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Multicenter observational study on practice of ventilation in brain injured patients: the VENTIBRAIN study protocol

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ABSTRACT

Introduction

Mechanical ventilatory is a crucial element of acute brain injured patients' management. The ventilatory goals to ensure lung protection during acute respiratory failure may not be adequate in case of concomitant brain injury. Therefore, there are limited data from which physicians can draw conclusions regarding optimal ventilator management in this setting.

The aim of the "Multicenter observational study on practice of ventilation in brain injured patients"-the VENTIBRAIN study, is to describe the current practice of ventilator settings and mechanical ventilation in acute brain injured patients. Secondary objectives include the description of ventilator settings among different countries, and their association with outcomes.

Methods and analysis

The VENTIBRAIN Study is an international multicenter prospective observational cohort study. Inclusion criteria will be adult patients admitted to the intensive care unit (ICU) with a diagnosis of traumatic brain injury or cerebrovascular diseases (intracranial hemorrhage, subarachnoid hemorrhage, ischemic stroke), requiring intubation and mechanical ventilation in the ICU. Exclusion criteria will be the following: patients aged < 18 years; pregnant patients; patients not intubated or not mechanically ventilated or receiving only non–invasive ventilation; patients under invasive mechanical ventilation before inclusion. Data related to clinical

examination, neuromonitoring if available, ventilator settings and arterial blood gases will be recorded at admission and daily for the first 7 days from admission and then at day 10 and 14. The Glasgow Outcome Scale Data on mortality and neurological outcome (as for extended (GOSE)) will be collected at discharge from ICU, hospital and at 6 months follow-up.

Ethics and dissemination

The study has been approved by the Ethic committee of Brianza at the Azienda Socio Sanitaria Territoriale (ASST)-Monza. Data will be disseminated to the scientific community by abstracts submitted to the European Society of Intensive Care Medicine annual conference and by original articles submitted to peer-reviewed journals.

Trial registration number: NCT04459884

Keywords: mechanical ventilation; brain injury; ventilator settings; outcome; Glasgow coma scale

Strengths and limitations of the study

- Results from this large multicenter study including mechanically ventilated acute brain injury patients admitted to the intensive care unit will provide a detailed description of the patients' characteristics, and ventilator strategies, and their association to clinical outcomes.
- The main strength of this study relies on the global approach, since it allows to explore clinical practice in a wide number of geographical regions with different public health issues, including low- and middle-income countries
- The main limitation of this study relies on the observational design with consequent difficulty to draw causal inferences.
- However, the results from this study will generate hypothesis for respiratory management of acute brain injured patients and help in better study design plans for future randomized controlled trials.

List of abbreviations and relevant definitions

ABI Acute Brain Injury
ARDS Acute Respiratory Distress Syndrome
CA Competent Authority
COPD Chronic Obstructive Pulmonary Disease
CPP Cerebral Perfusion Pressure
CRF Case Report Form
CT Computerized Tomography
DSMB Data safety Managing Board
ESICM European Society of Intensive Care
GCP General Clinical Practice
GCS Glasgow Coma Scale
GOSE Extended Outcome Scale
ICP Intra Cranial Pressure
ICU Intensive Care Unit
ICH Intra Cerebral Hemorrhage
MAP Mean Arterial Pressure
MV Mechanical Ventilation
NC National Coordinator
PaO2 Arterial Partial Pressure of Carbon Dioxide
PaO2 Arterial Partial Pressure of Oxygen
PbO2 Brain Tissue Oxygen Tension
PBW Predicted body weight
PEEP Positive End–expiratory Pressure
PI Principal Investigator
RM Recruitment Maneuvers
SAH – Subarachnoid Hemorrhage
SC Steering Committee
TCD Trans Cranial Doppler
TV Tidal Volume
VALI Ventilator–associated Lung Injury
WBP Personal Data Protection Act
WMO Medical Research Involving Human Subjects Act

BACKGROUND AND RATIONALE

Mechanical ventilation (MV) is a frequently applied and often a life–saving strategy in severely brain injured patients.[1] Paradoxically, ventilation itself has the potential to cause further pulmonary and cerebral damage and can increase mortality and morbidity.[2] Several experimental and clinical studies have shown how brain injury can cause secondary lung injury.[2-4] Lung injury could be due either to mechanical ventilation, which is often necessary in brain injured patients, or to inflammatory response that follows primary acute brain injury.[5]

The so–called '*protective lung ventilation*' strategies include the use of low tidal volume (TV), positive end expiratory pressure (PEEP), and eventually recruitment maneuvers (RMs), and are aimed to prevent lung damage and to reduce morbidity and mortality in patients with acute respiratory distress syndrome (ARDS).[6,7] In particular, the use of low tidal volume seems to have the greater importance,[8-11] and it is recommended in critically ill patients with ARDS. [12]

Results from one multicenter randomized controlled trial suggest that also intensive care unit (ICU) patients without ARDS could benefit from 'protective lung ventilation strategies'. [13]A recent meta–analysis showed a higher incidence of pulmonary complications and even increased mortality in patients who received 'conventional ventilation' with traditionally sized or higher tidal volumes compared to patients undergoing protective strategies .[14]

Therefore, the concept of 'protective lung ventilation' has shown to reduce morbidity and mortality of ICU patients with ARDS but seems also to have a

beneficial effect on patients with healthy lungs and in the perioperative settings. However, these recommendations often come into conflict with the management of patients affected by acute brain injury, because low tidal volumes, high PEEP and RMs can increase carbon dioxide levels (CO_2) and increase intrathoracic pressure, thus having detrimental effects on intracranial pressure (ICP) and cerebral perfusion pressure (CPP).[15-17] Because of this, brain injured patients have been traditionally excluded from the major trials regarding mechanical ventilation. There is therefore still uncertainty regarding the use of protective ventilation in brain injured ill patients, and, as suggested by a recent consensus of experts,[18] a multicenter international study on mechanical ventilation strategies in brain injured patients is currently missing.

METHODS

Study design

We designed a large international multicenter prospective observational cohort study including mechanically ventilated brain injured patients and planned 6-month follow-up.

Objectives

Primary objective is to describe ventilation settings of intubated and mechanically ventilated neurocritically ill patients admitted to the ICU.

Secondary objectives are:

- To describe the differences in ventilator settings among different countries.
- To evaluate the association of ventilator settings with pulmonary complications (including pneumonia, ARDS, neurogenic pulmonary edema)
-To describe differences in the ventilator settings in presence/absence of high intracranial pressure.
- To evaluate the association of ventilator settings with outcomes

Study population

We will collect data of consecutive patients with acute brain injury requiring endotracheal intubation and mechanical ventilation, who are admitted to the intensive care unit (ICU).

Inclusion criteria will be:

- Age ≥ 18 years
- Patients admitted to the ICU with a diagnosis of a primary non-anoxic brain injury, such as:
  - Traumatic brain injury (TBI)
  - Cerebrovascular diseases (intracranial hemorrhage, ICH; subarachnoid hemorrhage, SAH; acute ischemic stroke, AIS)
- Patients requiring intubation and mechanical ventilation in the ICU

Exclusion criteria

- Age < 18 years
- Pregnant patients
- Patients not intubated or not mechanically ventilated or receiving only non–invasive ventilation (i.e., patient never received invasive ventilation during the present admission)
- Patients under invasive mechanical ventilation before the 7-day period of inclusion

Outcomes

Enrolled patients will be followed until ICU–hospital discharge or death, whatever comes first.

Outcomes will be assessed as:

- 6-months mortality and neurological outcome (as for extended Glasgow Outcome Scale, GOSE).

- Pulmonary complications

-In-hospital and ICU mortality.

-Hospital length of stay (LOS).

- Duration of mechanical ventilation (in days), ventilator free days (days) at ICU discharge.

