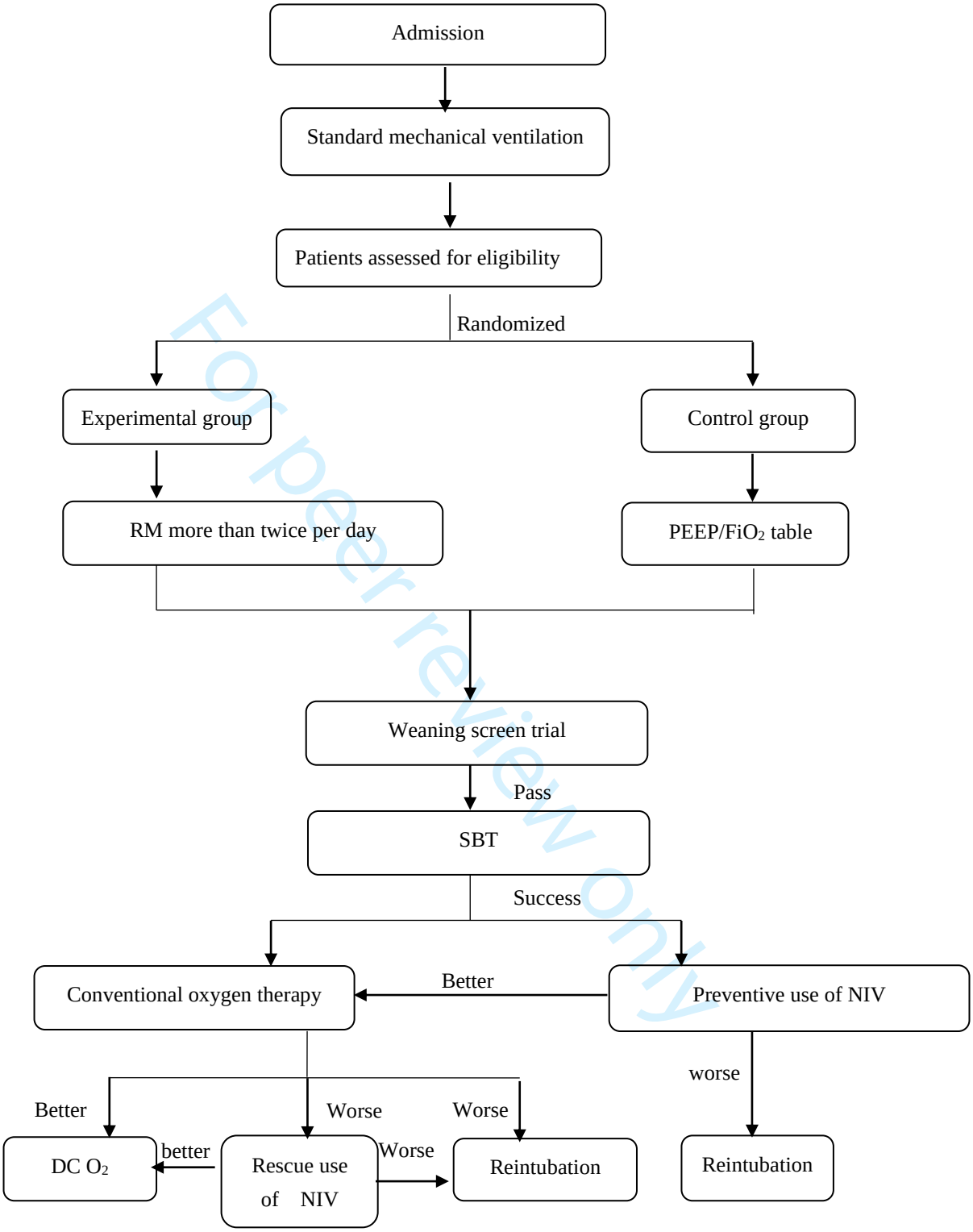
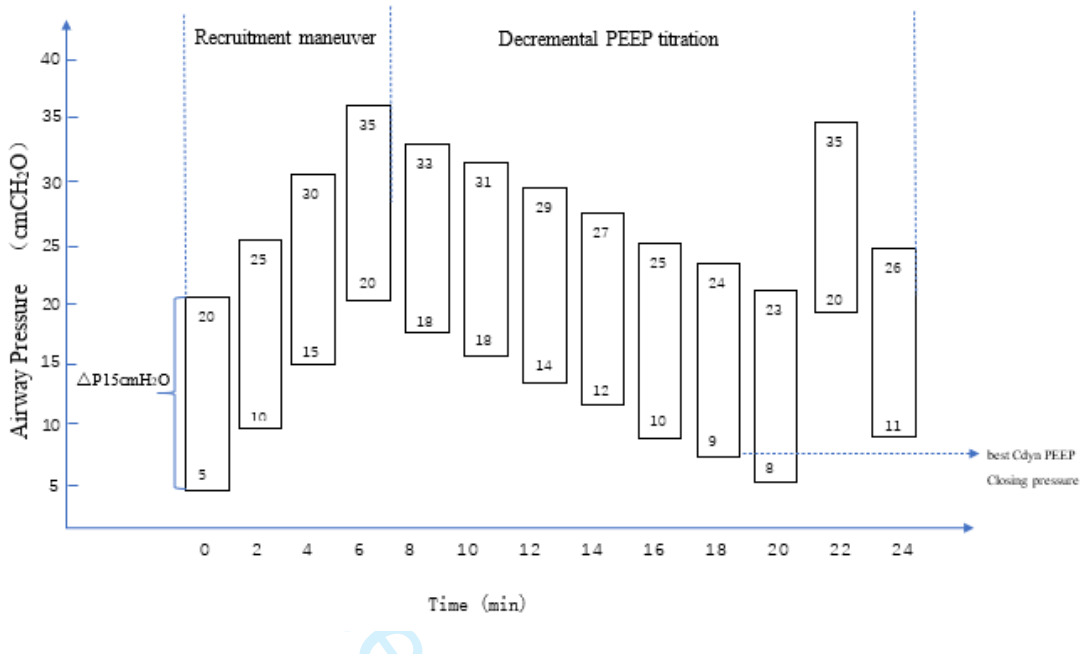


