

The effects of protective lung ventilation on regional cerebral oxygen saturation in intracranial tumor operation during dura opening—study protocol for a randomized controlled trial.

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Study protocol

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Abstract

Abstract Objective: To investigate the effects of protective lung ventilation on regional cerebral oxygen saturation during dura opening, that is from Ta (after dura opening) to Tb (before dura closing), in patients undergoing intracranial tumor surgery. **Methods:** This is a randomized, controlled trial which will be carried out at the second affiliated hospital of Soochow University. Fifty-four patients undergoing intracranial tumor surgery will be randomly allocated to the control group (C group) or the protective lung ventilation group (P group). In the C group, tidal volume (VT) will be set at 8 ml/kg of predicted body weight, but positive end-expiratory pressure (PEEP) and recruitment maneuvers will not be used. In the P group, VT will be set at 6 ml/kg of predicted body weight combined with individualized PEEP during dura opening, while in other periods of general anesthesia, VT will be set at 8 ml/kg of predicted body weight. Regional cerebral oxygen saturation (rSO₂), partial pressure of oxygen (PaO₂) and carbon dioxide (PaCO₂), oxygenation index (OI), lactic acid level (Lac) in arterial blood, and mean arterial pressure (MAP) will be compared before anesthesia (T₀), before dura opening (T₁), after dura closing (T₂) and 24 h after surgery (T₃). Lung ultrasound scores (LUS) will be performed at T₀ and T₃. The degree of brain relaxation at T₁ and T₂ will be evaluated by the surgeon using the brain relaxation scale. Amount of vasoactive drugs used and blood loss will be recorded during surgery. The duration of operation and reoperation rate will be recorded. **Discussion:** This study aims to determine whether protective lung ventilation during dura opening can improve regional cerebral oxygen saturation and the state of pulmonary ventilation in patients undergoing intracranial tumor surgery, and to investigate whether this strategy does not affect the degree of brain tissue swelling and the reoperation rate after operation. If our results are positive, this study will show that protective lung ventilation during dura opening can be used effectively and safely in neurosurgical patients undergoing craniotomy for tumor resection. **Trial registration:** chictr.org.cn, ID: ChiCTR1900025632. Registered on 3 September 2019. Study protocol version 2.0. **Keywords:** Randomized controlled trial, Regional cerebral oxygen saturation, Lung ultrasound, Brain relaxation, Craniotomy

Background

With the development of society and the progress of science and technology, more and more people receive delicate and complex procedures such as neurosurgery. Almost all these patients are under general anesthesia which is basically inseparable from mechanical ventilation. 15%–20% of patients had different degrees of alveolar collapse at the bottom of the lung before operation, and this phenomenon could persist for several days after operation due to the influence of mechanical ventilation of endotracheal intubation. The pulmonary complications play an important role in death and disability in patients with general anesthesia[1–3]. Craniotomy always needs a long time for general anesthesia and prolonged mechanical ventilation, which leads to a higher risk of postoperative atelectasis and pulmonary infection[4,5]. Atelectasis and pulmonary infection can seriously affect pulmonary ventilation, even lead to severe hypoxemia. Moreover, the long period of brain operation is more likely to cause the imbalance of brain oxygen supply and consumption. The changeunbalance of brain oxygen supply and consumption balance may lead to the changedeterioration of brain function, and the change ofsuch as postoperative

cognitive function[6]. Postoperative cognitive dysfunction (POCD) will lower the quality of life, increase mortality and aggravate the financial and mental burden of patients.

Protective lung ventilation (PLV) strategies have been recognized by many anesthesiologists and widely used in clinical anesthesia[7,8]. Relevant studies suggest that low-tide volume combined with PEEP ventilation and alveolar recruitment maneuver (ARM) is the most widely used lung protective ventilation strategy, which can reduce lung volume damage and pulmonary barotrauma, improve pulmonary function and decrease postoperative pulmonary complications[9]. Theoretically, low tide volume prevents excessive alveolar expansion[10] and higher PEEP prevents [pulmonary atelectasis](#)[11]. However, gradually increased PEEP to the level of 20 cm H₂O or even higher is often needed in traditional protective lung ventilation strategies[5,9] which will obviously affect the circulation and intracranial pressure of patients[12], and may increase airway pressure, reduce cerebral venous reflux and intraoperative operating space, thus limiting its application in patients with craniotomy. In addition, anesthesiologists often use a single PEEP or pulmonary retention mode, ignoring individual differences among patients, thus affecting the effect of protective lung ventilation[13,14].