Study procedures and settings

The protocol has been endorsed by the European Society of Intensive Care (ESICM): Worldwide, more than 200 centers from 56 countries have been contacted to participate in the VENTIBRAIN study (more information at https://www.esicm.org/research/trials/endorsed-trials/ongoing-projects-endorsed/).

The established recruitment window will open at the beginning of 2021. The inclusion period will be flexible for participating centers and determined at a later stage together with the study–coordinator. Centers will enroll consecutive patients for a minimum period of 3 months to a maximum period of 6 months.

Patients in participating centers will be screened on a daily basis. After 6 months from recruitment, the patients or their family members will be contacted by phone for the follow-up evaluation.

Data collection

The following data will be collected at admission, and daily until day 7, and then at day 10 and 14:

- Demographic data and baseline clinical data, including neurological, neuroradiological and respiratory severity scores (Table 1-4), neuromonitoring data, and the occurrence of neurological and systemic complications
- Ventilation settings, gas exchange variables and vital parameters
- Chest radiography data from available chest X–rays and/or Computed Tomography (i.e., no extra chest X–rays are obtained)
- Therapy Intensity Levels (TILs) and predefined complications recorded from medical chart (Table 5)

At ICU discharge data on mortality, length of stay (days) duration of mechanical ventilation (in days), ventilator free days (days) will be collected

At 6-months mortality and neurological outcome (as for extended Glasgow Outcome Scale, GOSE, Table 6), length of stay (in days), in hospital mortality will be collected

The GOSE at 6 months follow-up will be collected via phone-structured interviews to the patients and/or family members using a validated questionnaire. [19]Data on the cause and date of death will be also collected.

Data management

Anonymized data will be collected in a web-based electronic Case-Report Form (eCRF) and protected by encryption software and password provided to single users. Each patient will be associated to a numeric code generated by the central database. Data will be checked for consistency and completeness by the study coordinator and the core Steering Committee, to ensure the high quality of the collected data before the analysis and to limit the rate of errors and missing data.

The data will be securely stored at the University Milano-Bicocca; all procedures will comply with the EU Regulation 2016/679 on the protection of natural persons regarding personal data processing and movement. A Data Transfer Agreement to confirm the terms for data transfer from the centers to the Sponsor will be finalized.

Patients' demographic characteristics, co-morbidities, diagnosis, timing of acute events and clinical presentation of acute brain injury will be extracted from the patients' medical records.

STATISTICAL ANALYSIS

Sample size calculation

Since the hypotheses of the study are exploratory, no formal sample size calculation has not been performed. This international prospective observational study aims to recruit more than 4000 patients in coma after acute brain damage admitted to >200 Intensive Care Units (ICUs) in at least 50 countries. Recruitment will last 3-6 months at each center, aiming to enroll about 30 consecutive patients/center. The number

of enrolled patients and ICUs reflects is considered adequate to capture the range of variation in ventilator settings observed in the clinical practice. We aim to include also low-middle income countries, in order to have a representation of the variability worldwide.

Plan of analysis

Patient and ventilation characteristics will be described by means (standard deviation), medians (I-III quartiles) and proportions, as appropriate. The different ventilator settings will be described according to type of brain injury and countries.
The association between ventilator settings and outcomes will be evaluated by appropriate multivariable models adjusting for relevant confounders. Cox model will be applied to time to event outcomes (e.g., mortality) and logistic regression to dichotomous outcomes (e.g. poor neurological outcome at 6 month (GOSE <5), pulmonary complications). The heterogeneity induced by centers/nations will be eventually accounted for, in the regression models, through random effects.
The cumulative incidence in time of pulmonary complications during hospital stay will be estimated along with 95% confidence intervals accounting for mortality and discharge as competing events.
The occurrence of raised intracranial pressure (ICP value lasting more than 5 minutes >20 mmHg) will be described daily and ventilator setting preceding it will be described. A longitudinal model on raised intracranial pressure by time evaluating the possible impact of ventilator settings will be also applied adjusting for relevant confounders.
Statistical analyses will be conducted using R.

Patient and Public Involvement

No patient involved.

ETHICAL CONSIDERATIONS

Ethical standards

The PI and Steering Committee will ensure that this study is conducted in full conformity with the Declaration of Helsinki and Good Clinical Practices.

Ethics committee

Each NC/PI will notify the relevant ethics committee, in compliance with the local legislation and rules. The national coordinators will facilitate this process. The approval of the protocol (if required by local authorities) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the SC before the changes are implemented to the study.

Lack of capacity and Delayed Consent

Informed consent will be obtained from patients with no lack of capacity. For patients not able to provide informed consent at the time of recruitment, the responsible clinical/research staff will act as Consulter and consent eligible patients after discussion with the next- of-kin. If the patient has a Power of Attorney or a Legal tutor or an, he/she will act as Consultee and will be asked to consent/decline participation to the study on legal behalf of the patient.

In presence of patients' Advance Decision Plan, including participation in research studies, the Plan will be respected and recruitment pursued/abandoned accordingly.At follow-up, patients who have regained capacity will be asked to provide Informed Consent and will be given the possibility to:

- Provide Informed Consent for the acute data and follow-up.
- Deny research participation and request destruction of acute data collected.

Publication and data sharing policy

Data sharing policy

After the publication of the main papers, any requests for the use of the data will be made to the VENTIBRAIN Core Steering Committee (CR, GC, PP, FST), and decisions will be made in relation to these requests. The VENTIBRAIN investigators will have priority in requests to use the data set for subsequent studies.

Publication and Authorship

Data will be made available to the scientific community by means of abstract by scientific papers submitted to peer-reviewed journals. Authorship of the main manuscript will follow the ICMJE recommendations that base authorship on the

following 4 criteria:

• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

• Drafting the work or revising it critically for important intellectual content; AND

• Final approval of the version to be published; AND

• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A writing committee composed by the Core Steering Committee, biostatisticians and selected members of the advisory board will draft the manuscript and will be author of the manuscript. National coordinators will be authors if they will fulfill the ICMJE criteria and if they will promote the enrolment of at least 300 patients in their country. All the participant centers will be granted in the group authorship, "VENTIBRAIN". The corresponding author will specify the group name and will clearly identify the group members who can take credit and responsibility for the work as collaborators. For each center, a participant will be indicated in the group authorship list every 50 patients enrolled. The ESICM support will be acknowledged in each publication generated from the study. In the main manuscripts, CR and GC will share the first authorship, FST will be the third author, and PP will be the last author. After publication of the primary results, on request the pooled dataset will be available for all members of the VENTIBRAIN collaborators for preplanned substudies and secondary analysis, after judgement and approval of scientific quality and validity statement guidelines and checklists. Each secondary analysis or substudy approved will have to include the core Steering Committee as authors. Preplanned analysis include the evaluation of blood gas values (such as oxygen and carbon dioxide) and their association with patient's outcome, and the assessment of mechanical power used in this cohort of patients and its effect on outcomes.

DISCUSSION AND EXPECTED IMPACT OF THE STUDY

VENTIBRAIN is designed to obtain a detailed description of patient's characteristics,

management strategies resource use and association with clinical outcomes across many centers/countries. In particular, the study will provide insights in relation to clinical management, monitoring and treatment, practice variation in neuro-intensive care units around the world, differences in the ventilator management of brain injured patients and their potential association with outcome.

VENTIBRAIN has several strengths. First, its prospective design will increase the accuracy of data collection with potential minimization of the chance of residual confounding by unmeasured variables, which is a common limitation of retrospective design. Second, we aim to obtain a large sample size, able to provide information on neurological and systemic complications in mechanically ventilated brain injured patients, and eventually evaluate potential associations between ventilator settings and ICU/ 6 months patients' outcomes. Third, the inclusion of a large number of patients from different centers (dedicated and not dedicated neuroICUs), and countries, including low-income countries will provide information on geoeconomic differences in epidemiology, management strategies and outcomes of mechanically ventilated brain injured patients.