Figure 1 Enrollment and Study Protocol



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Patient demographics

patient ID _____ age _____ sex male□ female□

body weight _____kg height _____cm ethnic _____

Preoperative data

diagnosis _____

pulmonary infec yes□ no□ pulmonary a□yes (mild /moderate /s□no _____

airway stenosis yes□ no□

difficulty airway yes□ no□

Operative data

operative route middle incisi lateral incision□

bypass time,mins _____

Circulatory arres yes□ no□

Use of bloodpro yes□( ) ml no□

postoperative P/F(mmHg) _____ _____

ICU Admission

time _____ surgery _____

diagnosis _____

PRISM score _____ RACHS score _____

VIS score in 24 hours _____

(VIS score= dopamine + dobutamine + 100 × epinephrine + 10 × milrinone + 10 000 × Pituitrin+ 100 × nonepinephrine)

lowest P/F ,mmHg _____

Patient demographics

patient ID _____ age _____ sex male□ female□

body weight _____kg height _____cm ethnic _____

Preoperative data

diagnosis _____

pulmonary infec yes□ no□ pulmonary a□yes (mild /moderate /s□no _____

airway stenosis yes□ no□

difficulty airway yes□ no□

Operative data

operative route middle incisi lateral incision□

bypass time,mins _____

Circulatory arres yes□ no□

Use of bloodpro yes□( ) ml no□

postoperative P/F(mmHg) _____ _____

ICU Admission

time _____ surgery _____

diagnosis _____

PRISM score _____ RACHS score _____

(VIS score in 24 hours)

(VIS score= dopamine + dobutamine + 100 × epinephrine + 10 × milrinone + 10 000 × Pituitrin+ 100 × nonepinephrine)

lowest P/F ,mmHg _____

	D0	D1	D2	D3	D4
Date					
Circulatory system					
HR（ beat/min）					
BP（ mmHg）					
mean BP（mmHg ）					
CVP（ mmHg）					
fluid input（ ml）					
fluid output （ ml）					
dopamine μg/ kg·min）					
milrinone μg/ kg·min）					
epinephrine μg/ kg·min）					
nonepinephrine μg/ kg·r					
pituitrinμg/ kg·min）					
Respiratory system					
ventilation mode					
f（ /min）					
Pi（ cmH_2O）					
PEEP（ cmH_2O）					
FiO_2					
PaO_2					
PaO_2/FiO_2					
SaO_2					
Laboratory examination					
ABG					
pH					
PaO_2（ mmHg）					
$PaCO_2$（ mmHg）					
BE					
HCO_3^-（ mmHg）					
Lac（ mmol/L）					
Infectious index					
WBC（ $X10^9$）					
PCT					
CRP					
Liver function					
bilirubin					
ALT					
AST					
ALB（ g/L）					

Renal function

BUN

CREA umol/L

Blood routine examination

Plt

Hb g/L

	D0	D1	D2	D3	D4
date					
Etiological data					
positive sputum culture	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
pathogen					
Respiratory virus test					
influenza a virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
adenovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Bocavirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
rhinovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
H1N1	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Parainfluenza viru	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
chlamydia	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Human metapneumovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
influenza B virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Mycoplasma pneumoniae	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
H3N2	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
coronavirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
respiratory syncytial virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
TORCH		yes□ no□			
tomegalovirus antibody Ig		yes□ no□			
Rubella virus antibody IgM		yes□ no□			
lex virus antibody type I/II I		yes□ no□			
oplasma antibody(Tox-Ab)		yes□ no□			
Imaging finding					
new or progressive infiltra	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Body temperature（℃）					
highest body temperature					
lowest body temperature					

	D5	D6	D7	D8	D9
Date					
Circulatory system					
HR（ beat/min）					
BP（ mmHg）					
mean BP（mmHg ）					
CVP（ mmHg）					
fluid input（ ml）					
fluid output （ ml）					
dopamine μg/ kg·min）					
milrinone μg/ kg·min）					
epinephrine μg/ kg·min）					
nonepinephrine μg/ kg·r					
pituitrinμg/ kg·min）					
Respiratory system					
ventilation mode					
f（ /min）					
Pi（ cmH_2O）					
PEEP（ cmH_2O）					
FiO_2					
PaO_2					
PaO_2/FiO_2					
SaO_2					
Laboratory examination					
ABG					
pH					
PaO_2（ mmHg）					
$PaCO_2$（ mmHg）					
BE					
HCO_3^-（ mmHg）					
Lac（ mmol/L）					
Infectious index					
WBC（ $X10^9$）					
PCT					
CRP					
Liver function					
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ALB（ g/L）					

Renal function

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Blood routine examination

Plt

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	D5	D6	D7	D8	D9
date					
Etiological data					
positive sputum culture	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
pathogen					
Respiratory virus test					
influenza a virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
adenovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Bocavirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
rhinovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
H1N1	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Parainfluenza viru	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
chlamydia	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Human metapneumovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
influenza B virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Mycoplasma pneumoniae	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
H3N2	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
coronavirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
respiratory syncytial virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
TORCH		yes□ no□			
tomegalovirus antibody Ig					
Rubella virus antibody IgM					
lex virus antibody type I/II I					
oplasma antibody(Tox-Ab)					
Imaging finding					
new or progressive infiltra	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Body temperature（℃）					
highest body temperature					
lowest body temperature					