In recent years, with the development of medical monitoring equipment, regional cerebral oxygen saturation monitoring technology[15,16] has been gradually developed and used in clinical anesthesia. It provides a condition for real-time monitoring the perfusion level of brain tissue in patients undergoing craniotomy, and provides technical support for carrying out clinical research on protective pulmonary ventilation during craniotomy.

Near infrared spectrometer (NIRS) using near infrared technology is similar to the pulse oxygen monitor which is commonly used. Near-infrared light with wavelength of 650~1100nm has a good penetrability to human tissues such as scalp, skull and brain, even up to several centimeters. The major color base (Hemoglobin, Hb) attenuated in the intracranial area of NIR light result in the changes in the light intensity of penetrating human tissuesorganisms. The oxygenation of brain tissues was evaluated by measuring the changes in the absorption spectrum, which was accompanied with changes in oxygenation state[17].

Up to present, in consideration of the risks associated with PEEP and recruitment maneuvers, there are no correlative randomized controlled trials to studyexplore the efficacy and safety of intraoperative pulmonary protective ventilation strategies in patients undergoing craniotomy. However, due to the disappearance of intracranial pressure after the dura opening during craniotomy, individualized protective pulmonary ventilation strategy may avoid the adverse effects on cerebral perfusion, but there is no research on this. However, with the increasing number and complexity of neurosurgery, it is necessary to adopt appropriate protective ventilation strategies during anesthesia.. The purpose of this study is to evaluate the effects of protective lung ventilation strategies with individualized PEEP during dura opening and conventional ventilation on regional cerebral oxygen saturation in patients undergoing intracranial tumor surgery. Other outcomes include intraoperative brain relaxation, the lung ultrasound scores 24h after surgery, the reoperation rate within one week after operation, the amount of blood loss and dosage of vasoactive drugs during surgery.

Methods

Study design

This is a single-center, randomized, parallel-group controlled trial which is being conducted at the second affiliated hospital of Soochow University. Recruitment began in 3 September 2019–November 2019. Schedule of enrolment, interventions, and assessments will be shown in figure 1. Basic information of patients will be shown in table 1.

Randomization will be conducted via a computer-generated computer-generated randomized controlled table. Patients who meet the enrollment criteria will be randomly allocated to C group or P group within 24 h before surgery. The allocation ratio is 1:1. Permuted randomization will be used and stratified by age. The designated staff will perform the allocation sequence. The designated staff assistants will assign participants to interventions. This research staff will implement the allocation sequence through sealed, opaque and stapled envelopes. Corresponding envelopes will not be opened until the enrolled participants complete the trial. The anesthesiologist who is responsible for the anesthesia implementation will know the grouping but not participate in the follow-up visit. However, the neurosurgeon who evaluates brain relaxation will be blinded to the group allocation. The patients and the outcome assessor are all blinded to the grouping.

Fig. 1 Schedule of enrolment, interventions, and assessments

Tab 1. Patient Characteristics and Baseline Data

Characteristic	C Group	P Group
Male/female		
Age, yr		
BMI, kg/m ²		
Predicted body weight, kg		
ASA physical status, I/II		

Selection and withdrawal of participants

Recruitment

Participants will be recruited from the neurosurgical wards and identified by their presence on surgical lists. The investigator informs the participant or the participant's legal representative of all aspects. The study intervention will be completed immediately after the surgery, but follow-up visits will extend to 1 week after surgery. The medical records will be reviewed following hospital discharge for in-hospital complications and medication usage.