The need to particularly focus on the mechanical ventilator settings in this group of patients is related to the specific ventilator needs of brain injured patients.[18,20,21] Brain injured patients have a high number of pulmonary complications, ventilator associated pneumonia (VAP), and a high rate of need of tracheostomy and extubation failure.[22]

The optimal oxygenation and carbon dioxide targets are not clear in this population. Hypoxia has been largely recognized as a major cause of secondary brain injury; recently, also hyperoxia has shown to have potential detrimental effects on patients' outcome.[23,24]

Similarly, hypercapnia can cause cerebral vasodilation and increase intracranial pressure and should therefore be avoided, but hypocapnia and cerebral vasoconstriction can lead to cerebral ischemia and currently it is suggested only in case of life-threatening intracranial hypertension and risk of brain herniation.[25,26]

All in it, ventilator targets are unclear in this group of patients.

Moreover, the general principles and ventilator settings applied in the general population have not been established in brain injured patients.[19]

Recent literature has highlighted the importance of protective ventilation in ARDS and non ARDS patients,[27-32] as well as weaning protocols. However, country-specific practices, the lack of clear guidelines in the neuroICU population or different resources among countries may affect the implementation of all these interventions.

Protective ventilator strategies such as high PEEP or recruitment maneuvers with increased intrathoracic pressure and consequent jugular outflow reduction and intracranial hypertension;[33] low tidal volume and permissive hypercapnia may be contraindicated in this group of patients, and rescue therapies used in ARDS patients such as prone position can be contraindicated for the risk of increased ICP and neuromonitoring tools displacement and extracorporeal membrane oxygenation (ECMO) can be contraindicated for the risk of haemorrhage.[34]However, although these patients have been traditionally ventilated with high tidal volumes and low PEEP,[29] recent evidence suggests that the concept of protective ventilation is gaining interest even in the brain injured population.[19]

Results from the VENTIBRAIN study will allow to clarify the current status of the ventilator management of these patients, and in particular to discriminate the effects of tidal volume, PEEP and driving pressure on outcomes in brain injured patients with, at risk of, or without ARDS (using predefined scores), and the use of specific settings in case of intracranial hypertension. The VENTIBRAIN study offers a unique opportunity to globally uniform clinical guidelines regarding ventilator strategies in brain injured patients and eventually improving their outcome.

The VENTIBRAIN study has also several limitations that need to be addressed. First, we cannot exclude that ventilator settings and targets used by clinicians might be biased by the participation in the study, thus reducing the ability of VENTIBRAIN to represent the real ICU care of these patients. Second, the CRF designed for VENTIBRAIN was aimed to not cause excessive workload for the participating

centres. Therefore, some data regarding systemic complications will be potentially missing, while continuous data on respiratory and neuromonitoring might be incomplete. Similarly, due to the limited number of daily arterial blood gases and ventilator settings data collection, we will have a limited dataset that might not reflect completely real clinical practice.

Finally, the observational nature of VENTIBRAIN makes impossible to draw causal inferences between ventilator management and outcome in this group of patients. However, VENTIBRAIN is aimed to generate hypothesis for treatment effects and pave the way to design future randomized controlled trials of ventilation in these settings to draw causal inferences and improve clinical outcomes in ventilated brain injured patients.

CONCLUSIONS

VENTIBRAIN is designed to assess and describe the clinical practice in ventilator strategies in critically ill brain injured patients in a large number of different countries/centers worldwide. Results from this study will help to identify differences in clinical practices and could be used to plan new trials on mechanical ventilation in this specific subgroup of patients.

Figures headings:

Figure 1.Timetable of the study.

Contributors: CR, GC, FST, PP were equally responsible for writing of the manuscript and participated in study design. CR drafted the first version of the manuscript. FST, PP, GC, SG, PR reviewed the manuscript and agreed with

submission.

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Patient consent: Not required.

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Tables

Table 1. The Berlin Definition of ARDS. Abbreviations: ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; FiO2, fractional inspired oxygen; PaO2, arterial oxygen tension; PEEP, positive end-expiratory pressure.

Criteria	**Definition**		
Cause	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic oedema if no risk factors present (eg, echocardiography).		
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms.		
Chest imaging (Rx or CTscan)	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules.		
Oxygenation	Mild 200<PaO2/FiO2≤300 PEEP or CPAP≥5 cm H2O	Moderate 100<PaO2/FiO2≤200 PEEP ≥5 cm H2O	Severe PaO2/FiO2≤100 PEEP ≥5 cm H2O

Table 2. Glasgow Coma Scale

	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to pain	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Makes sounds	Words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion / Withdrawal to painful stimuli	Localizes to painful stimuli	Obeys commands

Table 3. Marshall classification of traumatic brain injury

Diffuse injury I (no visible pathology)	• no visible intracranial pathology
Diffuse injury II (swelling)	• midline shift of 0 to 5 mm • basal cisterns remain visible • no high or mixed density lesions >25 cm^3
Diffuse injury III	• midline shift of 0 to 5 mm • basal cisterns compressed or completely effaced • no high or mixed density lesions >25 cm^3
Diffuse injury IV (shift)	• midline shift >5 mm • no high or mixed density lesions >25 cm^3
Evacuated mass lesion V	• any lesion evacuated surgically
Non-evacuated mass lesion VI	• high or mixed density lesions >25 cm^3 • not surgically evacuated

Table 4. Fisher scale.

Grade 1	• no subarachnoid (SAH) or intraventricular hemorrhage (IVH) detected • incidence of symptomatic vasospasm: 21%
Grade 2	• diffuse thin (<1 mm) SAH • no clots • incidence of symptomatic vasospasm: 25%
Grade 3	• localized clots and/or layers of blood >1 mm in thickness • no IVH • incidence of symptomatic vasospasm: 37%
Grade 4	• diffuse or no SAH • ICH or IVH present • incidence of symptomatic vasospasm: 31%