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A no funding
Roles and responsibilities: sponsor and funder	#5c	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	N/A no funding
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	N/A no funding

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	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	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	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	6

		be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
Interventions: modifications	#11b	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)	10-11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-11
Outcomes	#12	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	11

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11-12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	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	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the	12

		sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A, always be blinded
Methods: Data collection, management, and analysis			
Data collection plan	#18a	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	12-13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	12-13

		collected for participants who discontinue or deviate from intervention protocols	
Data management	#19	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	12-13
Statistics: outcomes	#20a	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	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A no subgroup analyses
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	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	14

		protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	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	N/A No interim results
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	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)	14
Consent or assent	#26a	Who will obtain informed consent or assent from	14

		potential trial participants or authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	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	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
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	N/A
Dissemination policy: trial results	#31a	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	15

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	**Appendices**
Biological specimens	#33	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	N/A

BMJ Open

Study protocol for a single-center randomized controlled trial to investigate the effect of lung recruitment in pediatric patients after cardiac surgery

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Study protocol for a single-center randomized controlled trial to investigate the effect of lung recruitment in pediatric patients after cardiac surgery

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Key words: pediatric, lung recruitment, cardiac surgery, hypoxemic respiratory failure

Abstract

Introduction

A number of published studies have revealed that lung recruitment can improve oxygenation, shorten the duration of mechanical ventilation (MV), and decrease mortality in adults with acute hypoxemic respiratory failure, especially patients with acute respiratory distress syndrome. However, few articles have assessed lung recruitment in pediatric patients, especially after cardiac surgery. This clinical trial aimed to determine whether lung recruitment can reduce the duration of MV in pediatric patients with hypoxemic respiratory failure after cardiac surgery.

Method and analysis

In this trial, we will randomly assign 234 pediatric patients (aged 28 days to 14 years) within 72 hours after cardiac surgery with an arterial oxygen tension (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2) of ≤300 to either a lung recruitment group or a conventional group. The primary endpoint will be the duration of MV. The secondary endpoints will be ventilator-free days, PaO_2/FiO_2, respiratory system compliance, duration of non-invasive ventilation, reintubation rate, length of ICU stay, length of hospital stay, occurrence of serious adverse events (barotrauma, persistent hypotension and arrhythmia), postoperative pulmonary complications.

Ethics and dissemination

The ethics committee of West China Hospital of Sichuan University granted ethics approval for this study (20/8/2019). The results will be published in peer-reviewed journals and presented at conferences.

Trial registration number: ChiCTR1900025990

Strengths and limitations of this study:

1. The protocol will be a randomized controlled trial, so the reliability of the results will be very high.

2. The incidence of hypoxic respiratory failure in pediatrics with congenital heart disease after surgery is low, and it will take a long time to achieve the expected sample size.

3. Because of lack of sufficient research data on lung recruitment in pediatrics, we do not know whether the methods, parameters of RM and the indications of repeat RM are reasonable, which may affect the outcome of patients.

Introduction

Hypoxemic respiratory failure, especially acute respiratory distress syndrome (ARDS) after cardiac surgery, is the main cause of prolonged mechanical ventilation (MV). General anesthesia, extracorporeal circulation, procedure-related lung injury, and inappropriate ventilation strategies are risk factors for hypoxemic respiratory failure in patients after cardiac surgery [1]. A recent prospective multi-center study diagnosed 10% of patients with ARDS after cardiac surgery [2]. Compared with adults, pediatric patients are more likely to suffer from hypoxemic respiratory failure after cardiac surgery because of their anatomical and physiological characteristics.

Lung recruitment maneuvers(RM) can prevent alveolar collapse, improve oxygenation, and enhance respiratory system compliance by temporarily increasing transpulmonary pressure [3]. Over the past two decades, a number of studies have confirmed the effectiveness of lung recruitment for improving oxygenation, reducing the duration of MV, and decreasing mortality in adults with hypoxemic respiratory failure, especially those diagnosed with ARDS [4-8]. However, studies investigating the clinical use of lung recruitment in pediatric patients are limited. Although several studies have reported that lung recruitment maneuvers combined with positive end-expiratory pressure (PEEP) titration can improve oxygenation and decrease the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) in pediatric patients with hypoxemic respiratory failure, no studies have assessed the effectiveness of lung recruitment in reducing the duration of MV in pediatric patients after cardiac surgery [9-19].

As a result, this single-center study was designed to determine whether lung recruitment maneuvers combined with PEEP titration can reduce the duration of MV and intensive care unit (ICU) stay, as well as all-cause mortality rate, in pediatric patients after cardiac surgery.

Methods

Study setting

This study adopted a prospective, single-center, parallel group, randomized, controlled design and is ongoing at West China Hospital of Sichuan University (January 2020 to December 2022). The ethics committee of West China Hospital of Sichuan University granted ethics approval (20/8/2019).

Eligibility criteria

The inclusion criteria are as follows: 1) pediatric patients after cardiac surgery whose cardiac anatomical deficiency was completely corrected after surgery; 2) pediatric patients aged 28 days to 14 years; 3) partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2) of <300 with PEEP⩾5cm H_2O within 72 hours after surgery.

The exclusion criteria are as follows: 1) pediatric patients deemed unsuitable for lung recruitment by the attending intensivist; 2) presence of an uncuffed endotracheal tube; 3) pneumothorax; 4) severe hemodynamic instability (requiring norepinephrine >0.2 μg/kg/min or epinephrine >0.2 μg/kg/min); 5) lack of consent from the next of kin; 6) diaphragmatic paralysis; 7) central nervous system complications; 8) raised intracranial pressure (>20 mmHg); 9) bronchopleural fistula;10)intracardiac shunt.