Inclusion criteria

1. Patients scheduled to receive elective intracranial primary intra-axial tumor resection who are younger than 65 years and elder than 18 years (age stratification: a. 18~younger≤40; b. 40~elder≤65)
2. The maximum diameter of the tumor is 2~5 cm (imaging examination)
3. ASA class forⅡ-Ⅲ
4. 18.5~BMI~28
5. Glasgow Coma Scale score of more than 8 points

Exclusion criteria

1. Patients with chronic lung disease, pulmonary infection and other severe pulmonary complications such as acute respiratory failure
2. Patients with a history of pulmonary surgery
3. Patients with severe brain, heart, liver and kidney diseases
4. Patients with nerve injury affecting breathing preoperative
5. Pregnant women
6. Refuse to participate in the researcher

Termination criteria

1. Duration of anesthesia <4 h or >8 h; or duration of operation <2 h or >6 h
2. Patients with significantly increased intraoperative intracranial pressure or swelling of brain tissue
3. Patients with intraoperative endotracheal catheter after surgery
4. Repeat intubation or operation within 24 h after operation

Study intervention

Related parameter setting during operation

All patients will be randomly allocated to the C group and the P group according to the computer-generated random number table. In the C group, VT will be set at 8 ml/kg of ideal predicted body weight, with PEEP = 0, and recruitment maneuver will not be used. The ideal body of male patients is calculated as (centimeters height–80) ×0.7 and of female patients is calculated (centimeters height–70)×0.6. The predicted body weight is calculated as follows: for men, 50+0.91 (height in centimeters– 152.4); and for women, 45.5+0.91 (height in centimeters– 152.4)[18]. In the P group, VT will be set at 6 ml/kg of ideal predicted body weight combined with individualized PEEP (PEEPx) during intraoperative dura mater opening[6,7], but in other periods of general anesthesia, VT will be set at 8 ml/kg of ideal predicted body weight. Titration method of individualized PEEP[19]: VT and respiratory rate will be fixed at 6ml/kg and 15 beats per minute during PEEP trial. Titration can only begin once the dura is opened. The titration for the individual PEEP can then be initiated by increasing PEEP from 0 to 10 cm H₂O incrementally. Each PEEP level (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 cmH₂O) will be maintained for 1 minute, and the pulmonary compliance

of the last cycle will be recorded at each PEEP level. At last, the PEEP value at the highest compliance will be selected as the individual PEEP of patient.

PEEP may cause swelling of the brain and increase the risk of coughing during neurosurgery. To avoid coughing before using PEEP, sufficient anesthesia depth or adequate muscle relaxation will need to be achieved. All patients will be given volumetric controlled mechanical ventilation. the inhalation oxygen fraction (FiO_2) will be set at 0.5, (I: E) = 1:2, The respiration rate will be adjusted according to the result of end-expiratory carbon dioxide and the end-tidal CO_2 pressures will be maintained between 30–35 mmHg. Peripheral venous access will be established after the patient enters the operating room. If necessary, central venous access will be established. Noninvasive blood pressure (NBP), electrocardiogram (ECG), heart rate (HR), Oxygen saturation (SpO_2) and bispectral index (BIS) will be routinely monitored. Radial artery catheterization under local anesthesia will be used to monitor invasive arterial pressure and collect blood samples. All of the above data will be collected completely. Fentanyl 5ug/kg, etomidate 0.3mg /kg, rocuronium 0.6mg/kg will be used for induction which will be started after oxygen flow of 0.1 L/kg/min was given by mask for 2 min. Volume controlled mechanical ventilation will be conducted by Primus anesthesia machine (Drager, Germany) after endotracheal catheter is inserted to a correct position. The VT will be set 8 ml/kg of predicted body weight, the inhalation oxygen fraction (FiO_2) will be set at 0.5, the inhalation-expiration ratio (I: E) = 1:2, and the fresh gas flow will be set at 1 L/min. The respiration rate will be adjusted according to the result of end-expiratory carbon dioxide ($ETCO_2$), and the end-tidal CO_2 pressures ($PetCO_2$) will be maintained between 30–35 mmHg. The VT will be set 8 ml/kg of ideal body weight, the inhalation-expiration ratio (I: E) = 1:2, the oxygen flow 1 L/min, and the respiratory rate will be adjusted to maintain $PetCO_2$ at 30~35 mmHg. 1% sevoflurane combined with propofol and remifentanil to maintain anesthesia, and BIS value will be maintained at 45~55. During the process operation, intermittent injection of fentanyl and rocuronium will be used to deepen the anesthesia. Extubation indications: patients were awake and cooperated, and muscle relaxation monitoring train of four stimulation (TOF) >90% [20]. Intraoperative fluid intake and urine volume will be monitored closely. Regional cerebral oxygen saturation (rSO_2) will be recorded in the tumor surgery area of the patients before anesthesia (T0), before dura opening (T1), after dura closing (T2) and 24 h after surgery (T3). Arterial blood of the patients was collected for blood gas analysis to obtain oxygenation index and lactic acid level. Lung ultrasound scores (LUS) will be performed at T0 and T3. The degree of brain relaxation at T1 and T2 will be evaluated by the surgeon using the brain relaxation scale. Amount of vasoactive drugs used and blood loss will be recorded during surgery. The duration of operation and reoperation rate will be recorded.