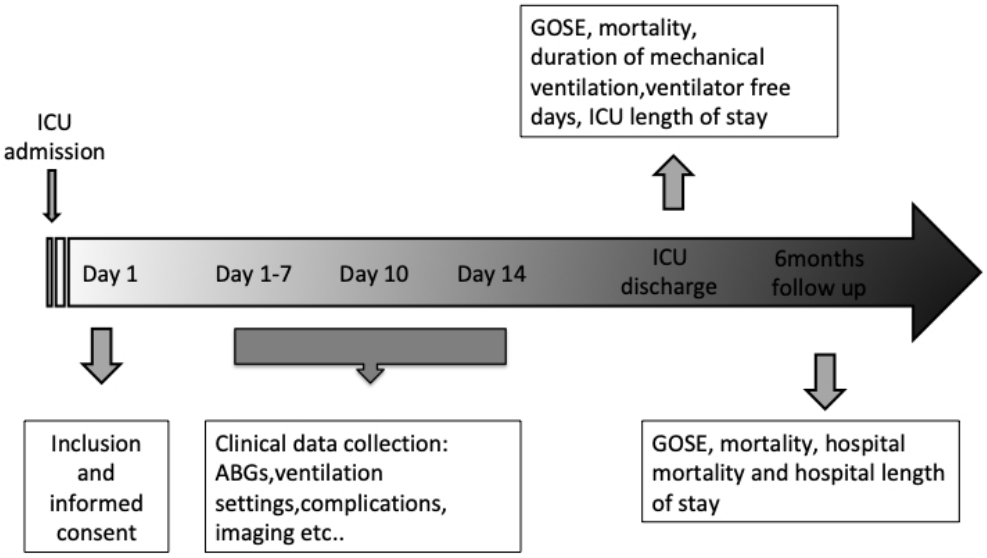
Table 5. Terapy intensity Level Scale

ITEM	DETAILS	SPECIFICS	SCORE	MAX
Positioning	head elevation for ICP control		1	1
	nursed flat (180°) for CPP management		1	
Sedation and neuromuscular blockade	low dose sedation (as required for mechanical ventilation)		1	8
	higher dose sedation for ICP control (but not aiming for burst suppression)		2	
	high dose propofol or barbiturates for ICP control (metabolic suppression)		5	
	neuromuscular blockade (paralysis)		3	
CSF drainage	CSF drainage – low volume	< 120ml/day (< 5ml/h)	2	3
	CSF drainage – high volume	≥ 120ml/day (≥ 5ml/h)	3	
CPP management	fluid loading for maintenance of cerebral perfusion		1	2
	vasopressor therapy required for management of cerebral perfusion		1	
Ventilatory management	mild hypocapnia for ICP control, based on arterial CO2 in mmHg	≥ 35, < 40	1	4
	moderate hypocapnia for ICP control	≥ 30, < 35	2	
	intensive hypocapnia for ICP control	< 30	4	
Hyperosmolar therapy	mannitol	≤ 2g/kg/24h	2	6
	mannitol	> 2g/kg/24h	3	
	hypertonic saline	≤ 0.3g/kg/24h	2	
	hypertonic saline	> 0.3g/kg/24h	3	

	treatment of fever (T> 38°C or spontaneous T < 34.5°C)		1	
	cooling for ICP control, ≥ 35°C		2	
	hypothermia < 35°C		5	
	intracranial operation for progressive mass lesion, NOT scheduled on admission		4	
	decompressive craniectomy		5	
Maximum total possible score				38

Table 6. Extended Glasgow Outcome Scale

Category number	Name	Definition
5	**Good recovery**	resumption of normal life (minor neurological or psychological deficits)
4	**Moderate disability**	disabled but independent for daily life; work capacity is reduced
3	**Sever disability**	conscious but dependent for daily life; unable to travel or go shopping without assistance
2	**Persistent vegetative state**	unresponsive and speechless
1	**Death**	



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Multicenter observational study on practice of ventilation in brain injured patients: the VENTIBRAIN study protocol

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Multicenter observational study on practice of ventilation in brain injured patients: the VENTIBRAIN study protocol

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ABSTRACT

Introduction

Mechanical ventilatory is a crucial element of acute brain injured patients' management. The ventilatory goals to ensure lung protection during acute respiratory failure may not be adequate in case of concomitant brain injury. Therefore, there are limited data from which physicians can draw conclusions regarding optimal ventilator management in this setting.

Methods and analysis

This is an international multicenter prospective observational cohort study. The aim of the "Multicenter observational study on practice of ventilation in brain injured patients"-the VENTIBRAIN study- is to describe the current practice of ventilator settings and mechanical ventilation in acute brain injured patients.

Secondary objectives include the description of ventilator settings among different countries, and their association with outcomes.

Inclusion criteria will be adult patients admitted to the intensive care unit (ICU) with a diagnosis of traumatic brain injury or cerebrovascular diseases (intracranial hemorrhage, subarachnoid hemorrhage, ischemic stroke), requiring intubation and mechanical ventilation and admission to the ICU. Exclusion criteria will be the following: patients aged < 18 years; pregnant patients; patients not intubated or not mechanically ventilated or receiving only non–invasive ventilation. Data related to clinical examination, neuromonitoring if available, ventilator settings and arterial blood gases will be recorded at admission and daily for the first 7 days and then at day 10 and 14. The Glasgow Outcome Scale Extended on mortality and neurological outcome (GOSE) will be collected at discharge from ICU, hospital and at 6 months follow-up.

Ethics and dissemination

The study has been approved by the Ethic committee of Brianza at the Azienda Socio Sanitaria Territoriale (ASST)-Monza. Data will be disseminated to the scientific community by abstracts submitted to the European Society of Intensive Care Medicine annual conference and by original articles submitted to peer-reviewed journals.

Trial registration number: NCT04459884

Keywords: mechanical ventilation; brain injury; ventilator settings; outcome; Glasgow coma scale

Strengths and limitations of the study

- Results from this large multicenter study including mechanically ventilated acute brain injury patients admitted to the intensive care unit will provide a detailed description of the patients' characteristics, ventilator strategies, and their association to clinical outcomes.
- The main strength of this study relies on the global approach, since it allows to explore clinical practice in a wide number of geographical regions with different public health issues, including low- and middle-income countries.
- The main limitation of this study relies on the observational design with consequent difficulty to draw causal inferences.
- The results from this study will generate hypotheses for respiratory management of acute brain injured patients and help in better study design plans for future randomized controlled trials.

List of abbreviations and relevant definitions

ABI Acute Brain Injury
ARDS Acute Respiratory Distress Syndrome
CA Competent Authority
COPD Chronic Obstructive Pulmonary Disease
CPP Cerebral Perfusion Pressure
CRF Case Report Form
CT Computerized Tomography
DSMB Data safety Managing Board
ESICM European Society of Intensive Care Medicine
GCP General Clinical Practice
GCS Glasgow Coma Scale
GOSE Glasgow Extended Outcome Scale
ICP Intra Cranial Pressure
ICU Intensive Care Unit
ICH Intra Cerebral Hemorrhage
MAP Mean Arterial Pressure
MV Mechanical Ventilation
NC National Coordinator
PaO_2 Arterial Partial Pressure of Carbon Dioxide
PaO_2 Arterial Partial Pressure of Oxygen
PbO_2 Brain Tissue Oxygen Tension
PBW Predicted body weight
PEEP Positive End–expiratory Pressure
PI Principal Investigator
RM Recruitment Maneuvers
SAH – Subarachnoid Hemorrhage
SC Steering Committee
TCD Trans Cranial Doppler
TV Tidal Volume
VALI Ventilator–associated Lung Injury
WBP Personal Data Protection Act
WMO Medical Research Involving Human Subjects Act

BACKGROUND AND RATIONALE

Mechanical ventilation (MV) is a frequently applied and often a life–saving strategy in severely brain injured patients.[1] Paradoxically, ventilation itself has the potential to cause further pulmonary and cerebral damage and can increase mortality and morbidity.[2] Several experimental and clinical studies have shown how brain injury can cause secondary lung injury.[2-4] Lung injury could be due either to mechanical ventilation, which is often necessary in brain injured patients, or to inflammatory response that follows primary acute brain injury, or a combination of both mechanisms.[5]

The so–called '*protective lung ventilation'* strategies include the use of low tidal volume (TV), positive end expiratory pressure (PEEP), and eventually recruitment maneuvers (RMs), and are aimed to prevent lung damage and to reduce morbidity and mortality in patients with acute respiratory distress syndrome (ARDS).[6,7] In particular, the use of low tidal volume seems to have the greater importance,[8-11] and it is recommended in critically ill patients with ARDS.[12]

Results from one multicenter randomized controlled trial suggest that intensive care unit (ICU) patients without ARDS could also benefit from 'protective lung ventilation strategies'.[13]A recent meta–analysis showed a higher incidence of pulmonary complications and even increased mortality in patients who received 'conventional ventilation' with traditionally sized or higher tidal volumes compared to patients undergoing protective strategies.[14]

Therefore, the concept of 'protective lung ventilation' has led to a clinical approach, which seems to reduce morbidity and mortality of ICU patients with ARDS but can also have a beneficial effect on patients with healthy lungs and in the perioperative settings. However, these recommendations often come into conflict with the management of patients affected by acute brain injury, because low tidal volumes, high PEEP and RMs can increase carbon dioxide levels (CO_2) and increase intrathoracic pressure, thus having detrimental effects on intracranial pressure (ICP) and cerebral perfusion pressure (CPP).[15-17] Because of this, brain injured patients have been traditionally excluded from the major trials regarding mechanical ventilation. There is therefore still uncertainty regarding the use of protective ventilation in brain injured ill patients and, as pointed out by a recent consensus of

experts,[18] a multicenter international study on mechanical ventilation strategies in brain injured patients is currently needed.