Participant selection and recruitment

Before identifying and screening patients for eligibility, all patients will be initially ventilated with synchronized intermittent mandatory ventilation-pressure control (SIMV-PC) using a Puritan Bennett™ 840 Ventilator (Covidien, Medtronic Inc., Minneapolis, MN) for 30 minutes (Figure 1). Then the first arterial blood gas analysis will be obtained. Specific ventilator settings are described in Table 1. $PetCO_2$, an index of $PaCO_2$, will be monitored using a carbon dioxide (CO_2) analyzer. Informed consent will be obtained by the doctor in charge. All information will be transferred into an electronic database so that the trial office can monitor recruitment and refusal rates.

Table 1. Ventilator mode and initial settings.

Age	Mode	F	Ti	Pi	Ps	FiO_2	PEEP	vsens
4 weeks < age ≤ 1 year	SIMV-PC	30	0.67	12	10	50%	5	1
1 year < age ≤ 3 years	SIMV-PC	25	0.80	12	10	50%	5	1
3 years < age ≤ 12 years	SIMV-PC	20	0.86	12	10	50%	5	1
Age > 12 years	SIMV-PC	15	1.0	12	10	50%	5	1

Intervention

The intervention group comprises patients who have undergone lung recruitment and PEEP titration. The control group comprises patients who have undergone conventional MV. Patients will be prospectively followed from the day of enrollment for at least 28 days or until discharge, whichever comes first.

In both groups, the ventilation and oxygenation goals are as follows: 1) arterial pH, 7.35~7.45; $PaCO_2$, 35–45 mm Hg; 2) SpO_2, 92%–97% for patients with a PEEP <10 cm H_2O and 88%–92% for patients with a PEEP >10 cm H_2O. To prevent ventilator-induced lung injury, the general principle of ventilator setting includes limiting driving pressure to 15cm H_2O, plateau pressure to 28cm H_2O (allowing for slightly higher plateau pressures (29–32 cm H_2O) for patients with increased chest wall elastance), PEEP to 20 cm H_2O. In patients with severe hypoxemia, FiO_2 can be more than 60%.[20] High-frequency oscillatory ventilation (HFOV) should be considered as an alternative ventilatory mode in patients in whom plateau airway pressures exceed 28 cm H_2O in the absence of clinical evidence of reduced chest wall compliance. ECMO may be considered in patients whose ventilation parameters have been maximized but still cannot achieve adequate gas exchange.[13]

In the conventional group, PEEP and FiO_2 will be adjusted according to the PEEP-FiO_2 table (Table 2) to achieve the target SpO_2 described above. In the lung recruitment group, RM and decremental PEEP

titration will be performed immediately after enrollment and applied at least twice a day until extubation. RM will also be repeated if patients meet any of the following three conditions: 1) $PaO_2 \leq 60$ mmHg; 2) $SpO_2 \leq 88\%$; 3) $PaCO_2 > 45$ mmHg. Additionally, physicians will apply routine care interventions for the general management of critically ill patients, according to current guideline standards.

Table 2. PEEP-FiO_2 table

FiO_2	PEEP	Adjustment
$FiO_2 \leq 40\%$	PEEP $\leq$ 8 cm H_2O	Increase in PEEP or FiO_2
	PEEP > 8 cm H_2O	Increase in FiO_2
FiO_2 ＞40%	PEEP $\leq$ 8 cm H_2O	Increase in PEEP
	PEEP > 8 cm H_2O	Increase in FiO_2

RM Procedure

Patients will be placed in SIMV-PC mode with a fixed driving pressure of 15 cm H_2O above PEEP. Respiratory rate (RR), inspiratory time (Ti), and FiO_2 will remain unchanged from baseline. Sequential RM will be performed, increasing PEEP by 5 cm H_2O every 2 minutes until a maximum PEEP of 20 cm H_2O. Then, PEEP will be decreased by 2 cm H_2O every 2 minutes when PEEP is >10 cm H_2O or by 1 cm H_2O every 2 minutes when PEEP is <10 cm H_2O. During the decremental phase of the maneuver, PEEP will be optimized to achieve better dynamic compliance (Cdyn) (decremental PEEP trial). Then, PEEP will be increased to 20 cm H_2O and maintained for 2 minutes. After RM, optimal PEEP will be set at the PEEP with the best Cdyn plus 2 cm H_2O, and the other parameters will be returned back to the previous level. Maneuvers will be manually performed using the Puritan Bennett™ 840 Ventilator (Covidien, Medtronic Inc., Minneapolis, MN) （Figure 2）. In our trial, RM will be performed by two respiratory therapists, one performing the procedure and the other monitoring the process.

Weaning from MV

All patients will follow the same analgesia and sedation protocols and treatment principles. Additionally, physicians will apply the same care interventions for general management of patients according to current guideline standards. Physicians will interrupt sedation once daily, and respiratory therapists will manage patients with the Spontaneous Breathing Trials (SBT) safety screen every morning. Patients who pass the SBT safety screen will undergo a 30-minute SBT with a pressure support ventilation of 5–7 cm H_2O, PEEP of 5 cm H_2O, and FiO_2 of ≤40%. When the SBT safety screen is successful, physicians and respiratory therapists will extubate patients [21].