Study objective

Primary outcome

The primary outcome of this study is to investigate whether the pulmonary protective ventilation significantly improve the regional cerebral oxygen saturation (rSO_2) in patients.

The secondary outcomes are as follows:

1. Changes between preoperative and postoperative in pulmonary Lung ultrasound in patients who use the pulmonary protective ventilation.. Lung ultrasound scores will be used to evaluate postoperative atelectasis. The patient's chest is divided into 12 quadrants. Each of the 12 quadrants is assigned a score of 0 to 3 according to a modified grading system (Table 2). The LUS score (0–36) is then calculated by adding up the 12 individual quadrant scores with higher scores indicating more severe atelectasis[21].Lung ultrasound score based on a comprehensive 12 area per lung investigation will be used to evaluate postoperative atelectasis: the lowest score is 0, that is no atelectasis occurred, and the highest score is 36[21].
2. The mean arterial pressure changes significantly during intraoperative pulmonary protective ventilation.
3. The partial pressure of oxygen and carbon dioxide, oxygenation index, lactic acid level in arterial blood changes significantly during intraoperative pulmonary protective ventilation.
4. The amount of vasoactive drugs and blood loss will be compared in two groups significantly changed during surgerythe pulmonary protective ventilation.
5. Intraoperative brain relaxation. Brain relaxation will be scored by the neurosurgeon after opening the cranium and before opening the dura. They will use a 4-point scale[22]: 1, completely relaxed; 2, satisfactorily relaxed; 3, firm brain; 4, bulging brain
6. The secondary operation rate in one week after surgery (Reoperation rate).

Table 2. Modified Lung Ultrasound Scores

	Normal Aeration	Small Loss of Aeration	Moderate Loss of Aeration	Severe Loss of Aeration
Quotation	0	1	2	3
Modified lung ultrasound score	0-2 B lines	≥3 B lines OR 1 or multiple small subpleural consolidations separated by a normal pleural line	Multiple coalescent B lines OR Multiple small subpleural consolidations separated by a thickened or irregular pleural line	Consolidation OR Small subpleural consolidation of >1 × 2 cm in diameter

Lung ultrasound scores can be calculated by adding up the 12 individual pulmonary quadrant scores yielding a score between 0 (no aeration loss) and 36 (complete aeration loss).

Tab 3. Perioperative parameters

	C Group	P Group
Tidal volume, ml		
Individual PEEP, cmH ₂ O		
Duration of anesthesia, min		
Duration of operation, min		
Duration of dura opening, min		
Tumor size (maximum diameter)		
Brain relaxation scale (T1)		
Brain relaxation scale (T2)		
Lung ultrasound score (T0)		
Lung ultrasound score (T3)		

The volume of total fluid, ml		
The amount of bleeding, ml		
The volume of urine, ml		
Dosage of vasoactive agent, mg		
Reoperation rates		

Tab 4. Comparison of rSO₂, PaO₂, PaCO₂, OI, Lac and MAP

		T0	T1	T2	T3
rSO ₂	C Group				
	P Group				
PaO ₂	C Group				
	P Group				

PaCO₂ C Group
P Group

OI C Group
P Group

Lac C Group
P Group

MAP C Group
P Group

T0:Before anesthesia; T1: Before dura opening; T2:After dura closing; T3:24h after surgery; rSO₂: regional cerebral oxygen saturation; PaO₂: partial pressure of oxygen; PaCO₂: partial pressure of carbon dioxide; OI: oxygenation index; Lac: lactic acid level; MAP: mean arterial pressure.

Reporting of adverse events

All adverse events will be recorded and closely monitored until resolution or stabilization. In the event of any serious adverse event (\geq grade 3)[23], it will be immediately reported to the Endpoint Adjudication Committee, which will determine the severity and causality of the adverse events. The chief investigator will be responsible for all adverse event reporting.