METHODS

Study design

We designed a large international multicenter prospective observational cohort study including mechanically ventilated brain injured patients and planned 6-month follow-up.

Objectives

Primary objective is to describe ventilation settings of intubated and mechanically ventilated neurocritically ill patients admitted to the ICU.

Secondary objectives are:

- To describe the differences in ventilator settings among different countries.
- To evaluate the association of ventilator settings with pulmonary complications (including pneumonia, acute distress respiratory failure, neurogenic pulmonary edema).
-To describe differences in the ventilator settings in presence/absence of high intracranial pressure.
- To evaluate the association of ventilator settings with outcomes (i.e. 6-months mortality and neurological outcome, in-hospital and ICU mortality, hospital length of stay, duration of mechanical ventilation, ventilator free days at ICU discharge).

Study population

We will collect data of consecutive patients with acute brain injury requiring endotracheal intubation and mechanical ventilation, who are admitted to the intensive care unit (ICU).

Inclusion criteria will be:

- Age ≥ 18 years.
- Patients admitted to the ICU with a diagnosis of a primary non-anoxic brain injury, such as:
  - Traumatic brain injury (TBI)
  - Cerebrovascular diseases (intracranial hemorrhage, ICH; subarachnoid hemorrhage, SAH; acute ischemic stroke, AIS)
- Patients requiring intubation, mechanical ventilation, or needing mechanical ventilation during ICU stay.

Exclusion criteria

- Age < 18 years.
- Pregnant patients.
- Patients not intubated or not mechanically ventilated or receiving only non–invasive ventilation (i.e., patient never received invasive ventilation during the present admission).

Outcomes

Enrolled patients will be followed until ICU–hospital discharge or death, whatever comes first and at 6 months follow up.

Outcomes will be assessed as:

- 6-months mortality and neurological outcome (as for extended Glasgow Outcome Scale, GOSE).

- Pulmonary complications (defined as: acute distress respiratory failure, pulmonary infection, pneumothorax, pleural effusion, atelectasis, non-cardiogenic pulmonary edema).

-In-hospital and ICU mortality.

-Hospital length of stay (LOS) in patients discharged alive.

- Duration of mechanical ventilation (in days), ventilator free days (days) at ICU discharge.

Study procedures and settings

The protocol has been endorsed by the European Society of Intensive Care Medicine (ESICM). Worldwide, more than 200 centers from 56 countries have been contacted to participate in the VENTIBRAIN study (more information at https://www.esicm.org/research/trials/endorsed-trials/ongoing-projects-endorsed/).

The established recruitment window will open in spring-summer 2021. The inclusion period will be flexible for participating centers and determined at a later stage together with the study–coordinator. Centers will enroll consecutive patients for a minimum period of 3 months to a maximum period of 6 months.

Patients in participating centers will be screened on a daily basis. After 6 months from recruitment, the patients or their family members will be contacted by phone for the follow-up evaluation.

Data collection

The following data will be collected at admission, and daily until day 7, and then at day 10 and 14 from start ventilation(Figure1):

- Demographic data and baseline clinical data, including neurological, neuroradiological and respiratory severity scores (Table 1-4), neuromonitoring data, and the occurrence of neurological and systemic complications.
- Ventilator settings, in particular: modality of ventilator, tidal volume, plateau pressure, peak pressure, mean airway pressure, positive end expiratory pressure, respiratory rate, inspired fraction of oxygen.
- Gas exchange variables and vital parameters.
- Chest radiography data from available chest X–rays and/or Computed Tomography (i.e., no extra chest X–rays are obtained).
- Therapy Intensity Levels (TILs) and predefined complications recorded from medical chart (Table 5).

At ICU and hospital discharge, data on mortality, length of stay (days) duration of mechanical ventilation (in days), ventilator free days (days) will be collected.

At 6-months, mortality and neurological outcome (as for extended Glasgow Outcome Scale, GOSE, Table 6) will be collected.

The GOSE at 6 months follow-up will be collected via phone-structured interviews to the patients and/or family members using a validated questionnaire. [19]Data on the cause and date of death will be also collected.

Data management

Anonymized data will be collected in a web-based electronic Case-Report Form (eCRF) and protected by encryption software and password provided to single users. Each patient will be associated to a numeric code generated by the central database. Data will be checked for consistency and completeness by the study coordinator and the core Steering Committee, to ensure the high quality of the collected data before the analysis and to limit the rate of errors and missing data. Also, a strict monitoring of data quality during the study will be performed.

The data will be securely stored at the University Milano-Bicocca; all procedures will comply with the EU Regulation 2016/679 on the protection of natural persons regarding personal data processing and movement. A Data Transfer Agreement to confirm the terms for data transfer from the centers to the Sponsor will be finalized. Patients' demographic characteristics, co-morbidities, diagnosis, timing of acute events and clinical presentation of acute brain injury will be extracted from the patients' medical records.

STATISTICAL ANALYSIS

Sample size calculation

Since the hypotheses of the study are exploratory, no formal sample size calculation has been performed. This international prospective observational study aims to recruit more than 3000 patients after acute brain damage. Recruitment will last 3-6 months at each center, aiming to enroll an average of 30 consecutive patients/center. This timeframe has been set according to a previous study[20] similar

to VENTIBRAIN, and including a similar network of centers. The number of enrolled patients and ICUs is considered adequate to capture the range of variation in ventilator settings observed in the clinical practice. We aim to include also low-middle income countries, in order to have a representation of the variability worldwide.

Plan of analysis

Patient and ventilation characteristics will be described by means (standard deviation), medians (I-III quartiles) and proportions, as appropriate. The different ventilator settings will be described according to type of brain injury (i.e. TBI, AIS and SAH), presence and severity of lung damage and countries. The association between daily ventilator settings and outcomes will be evaluated by appropriate multivariable models adjusting for relevant confounders at baseline (such as age, sex, cardiovascular and neurological history, primary diagnosis, GCS, pupillary reactivity and the severity of pulmonary and neurological conditions). We will explore the role of currently known threshold for other ICU populations of ventilator settings; however, as in this population no specific thresholds have been defined, we will aim to assess the distribution of these settings and eventually define new thresholds for the brain injured population.

Cause specific Cox model will be applied to time to event outcomes (i.e., mortality, pulmonary complications) and logistic regression to dichotomous outcomes (i.e. poor neurological outcome at 6 month, GOSE <5). Multilevel regression models will be applied to account for repeated measurements on patients and heterogeneity induced by centers and, if residual variation will be present, by countries

The cumulative incidence in time of pulmonary complications during hospital stay will be estimated along with 95% confidence intervals accounting for mortality and discharge as competing events by the Aalen-Johansen estimator.

The occurrence of raised intracranial pressure value lasting more than 5 minutes >20 mmHg will be described daily together with the earlier ventilator settings. A multilevel longitudinal model on daily raised intracranial pressure will be also applied to evaluate the possible impact of ventilator settings adjusting for relevant confounders (as defined before); this model will include only ICP monitored patients.

A sensitivity analysis excluding data from centers that recruited less than 20 patients will be performed. Multiple imputation on covariates will be performed if missing will exceed 10%. Statistical analyses will be conducted using R and SAS.

Patient and Public Involvement

No patient involved.

ETHICAL CONSIDERATIONS

Ethical standards

The PI and Steering Committee will ensure that this study is conducted in full conformity with the Declaration of Helsinki and Good Clinical Practices.

Ethics committee

Each NC/PI will notify the relevant ethics committee, in compliance with the local legislation and rules. The national coordinators will facilitate this process. The approval of the protocol (if required by local authorities) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the SC before the changes are implemented to the study.