Management of nasal continuous positive airway pressure (NCPAP)

Patients considered high-risk for failed extubation will receive preventative NCPAP in the immediate post-extubation period. Risk factors for extubation failure are as follows: 1) decreased left ventricular systolic function; 2) refractory atelectasis; 3) O-shaped tracheal cartilage and airway stenosis caused by cardiac expansion; 4) >20% decrease in PaO_2 after SBT. Patients without these risk factors will receive conventional oxygen therapy, shifting to NIV if any of the following five indications appear: 1) mild-to-moderate dyspnea, retraction or accessory muscle use, grunting, nasal flaring, head bobbing; 2) abnormal outcomes on arterial blood gas analysis (pH < 7.35, $PaCO_2$ > 45 mmHg [1 mmHg = 0.133 kPa], or PaO_2/FiO_2 < 250 mmHg); 3) SpO_2 < 92% with supplemental O_2; 4) requiring an oxygen flow of >2 L/min; 5) tachypnea, RR of >50 breaths per min (<1 year old) or RR >40 breaths per min (1–4 years old) [22-24].

In the initial stage of NCPAP, patients will receive CPAP at 4–6 cm H_2O and a total flow of either 6–12 L/min (infants) or 8–20 L/min (pediatrics) depending on their age. CPAP, FiO_2, and total flow will be adjusted to achieve target oxygenation and ventilation goals, as described above. If SpO_2 is <92%,

CPAP will be increased by 1–2 cm H_2O (maximum, 10 cm H_2O) and FiO_2 by 0.05–0.10 per increment. For patients with a SpO_2 of >97%, FiO_2 will be decreased first by 0.05 per decrement until FiO_2 is <0.35. If SpO_2 is still >97%, CPAP will be decreased by 1 cm H_2O per decrement. When a CPAP of 2–3 cm H_2O combined with a FiO_2 <0.35 is sufficient to maintain target oxygenation and ventilation goals, patients will be switched to conventional oxygen therapy.

Indications for reintubation are as follows: 1) respiratory acidosis (pH < 7.35 and $PaCO_2$ > 45 mmHg, or an increase in $PaCO_2$ of >15% compared with pre-extubation level); 2) hypoxemia (FiO_2 > 50%, PaO_2 < 60 mmHg, or SpO_2 < 90%); 3) rapid RR as defined in Table 3; 4) respiratory fatigue and severe dyspnea; 5) inability to maintain the natural airway；6）persistent respiratory acidosis, hypoxemia, dyspnea even on NCPAP/NIV [25].

Patients with occurrence of the first indication, the second indication, or any other two indications will be reintubated.

Table 3. Rapid RR based on ages

Age (years)	Respiratory rate (breaths per min)
<1	>60
1–2	>45
2–5	>40
>5	>35

Patient termination and withdrawal criteria

At any time, the next of kin can retreat patients from the study. Patients may be withdrawn from the study because of: (1)severe adverse events(barotrauma ， arrhythmia and cardiac arrest); or (2) violating or

deviating from the protocol；or（3）severe hypoxemia who meet the indication of ECMO or HFOV. If a patient is withdrawn for one of the three reasons mentioned, security analysis will be implemented.

Outcomes

The primary outcome is the duration of MV. The duration of MV refers to the time between admission to the ICU and extubation(hours). The secondary endpoints include PaO_2/FiO_2 (mmHg), respiratory system compliance, duration of non-invasive ventilation（from the initiation to the weaning ,hours）, reintubation rate in 48 hours after extubation, length of ICU stay(from the admission the ICU to discharge from ICU, days), length of hospital stay(from the admission the hospital to discharge from hospital ,days), occurrence of serious adverse event(barotrauma, arrhythmia and cardiac arrest) , postoperative pulmonary complications(respiratory infection, respiratory failure, pleural effusion, pneumothorax, atelectasis, bronchospasm, etc.). Before recruiting subjects, ventilator-free days through day 28 was added as a secondary outcome measure based on the lung recruitment studies in adults with ARDS and reviewers' opinions (If the patient dies before 28 days, ventilator-free days equals 0; If the patient is successfully weaned from mechanical ventilation within 28 days, ventilator-free days equals (28-x) ; If the patient requires mechanical ventilation for 28 days or more; ventilator-free days equals 0) .

Sample size

The duration of mechanical ventilation following cardiac surgery vary substantially across hospitals.[26] At the same time, no previous studies can be used as a reference.According to the information system data of health care before and after the implementation of RM in our PICU（2019 vs 2020）, the average duration of mechanical ventilation in pediatrics after cardiac surgery was 16 hours and 11 hours, respectively. The study sample size was calculated on the basis of an expected 11 hours of MV in the lung recruitment group and 16 hours in the conventional group. Allowing for a 10% dropout rate, 117

patients are required for each group. After reviewing multiple adult lung recruitment studies, we conclude that the sample size of 234 cases will be sufficient[5 27 28] .

Randomization

Patients will be randomized in a 1:1 ratio to a conventional group or to a lung recruitment group. The random allocation list was generated by a statistician with no clinical involvement in the trial using a computer-generated random number list. Then the statistician will use sequentially numbered containers to implement the random allocation sequence, and the treatment allocation group will be hidden beyond the coated card in the container. For patients who meet the required criteria, the investigator will open a randomized card that records the treatment allocation group. Hence, treatment allocation will be concealed.

Patient and Public Involvement

No patient and public involved.