Withdrawal from the trial

We will consider patient withdrawal from the trial if the following conditions occur: (1) severe brain swelling during the operation; (2) the patient has a cough during surgery; (3) the patient has persistent

hypotension and circulatory instability.

Data collect and management

All the patient information will be obtained through the electronic medical record system. The consent of the treating neurosurgeon, who will help us make the neurological diagnosis, has also been obtained. All personal information will be collected through the hospitalized medical records by a member of the research team and be kept strictly confidential for research purposes only. The research team members will be responsible for maintaining personal data. Only the primary investigator and the designated researcher can obtain interim results and final test data.

Data Monitoring Committee (DMC)

The project will be monitored by a Data Monitoring Committee (DMC) composed of specialists in anesthesiology, ethics, statistics and methodology. The DMC will audit through regular interviews or telephone calls.

Sample size and justification

We calculated the sample size through the website <http://www.sample-size.net/sample-size-proportions/>.

The difference of brain oxygen saturation before and after surgery was 3.6 ± 4.1 , $\alpha = 0.05$, $\beta = 0.2$ [7]. Based on this, it can be calculated that the sample size required for our study is 44 cases, plus 20% shedding rate, a total of 53 cases ($44+44*20\%$) need to be recruited. Due to the 1:1 distribution ratio, a total of 54 cases will be recruited.

Statistics

The SPSS 19.0 software package for Windows (SPSS, Inc., Chicago, IL, USA) will be used for all statistical analyses. The quantitative variables will be expressed as mean \pm SD or median (interquartile range (IQR)), and be analyzed by using the analysis of variance (ANOVA) or Mann-Whitney U test. The regional cerebral oxygen saturation, arterial oxygenation index and lactic acid level will be analyzed by using the chi-square test (χ^2). Brain relaxation will use the Mann-Whitney U test for analysis. The incidence of reoperation rate will be expressed as the number of patients (percentage), and be analyzed by using the chi-square (χ^2). P value < 0.05 will be considered to be statistically significant. After the follow-up of half of the cases, the interim analysis will be conducted to evaluate the validity of the main results.

Discussion

This study is a single-center, randomized, parallel-controlled trial of exploring whether protective lung ventilation during intraoperative dura opening can improve regional cerebral oxygen saturation in neurosurgical patients.

The incidence of postoperative pulmonary complications (PPCs) is high due to the long mechanical ventilation in neurosurgery. Qaseem et al.[24] reported that the risk of PPCs increased when operation time is more than 4 h. The incidence of PPCs was 28.4% (20.2–37.9%) in patients with neurosurgery lasting for longer than 300 min[25]. PEEP can lower the incidence of postoperative respiratory complications, prevent atelectasis and reduce the risk of VILI. ventilators associated with lung injury.

In this study, individual PEEP (< 10cmH₂O) will be used to avoid the effect of high PEEP on intracranial pressure (ICP). It is a crucial issue that PEEP can be safely used in craniotomy. Therefore, pulmonary protective ventilation will be performed during dura opening and cerebral relaxation will be assessed before dura incision. If the intracranial pressure is elevated enough to affect the operation for using PEEP, we will abandon the case and change ventilation parameters. The case will be reported to the principal investigator.

Regional cerebral oxygen saturation (rSO₂) is actually the mixed oxygen saturation of local brain tissues, which can better reflect the change of brain oxygen supply and consumption balance during perioperative period. Samra et al. [26] studied 100 patients who underwent carotid endarterectomy, then found that if the rSO₂ value decreased by 20% compared with the baseline value after internal carotid artery occlusion, it predicted the possibility of neurological complications, and indicated that its sensitivity was 80% and specificity was 82%. Since the ratio of cerebral blood volume to arterial/venous blood flow is approximately 20:80, NIRS mainly represents cerebral venous oxygen saturation, which is completely unaffected by hypoxemia and hypocarbonemia, and better reflects the changes in the balance of oxygen supply and consumption in the brain[27]. Near infrared spectroscopy (NIRS) as a brain oxygen monitoring method has following characters: continuous and noninvasive, convenient, high degree of sensitivity and specificity[28]. Monitoring regional cerebral oxygen saturation can detect changes of the cerebral blood flow and oxygen supply and consumption balance in the brain area as early as possible, and judge the degree of cerebral ischemia and hypoxia and the changes of brain function. Timely adjustment of anesthesia plan is helpful to guide perioperative anesthesia management, so as to prevent POCD, shorten hospitalization period and improve quality of life.