Lack of capacity and Delayed Consent

Informed consent will be obtained from patients with no lack of capacity. For patients not able to provide informed consent at the time of recruitment, the responsible clinical/research staff will act as Consulter and consent eligible patients after discussion with the next of kin. If the patient has a Power of Attorney or a Legal tutor or an, he/she will act as Consultee and will be asked to consent/decline participation to the study on legal behalf of the patient.

In presence of patients' Advance Decision Plan, including participation in research studies, the Plan will be respected and recruitment pursued/abandoned accordingly.

At follow-up, patients who have regained capacity will be asked to provide Informed Consent and will be given the possibility to:

- Provide Informed Consent for the acute data and follow-up.
- Deny research participation and request destruction of acute data collected.

Dissemination

Data will be disseminated to the scientific community by abstracts submitted to the European Society of Intensive Care Medicine annual conference and by original articles submitted to peer-reviewed journals.

Publication and data sharing policy

Data sharing policy

After the publication of the main papers, any requests for the use of the data will be made to the VENTIBRAIN Core Steering Committee (CR, GC, PP, FST), and decisions will be made in relation to these requests. The VENTIBRAIN investigators will have priority in requests to use the data set for subsequent studies.

Publication and Authorship

Data will be made available to the scientific community by means of abstract by scientific papers submitted to peer-reviewed journals. Authorship of the main manuscript will follow the ICMJE recommendations that base authorship on the following 4 criteria:

• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

• Drafting the work or revising it critically for important intellectual content; AND

• Final approval of the version to be published; AND

• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A writing committee composed by the members of the core steering committee and biostatisticians and a part of the enlarged steering committee will draft the manuscript and will be author of the manuscript. National coordinators will be authors if they will fulfill the ICMJE criteria and if they will promote the enrolment of at least 300 patients in their country. All the participant centers will be granted in the group authorship, “VENTIBRAIN”. The corresponding author will specify the group name and will clearly identify the group members who can take credit and responsibility for the work as collaborators. For each center, a participant will be

indicated in the group authorship list every 10 patients enrolled. The ESICM support will be acknowledged in each publication generated from the study. In the main manuscripts, CR and GC will share the first authorship, FST will be the third author, and PP will be the last author. After publication of the primary results, on request the pooled dataset will be available for all members of the VENTIBRAIN collaborators for preplanned substudies and secondary analysis, after judgement and approval of scientific quality and validity statement guidelines and checklists. Each secondary analysis or substudy approved will have to include the core Steering Committee as authors. Preplanned analyses include the evaluation of blood gas values (such as oxygen and carbon dioxide) and their association with patient's outcome, and the assessment of mechanical power used in this cohort of patients and its effect on outcomes.

DISCUSSION AND EXPECTED IMPACT OF THE STUDY

VENTIBRAIN is designed to obtain a detailed description of patient's characteristics, management strategies resource use and association with clinical outcomes across many centers/countries. In particular, the study will provide insights in relation to clinical management, monitoring and treatment, practice variation in neuro-intensive care units around the world, differences in the ventilator management of brain injured patients and their potential association with outcome.

VENTIBRAIN has several strengths. First, its prospective design will increase the accuracy of data collection with potential minimization of the chance of residual confounding by unmeasured variables, which is a common limitation of retrospective design. Second, we aim to obtain a large sample size, able to provide information on neurological and systemic complications in mechanically ventilated brain injured patients, and eventually evaluate potential associations between ventilator settings and ICU/ 6 months patients' outcomes. Third, the inclusion of a large number of patients from different centers (dedicated and not dedicated neuroICUs), and countries, including low-income countries will provide information on geoeconomics differences in epidemiology, management strategies and outcomes of mechanically ventilated brain injured patients.

The need to particularly focus on the mechanical ventilator settings in this group of patients is related to the specific ventilator needs of brain injured patients.[18,21] Brain injured patients have a high number of pulmonary complications, ventilator associated pneumonia, and a high rate of need of tracheostomy and extubation failure.[22]

The optimal oxygenation and carbon dioxide targets are not clear in this population.

Hypoxia has been largely recognized as a major cause of secondary brain injury; recently, also hyperoxia has shown to have potential detrimental effects on patients' outcome.[23,24]

Similarly, hypercapnia can cause cerebral vasodilation and increase intracranial pressure and should therefore be avoided, but hypocapnia and cerebral vasoconstriction can lead to cerebral ischemia and currently it is suggested only in case of life-threatening intracranial hypertension and risk of brain herniation.[25,26]

All in it, ventilator targets are unclear in this group of patients.

Moreover, the general principles and ventilator settings applied in the general population have not been established in brain injured patients.[19]

Recent literature has highlighted the importance of protective ventilation in ARDS and non-ARDS patients,[27-32] as well as weaning protocols. However, country-specific practices, the lack of clear guidelines in the neuroICU population or different resources among countries may affect the implementation of all these interventions.

Protective ventilator strategies such as high positive end expiratory pressure or recruitment maneuvers may increase intrathoracic pressure and consequently reduce jugular outflow;[33] low tidal volume and permissive hypercapnia may be detrimental in this group of patients, and rescue therapies used in ARDS patients such as prone position can be contraindicated for the risk of increased ICP and neuromonitoring tools displacement. Finally, extracorporeal membrane oxygenation (ECMO) can be contraindicated for the risk of haemorrhage.[34]However, although these patients have been traditionally ventilated with high tidal volumes and low positive end expiratory pressure,[29] recent evidence suggests that the concept of protective ventilation is gaining interest even in the brain injured population.[19]

Results from the VENTIBRAIN study will allow to clarify the current status of the ventilator management of these patients, and in particular to discriminate the effects of tidal volume, positive end expiratory pressure and driving pressure on outcomes in brain injured patients with, at risk of, or without acute distress respiratory pressure (using predefined scores), and the use of specific settings in case of intracranial hypertension. The VENTIBRAIN study offers a unique opportunity to globally uniform clinical guidelines regarding ventilator strategies in brain injured patients and eventually improving their outcome.

The VENTIBRAIN study has also several limitations that need to be addressed. First, we cannot exclude that ventilator settings and targets used by clinicians might be biased by the participation in the study, thus reducing the ability of VENTIBRAIN to represent the real ICU care of these patients. Second, the CRF designed for VENTIBRAIN was aimed to not cause excessive workload for the participating centres. Therefore, some data regarding systemic complications will be potentially missing, while continuous data on respiratory and neuromonitoring might be incomplete. Similarly, due to the limited number of daily arterial blood gases and ventilator settings data collection, we will have a limited view that might not reflect completely real clinical practice.

Finally, the observational nature of VENTIBRAIN makes impossible to draw causal inferences between ventilator management and outcome in this group of patients. However, VENTIBRAIN is aimed to generate hypotheses for treatment effects and pave the way to design future randomized controlled trials of ventilation in these settings to draw causal inferences and improve clinical outcomes in ventilated brain injured patients.

VENTIBRAIN is designed to assess and describe the clinical practice in ventilator strategies in critically ill brain injured patients in a large number of different countries/centers worldwide. Results from this study will help to identify differences in clinical practices and could be used to plan new trials on mechanical ventilation in this specific subgroup of patients.

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Figures headings:

Figure 1.Timetable of the study. Abbreviations: ABGs, arterial blood gases; ICU, intensive care unit; GOSE, Glasgow outcome scale extended.

Tables

Table 1. The Berlin Definition of ARDS. Abbreviations: ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; FiO2, fractional inspired oxygen; PaO2, arterial oxygen tension; PEEP, positive end-expiratory pressure.