Data collection and inspection

The principal investigators will centralize all data weekly and examine the accuracy of these data to promote data quality. Data collection for each patient will begin on the day that informed consent was received from the patient and will continue until the patient is discharged or transferred to another hospital. Data will be collected using a paper-based case report form (see Online Supplementary files 1-3) and an electronic database. Investigators will follow a schedule for data collection, including: (1) screening data, informed consent, demographic data, inclusion and exclusion criteria, and enrollment data; (2) baseline information (age, sex, ID, height, weight, diagnosis, type of surgery, pulmonary infection, airway stenosis, pulmonary hypertension, duration of cardiopulmonary bypass, Pediatric Risk of Mortality score, Risk Adjustment in Congenital Heart Surgery score(RACHS score), vasoactive-

inotropic score(VIS score), antibiotic therapy); (3) daily information on cardiovascular system (heart rate, blood pressure, central venous pressure, urine output, dosage of vasoactive agents), respiratory system (ventilator settings, PaO_2, $PaCO_2$, lung compliance), infection (white blood count, procalcitonin, C-reactive protein, interleukin-6), liver function (bilirubin, alanine aminotransferase, aspartate aminotransferase, albumin), renal function (urea nitrogen, creatinine); 4)prognosis: time of admission to ICU , extubation, initiation of NIV and reintubation , date of transferring out of the intensive care unit and date of discharge/death, whichever comes first**.**

Adverse events

RM related adverse events include transient hypotension (4weeks-1year SBP < 65mmHg, 1year-4years SBP < 70mmHg, 5years-12 years SBP < 80mmHg, >12 years SBP < 90mmHg), hypoxemia (SpO_2 < 84%) for more than 1 minute, and heart rate decreased or increased by more than 20% of the base value. RM won't be continued in those patients with adverse events and will be started again at another time. Severe adverse events include barotrauma (such as, pneumothorax, subcutaneous emphysema, mediastinal emphysema, interstitial emphysema), arrhythmias and cardiac arrest, etc. If severe adverse events happen, patient will be retreated from RM group. All patients who will receive RM will be monitored for blood pressure, SpO_2, and ECG, and will receive physical examination to assess barotrauma in real time. If necessary, lung ultrasound or chest imaging can be performed during or after the RM. Researchers will record and report adverse events and severe adverse events timely, at the same time, appropriate treatment for those adverse events will be prescribed to patients.

Data analysis

Descriptive statistics will be expressed as mean ± SD or median and interquartile range depending on the nature and distribution of the variables. Inferential statistics will use estimates of the mean of the

differences and their 95 % confidence intervals (CI). Variables normally distributed will be compared with the Student's t test. For variables without a normal distribution, the Mann-Whitney U rank test will be used for comparison. Categorical variables will be compared using Fisher's exact test. The primary outcome variable (total duration of MV) and ventilator-free days through day 28 will be assessed with the Student's t test or the Mann-Whitney U rank test dependent on the distribution of the data. The relative risks and their 95 % CIs will be estimated. For all these comparisons, we will consider a difference to be statistically significant if $p < 0.05$.

Safety and quality control

Recent studies have demonstrated the efficacy and safety of lung recruitment performed by incremental and decremental PEEP [8 10 11]. The study applicants and other primary investigators performed detailed and rigorous lung recruitment, which was applied to more than 200 patients at our pediatric ICU. Each patient demonstrated an increase in PaO_2, improved lung compliance, and a decrease in PaO_2, while none of them showed pneumothorax, subcutaneous emphysema, or other complications.

Ethics and dissemination

The protocol has been registered at the Chinese Clinical Trial registry (registration number: ChiCTR1900025990). Any revisions to the protocol will be documented in the ClinicalTrials.gov registry. Written informed consent has and will be obtained from all patients. All included patients will be able to access and correct the data. In the event of additional studies from the database, all investigators will keep the results confidential until publicly available, and they will not publish any data related to the database without approval of the principal investigator. We will publish the results of this trial in peer reviewed clinical journals and present the findings at conferences for widespread dissemination.

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Author Contributions

LJD and GPL together designed the study. ND and MMG drafted the manuscript. LJD and ND critically revised the manuscript. ND, MMG and WXX contributed to the study development. ND and MMG contributed equally to this paper.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The study has been approved by the ethics committee of West China Hospital, Sichuan University.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional unpublished data are available.