We focus on whether pulmonary protective ventilation strategy can affect cerebral venous reflux and brain tissue oxygenation, and ultimately, the prognosis of patients. Protective lung ventilation after incision of dura can reduce the returned blood volume that results in exposing potential bleeding spots, which is beneficial for the surgeon to stop bleeding. Due to the opening dura, the intracranial pressure disappeared, and the decreased cerebral perfusion pressure caused by the expansion of the lung would be improved.

This study is a prospective, randomized controlled trial. This study aims to investigate the effect of intraoperative pulmonary protective ventilation in neurosurgical craniotomy. If we are able to demonstrate the safety and effectiveness of intraoperative pulmonary protective ventilation with individualized PEEP during dura opening in neurosurgical craniotomy, it will improve the prognosis of neurosurgical patients and reduce the medical costs.

Trial Status

The study was also registered on the registry website [http:// chictr.org.cn/](http://chictr.org.cn/) with the registration number ChiCTR1900025632 on 3 September 2019. Protocol version 12.0, 3/9/2019. The study began on 3 September 2019, and the planned completion date will be September 2020. Trial status was currently recruiting. The recruitment began on 3 September 2019, and the planned completion date will be June 2020.

List Of Abbreviations

VT: tidal volume

PEEP: positive end-expiratory pressure

rSO₂: regional cerebral oxygen saturation

PaO₂: partial pressure of oxygen

PaCO₂: carbon dioxide

OI: oxygenation index

Lac: lactic acid level

MAP: mean arterial pressure

PLV: protective lung ventilation

ARM: alveolar recruitment maneuver

NIRS: near infrared spectrometer

PPCs: postoperative pulmonary complications

ICP: intracranial pressure

FiO₂: oxygen fraction

NBP: noninvasive blood pressure

ECG: electrocardiogram

HR: heart rate

SpO₂: oxygen saturation

BIS: bispectral index

ETCO₂: end-expiratory carbon dioxide

PetCO₂: end-tidal CO₂ pressures

Declarations

Ethics approval and consent to participate

Ethics Committee of the Second Affiliated Hospital of Soochow University approved the study on November 23, 2018 (File number EC-AF (JD)-06/6.1, study protocol version 21.0). The study is designed in accordance to the principles of the Declaration of Helsinki. Written informed consent was obtained from every enrolled patient upon request by the review board.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing non-financial/financial interests.

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This study was not funded.

Authors' contributions

Hairui Liu conceived and designed the study, coordinates the overall study, and contributed to the final manuscript. Jinlu Li conceived and designed the study, coordinates the overall study, and contributed to the final manuscript. Xuemei Wu participated in the design of the study and drafted the manuscript. Ying Huang and Yueqin Liu performed the sample size calculation, drafted the statistical analysis plan and collected the data. Hong Xie participated in the design of the study. Jun Dong conceived the study, and guided the calculation of the sample size and the plans of the statistical analysis. All authors read and approved the final manuscript.

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Authors' information

Not applicable.

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Figures

TIMEPOINT**	STUDY PERIOD								
	Enrolment	Allocation	Post-allocation						
	-1day	Surgery day	T0	T1	Ta	Tb	T2	T3	
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Random allocation		X							
INTERVENTIONS:									
<i>the control group</i>									
<i>the protective ventilation group</i>									
ASSESSMENTS:									
<i>Regional cerebral oxygen saturation</i>			X	X			X	X	
<i>Partial pressure of oxygen</i>			X	X			X	X	
<i>Partial pressure of carbon dioxide</i>			X	X			X	X	
<i>Oxygenation index</i>			X	X			X	X	
<i>Lactic acid</i>			X	X			X	X	
<i>Mean arterial pressure</i>			X	X			X	X	
<i>Lung ultrasound score</i>			X					X	
<i>The amount of vasoactive drugs</i>							X		
<i>Blood loss</i>							X		
<i>Brain relaxation</i>				X			X		
<i>The secondary operation rate</i>									

Figure 1

Schedule of enrolment, interventions, and assessments T0:Before anesthesia;T1:Before dura opening;Ta:After dura opening; Tb:Before dura closing;T2:After dura closing;T3:24h after surgery