Criteria	**Definition**		
Cause	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic oedema if no risk factors present (eg, echocardiography).		
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms.		
Chest imaging (Rx or CTscan)	Characteristics of the lung images		
Oxygenation	Mild 200<PaO2/FiO2≤300 PEEP or CPAP≥5 cm H2O	Moderate 100<PaO2/FiO2≤200 PEEP ≥5 cm H2O	Severe PaO2/FiO2≤100 PEEP ≥5 cm H2O

Table 2. Glasgow Coma Scale

	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to pain	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Makes sounds	Words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion / Withdrawal to painful stimuli	Localizes to painful stimuli	Obeys commands

Table 3. Marshall classification of traumatic brain injury

Diffuse injury I (no visible pathology)	• no visible intracranial pathology
Diffuse injury II (swelling)	• midline shift of 0 to 5 mm • basal cisterns remain visible • no high or mixed density lesions >25 cm^3
Diffuse injury III	• midline shift of 0 to 5 mm • basal cisterns compressed or completely effaced • no high or mixed density lesions >25 cm^3
Diffuse injury IV (shift)	• midline shift >5 mm • no high or mixed density lesions >25 cm^3
Evacuated mass lesion V	• any lesion evacuated surgically
Non-evacuated mass lesion VI	• high or mixed density lesions >25 cm^3 • not surgically evacuated

Table 4. Fisher scale.

Grade 1	• no subarachnoid (SAH) or intraventricular hemorrhage (IVH) detected • incidence of symptomatic vasospasm: 21%
Grade 2	• diffuse thin (<1 mm) SAH • no clots • incidence of symptomatic vasospasm: 25%
Grade 3	• localized clots and/or layers of blood >1 mm in thickness • no IVH • incidence of symptomatic vasospasm: 37%
Grade 4	• diffuse or no SAH • ICH or IVH present • incidence of symptomatic vasospasm: 31%

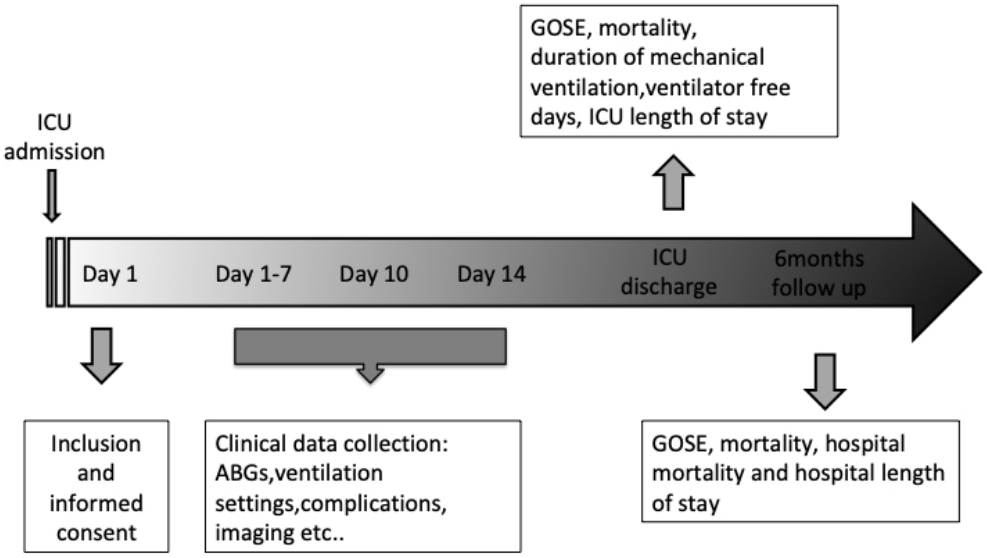
Table 5. Therapy intensity Level Scale. Abbreviations: ICP, intracranial pressure; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid;CO_2, carbon dioxide;

ITEM	DETAILS	SPECIFICS	SCORE	MAX
Positioning	head elevation for ICP control		1	1
	nursed flat (180°) for CPP management		1	
Sedation and neuromuscular blockade	low dose sedation (as required for mechanical ventilation)		1	8
	higher dose sedation for ICP control (but not aiming for burst suppression)		2	
	high dose propofol or barbiturates for ICP control (metabolic suppression)		5	
	neuromuscular blockade (paralysis)		3	
CSF drainage	CSF drainage – low volume	< 120ml/day (< 5ml/h)	2	3
	CSF drainage – high volume	≥ 120ml/day (≥ 5ml/h)	3	
CPP management	fluid loading for maintenance of cerebral perfusion		1	2
	vasopressor therapy required for management of cerebral perfusion		1	
Ventilatory management	mild hypocapnia for ICP control, based on arterial CO_2 in mmHg	≥ 35, < 40	1	4
	moderate hypocapnia for ICP control	≥ 30, < 35	2	
	intensive hypocapnia for ICP control	< 30	4	
Hyperosmolar therapy	mannitol	≤ 2g/kg/24h	2	6
	mannitol	> 2g/kg/24h	3	
	hypertonic saline	≤ 0.3g/kg/24h	2	
	hypertonic saline	> 0.3g/kg/24h	3	

	treatment of fever (T> 38°C or spontaneous T < 34.5°C)		1	
	cooling for ICP control, ≥ 35°C		2	
	hypothermia < 35°C		5	
	intracranial operation for progressive mass lesion, NOT scheduled on admission		4	
	decompressive craniectomy		5	
Maximum total possible score				38

Table 6. Extended Glasgow Outcome Scale

Category number	**Definition**
1	Upper good recovery
2	Lower good recovery
3	Upper moderate disability
4	Lower moderate disability
5	Upper severe disability
6	Lower severe disability
7	Vegetative State
8	Death



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Multicenter observational study on practice of ventilation in brain injured patients: the VENTIBRAIN study protocol

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Multicenter observational study on practice of ventilation in brain injured patients: the VENTIBRAIN study protocol

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ABSTRACT

Introduction

Mechanical ventilatory is a crucial element of acute brain injured patients' management. The ventilatory goals to ensure lung protection during acute respiratory failure may not be adequate in case of concomitant brain injury. Therefore, there are limited data from which physicians can draw conclusions regarding optimal ventilator management in this setting.

Methods and analysis

This is an international multicenter prospective observational cohort study. The aim of the "Multicenter observational study on practice of ventilation in brain injured patients"-the VENTIBRAIN study- is to describe the current practice of ventilator settings and mechanical ventilation in acute brain injured patients.

Secondary objectives include the description of ventilator settings among different countries, and their association with outcomes.

Inclusion criteria will be adult patients admitted to the intensive care unit (ICU) with a diagnosis of traumatic brain injury or cerebrovascular diseases (intracranial hemorrhage, subarachnoid hemorrhage, ischemic stroke), requiring intubation and mechanical ventilation and admission to the ICU. Exclusion criteria will be the following: patients aged < 18 years; pregnant patients; patients not intubated or not mechanically ventilated or receiving only non–invasive ventilation. Data related to clinical examination, neuromonitoring if available, ventilator settings and arterial blood gases will be recorded at admission and daily for the first 7 days and then at day 10 and 14. The Glasgow Outcome Scale Extended on mortality and neurological outcome (GOSE) will be collected at discharge from ICU, hospital and at 6 months follow-up.

Ethics and dissemination

The study has been approved by the Ethic committee of Brianza at the Azienda Socio Sanitaria Territoriale (ASST)-Monza. Data will be disseminated to the scientific community by abstracts submitted to the European Society of Intensive Care Medicine annual conference and by original articles submitted to peer-reviewed journals.

Trial registration number: NCT04459884

Keywords: mechanical ventilation; brain injury; ventilator settings; outcome; Glasgow coma scale

Strengths and limitations of the study

- Results from this large multicenter study including mechanically ventilated acute brain injury patients admitted to the intensive care unit will provide a detailed description of the patients' characteristics, ventilator strategies, and their association to clinical outcomes.
- The main strength of this study relies on the global approach, since it allows to explore clinical practice in a wide number of geographical regions with different public health issues, including low- and middle-income countries.
- The main limitation of this study relies on the observational design with consequent difficulty to draw causal inferences.
- The results from this study will generate hypotheses for respiratory management of acute brain injured patients and help in better study design plans for future randomized controlled trials.