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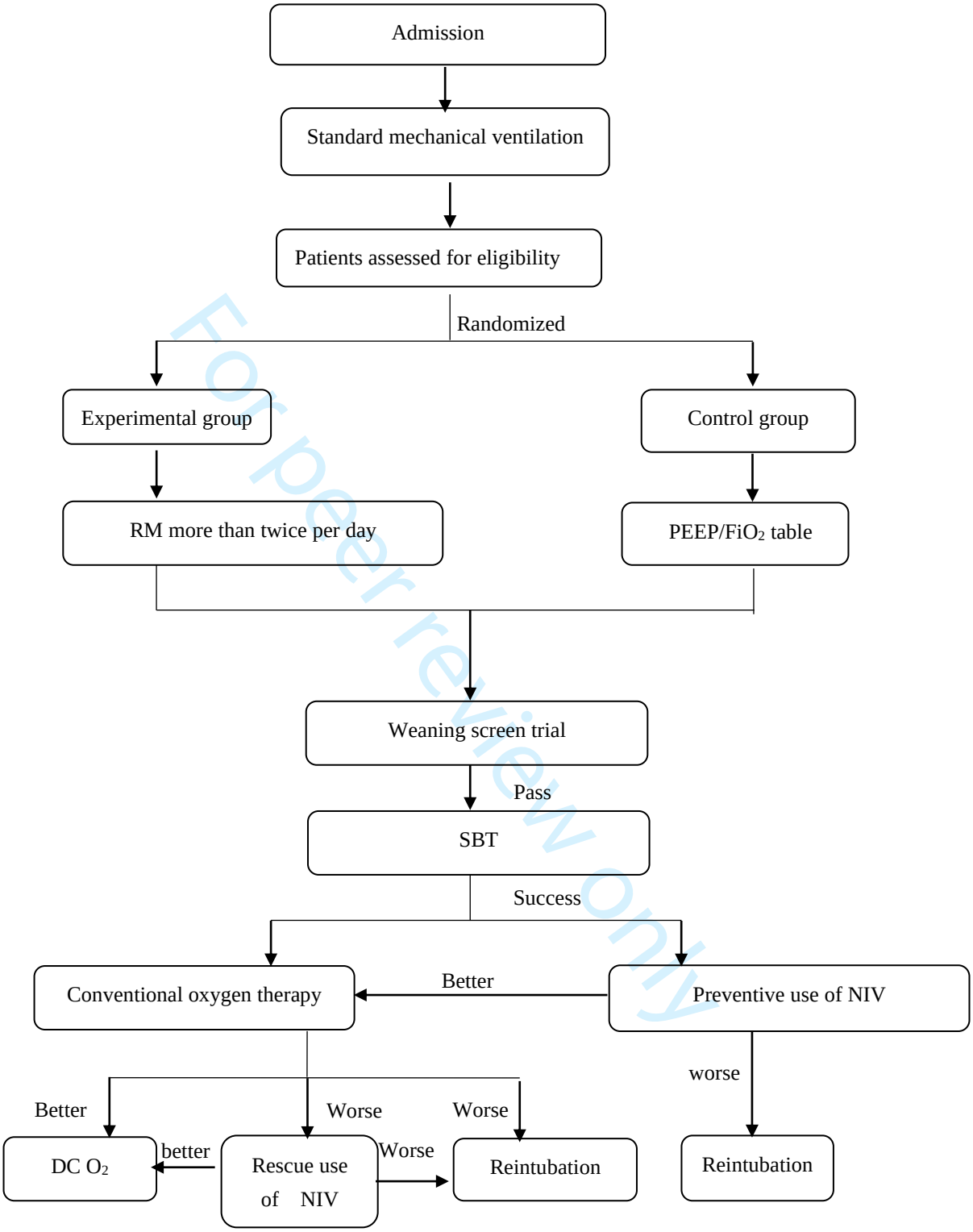
Figure 1. Enrollment and Study Protocol.

Figure 2. Recruitment maneuver (RM) procedure. The RM will be performed in synchronized intermittent mandatory ventilation-pressure control (SIMV-PC) mode with a fixed driving pressure (DP) of 15 cmH_2O above positive end-expiratory pressure (PEEP). PEEP will be increased by 5 cmH_2O every 2 minutes to a maximum of 25 cmH_2O. During the decremental phase of the RM, PEEP will be optimized to achieve better dynamic compliance (Cdyn; decremental PEEP trial). The PEEP with the best Cdyn is called the closing pressure. After the decremental PEEP trial, the RM will be repeated with a PEEP of 20 cmH_2O and a DP of 15 cmH_2O. The optimal PEEP will be the closing pressure plus

2 cmH_2O. For example, Figure 2 shows that the PEEP with the best Cdyn is 9 cmH_2O. Thus, PEEP will be set to 11 cmH_2O.



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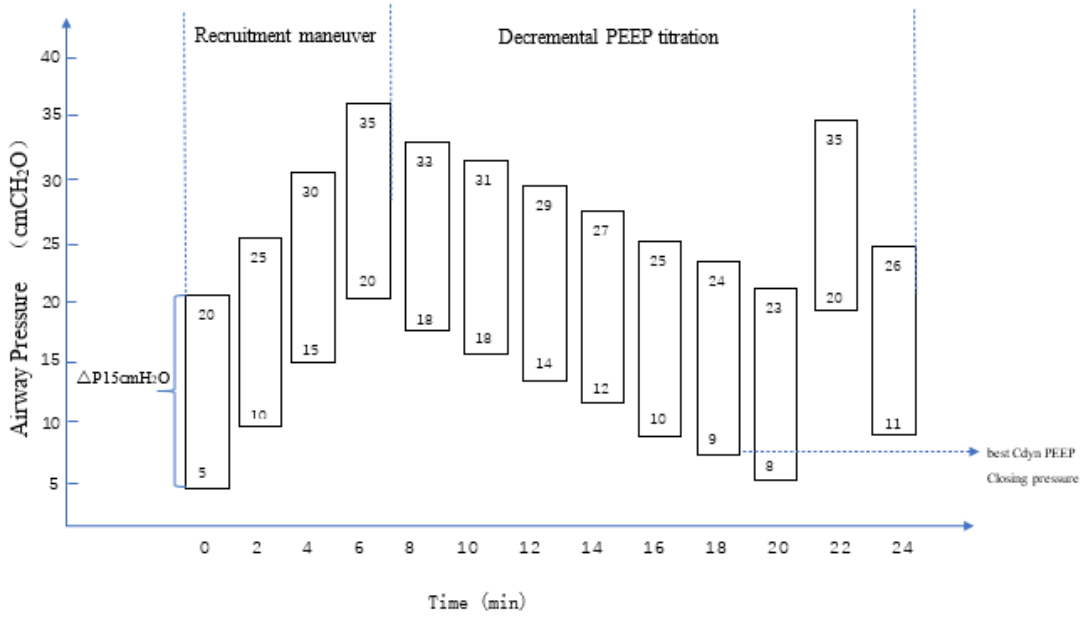

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Patient demographics

patient ID _____ age _____ sex male□ female□

body weight _____kg height _____cm ethnic _____

Preoperative data

diagnosis _____

pulmonary infec yes□ no□ pulmonary a□yes (mild /moderate /s□no _____

airway stenosis yes□ no□

difficulty airway yes□ no□

Operative data

operative route middle incisi lateral incision□

bypass time,mins _____

Circulatory arres yes□ no□

Use of bloodpro yes□( ) ml no□

postoperative P/F(mmHg) _____ _____

ICU Admission

time _____ surgery _____

diagnosis _____

PRISM score _____ RACHS score _____

VIS score in 24 hours _____

(VIS score= dopamine + dobutamine + 100 × epinephrine + 10 × milrinone + 10 000 × Pituitrin+ 100 × nonepinephrine)

lowest P/F ,mmHg _____

Patient demographics

patient ID _____ age _____ sex male□ female□

body weight _____kg height _____cm ethnic _____

Preoperative data

diagnosis _____

pulmonary infec yes□ no□ pulmonary a□yes (mild /moderate /s□no _____

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postoperative P/F(mmHg) _____ _____

ICU Admission

time _____ surgery _____

diagnosis _____

PRISM score _____ RACHS score _____

(VIS score in 24 hours)

(VIS score= dopamine + dobutamine + 100 × epinephrine + 10 × milrinone + 10 000 × Pituitrin+ 100 × nonepinephrine)

lowest P/F ,mmHg _____

	D0	D1	D2	D3	D4
Date					
Circulatory system					
HR（beat/min）					
BP（mmHg）					
mean BP（mmHg）					
CVP（mmHg）					
fluid input（ml）					
fluid output （ml）					
dopamine μg/（kg·min）					
milrinone μg/（kg·min）					
epinephrine μg/（kg·min）					
nonepinephrine μg/（kg·r					
pituitrinμg/（kg·min）					
Respiratory system					
ventilation mode					
f（/min）					
Pi（cmH_2O）					
PEEP（cmH_2O）					
FiO_2					
PaO_2					
PaO_2/FiO_2					
SaO_2					
Laboratory examination					
ABG					
pH					
PaO_2（mmHg）					
$PaCO_2$（mmHg）					
BE					
HCO_3^-（mmHg）					
Lac（mmol/L）					
Infectious index					
WBC（$X10^9$）					
PCT					
CRP					
Liver function					
bilirubin					
ALT					
AST					
ALB（g/L）					

Renal function

BUN

CREA（umol/L）

Blood routine examination

Plt

Hb（g/L）

	D0	D1	D2	D3	D4
date					
Etiological data					
positive sputum culture	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
pathogen					
Respiratory virus test					
influenza a virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
adenovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Bocavirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
rhinovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
H1N1	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Parainfluenza viru	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
chlamydia	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Human metapneumovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
influenza B virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Mycoplasma pneumoniae	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
H3N2	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
coronavirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
respiratory syncytial virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
TORCH		yes□ no□			
tomegalovirus antibody Ig		yes□ no□			
Rubella virus antibody IgM		yes□ no□			
lex virus antibody type I/II I		yes□ no□			
oplasma antibody(Tox-Ab)I		yes□ no□			
Imaging finding					
new or progressive infiltra	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Body temperature（℃）					
highest body temperature					
lowest body temperature					

	D5	D6	D7	D8	D9
Date					
Circulatory system					
HR（beat/min）					
BP（mmHg）					
mean BP（mmHg）					
CVP（mmHg）					
fluid input（ml）					
fluid output （ml）					
dopamine μg/（kg·min）					
milrinone μg/（kg·min）					
epinephrine μg/（kg·min）					
nonepinephrine μg/（kg·r					
pituitrinμg/（kg·min）					
Respiratory system					
ventilation mode					
f（/min）					
Pi（cmH_2O）					
PEEP（cmH_2O）					
FiO_2					
PaO_2					
PaO_2/FiO_2					
SaO_2					
Laboratory examination					
ABG					
pH					
PaO_2（mmHg）					
$PaCO_2$（mmHg）					
BE					
HCO_3^-（mmHg）					
Lac（mmol/L）					
Infectious index					
WBC（$X10^9$）					
PCT					
CRP					
Liver function					
bilirubin					
ALT					
AST					
ALB（g/L）					

Renal function

BUN

CREA（umol/L）

Blood routine examination

Plt

Hb（g/L）

	D5	D6	D7	D8	D9
date					
Etiological data					
positive sputum culture	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
pathogen					
Respiratory virus test					
influenza a virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
adenovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Bocavirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
rhinovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
H1N1	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Parainfluenza viru	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
chlamydia	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Human metapneumovirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
influenza B virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Mycoplasma pneumoniae	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
H3N2	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
coronavirus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
respiratory syncytial virus	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
TORCH		yes□ no□			
tomegalovirus antibody Ig					
Rubella virus antibody IgM					
lex virus antibody type I/II I					
oplasma antibody(Tox-Ab)I					
Imaging finding					
new or progressive infiltra	yes□ no□	yes□ no□	yes□ no□	yes□ no□	yes□ no□
Body temperature（℃）					
highest body temperature					
lowest body temperature					

Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A no funding
Roles and responsibilities: sponsor and funder	#5c	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	N/A no funding
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	N/A no funding

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	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	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	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	6

		be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
Interventions: modifications	#11b	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)	10-11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-11
Outcomes	#12	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	11

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11-12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	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	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the	12

		sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A, always be blinded
Methods: Data collection, management, and analysis			
Data collection plan	#18a	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	12-13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	12-13

		collected for participants who discontinue or deviate from intervention protocols	
Data management	#19	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	12-13
Statistics: outcomes	#20a	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	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A no subgroup analyses
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	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	14

		protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	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	N/A No interim results
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	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)	14
Consent or assent	#26a	Who will obtain informed consent or assent from	14

		potential trial participants or authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	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	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
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	N/A
Dissemination policy: trial results	#31a	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	15

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	**Appendices**
Biological specimens	#33	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	N/A