List of abbreviations and relevant definitions

ABI Acute Brain Injury
ARDS Acute Respiratory Distress Syndrome
CA Competent Authority
COPD Chronic Obstructive Pulmonary Disease
CPP Cerebral Perfusion Pressure
CRF Case Report Form
CT Computerized Tomography
DSMB Data safety Managing Board
ESICM European Society of Intensive Care Medicine
GCP General Clinical Practice
GCS Glasgow Coma Scale
GOSE Glasgow Extended Outcome Scale
ICP Intra Cranial Pressure
ICU Intensive Care Unit
ICH Intra Cerebral Hemorrhage
MAP Mean Arterial Pressure
MV Mechanical Ventilation
NC National Coordinator
PaO_2 Arterial Partial Pressure of Carbon Dioxide
PaO_2 Arterial Partial Pressure of Oxygen
PbO_2 Brain Tissue Oxygen Tension
PBW Predicted body weight
PEEP Positive End–expiratory Pressure
PI Principal Investigator
RM Recruitment Maneuvers
SAH – Subarachnoid Hemorrhage
SC Steering Committee
TCD Trans Cranial Doppler
TV Tidal Volume
VALI Ventilator–associated Lung Injury
WBP Personal Data Protection Act
WMO Medical Research Involving Human Subjects Act

BACKGROUND AND RATIONALE

Mechanical ventilation (MV) is a frequently applied and often a life–saving strategy in severely brain injured patients.[1] Paradoxically, ventilation itself has the potential to cause further pulmonary and cerebral damage and can increase mortality and morbidity.[2] Several experimental and clinical studies have shown how brain injury can cause secondary lung injury.[2-4] Lung injury could be due either to mechanical ventilation, which is often necessary in brain injured patients, or to inflammatory response that follows primary acute brain injury, or a combination of both mechanisms.[5]

The so–called '*protective lung ventilation'* strategies include the use of low tidal volume (TV), positive end expiratory pressure (PEEP), and eventually recruitment maneuvers (RMs), and are aimed to prevent lung damage and to reduce morbidity and mortality in patients with acute respiratory distress syndrome (ARDS).[6,7] In particular, the use of low tidal volume seems to have the greater importance,[8-11] and it is recommended in critically ill patients with ARDS.[12]

Results from one multicenter randomized controlled trial suggest that intensive care unit (ICU) patients without ARDS could also benefit from 'protective lung ventilation strategies'.[13]A recent meta–analysis showed a higher incidence of pulmonary complications and even increased mortality in patients who received 'conventional ventilation' with traditionally sized or higher tidal volumes compared to patients undergoing protective strategies.[14]

Therefore, the concept of 'protective lung ventilation' has led to a clinical approach, which seems to reduce morbidity and mortality of ICU patients with ARDS but can also have a beneficial effect on patients with healthy lungs and in the perioperative settings. However, these recommendations often come into conflict with the management of patients affected by acute brain injury, because low tidal volumes, high PEEP and RMs can increase carbon dioxide levels (CO_2) and increase intrathoracic pressure, thus having detrimental effects on intracranial pressure (ICP) and cerebral perfusion pressure (CPP).[15-17] Because of this, brain injured patients have been traditionally excluded from the major trials regarding mechanical ventilation. There is therefore still uncertainty regarding the use of protective ventilation in brain injured ill patients and, as pointed out by a recent consensus of

experts,[18] a multicenter international study on mechanical ventilation strategies in brain injured patients is currently needed.

METHODS

Study design

We designed a large international multicenter prospective observational cohort study including mechanically ventilated brain injured patients and planned 6-month follow-up.

Objectives

Primary objective is to describe ventilation settings of intubated and mechanically ventilated neurocritically ill patients admitted to the ICU.

Secondary objectives are:

- To describe the differences in ventilator settings among different countries.
- To evaluate the association of ventilator settings with pulmonary complications (including pneumonia, acute distress respiratory failure, neurogenic pulmonary edema).
-To describe differences in the ventilator settings in presence/absence of high intracranial pressure.
- To evaluate the association of ventilator settings with outcomes (i.e. 6-months mortality and neurological outcome, in-hospital and ICU mortality, hospital length of stay, duration of mechanical ventilation, ventilator free days at ICU discharge).

Study population

We will collect data of consecutive patients with acute brain injury requiring endotracheal intubation and mechanical ventilation, who are admitted to the intensive care unit (ICU).

Inclusion criteria will be:

- Age ≥ 18 years.
- Patients admitted to the ICU with a diagnosis of a primary non-anoxic brain injury, such as:
  - Traumatic brain injury (TBI)
  - Cerebrovascular diseases (intracranial hemorrhage, ICH; subarachnoid hemorrhage, SAH; acute ischemic stroke, AIS)
- Patients requiring intubation, mechanical ventilation, or needing mechanical ventilation during ICU stay.

Exclusion criteria

- Age < 18 years.
- Pregnant patients.
- Patients not intubated or not mechanically ventilated or receiving only non–invasive ventilation (i.e., patient never received invasive ventilation during the present admission).

Outcomes

Enrolled patients will be followed until ICU–hospital discharge or death, whatever comes first and at 6 months follow up.

Outcomes will be assessed as:

- 6-months mortality and neurological outcome (as for extended Glasgow Outcome Scale, GOSE).

- Pulmonary complications (defined as: acute distress respiratory failure, pulmonary infection, pneumothorax, pleural effusion, atelectasis, non-cardiogenic pulmonary edema).

-In-hospital and ICU mortality.

-Hospital length of stay (LOS) in patients discharged alive.

- Duration of mechanical ventilation (in days), ventilator free days (days) at ICU discharge.

Study procedures and settings

The protocol has been endorsed by the European Society of Intensive Care Medicine (ESICM). Worldwide, more than 200 centers from 56 countries have been contacted to participate in the VENTIBRAIN study (more information at https://www.esicm.org/research/trials/endorsed-trials/ongoing-projects-endorsed/).

The established recruitment window will open in spring-summer 2021. The inclusion period will be flexible for participating centers and determined at a later stage together with the study–coordinator. Centers will enroll consecutive patients for a minimum period of 3 months to a maximum period of 6 months.

Patients in participating centers will be screened on a daily basis. After 6 months from recruitment, the patients or their family members will be contacted by phone for the follow-up evaluation.

Data collection

The following data will be collected at admission, and daily until day 7, and then at day 10 and 14 (Figure1):

- Demographic data and baseline clinical data, including neurological, neuroradiological and respiratory severity scores (Table 1-4), neuromonitoring data, and the occurrence of neurological and systemic complications.
- Ventilator settings, in particular: modality of ventilator, tidal volume, plateau pressure, peak pressure, mean airway pressure, positive end expiratory pressure, respiratory rate, inspired fraction of oxygen.
- Gas exchange variables and vital parameters.
- Chest radiography data from available chest X–rays and/or Computed Tomography (i.e., no extra chest X–rays are obtained).
- Therapy Intensity Levels (TILs) and predefined complications recorded from medical chart (Table 5).

At ICU and hospital discharge, data on mortality, length of stay (days) duration of mechanical ventilation (in days), ventilator free days (days) will be collected.

At 6-months, mortality and neurological outcome (as for extended Glasgow Outcome Scale, GOSE, Table 6) will be collected.

The GOSE at 6 months follow-up will be collected via phone-structured interviews to the patients and/or family members using a validated questionnaire. [19]Data on the cause and date of death will be also collected.

Data management

Anonymized data will be collected in a web-based electronic Case-Report Form (eCRF) and protected by encryption software and password provided to single users. Each patient will be associated to a numeric code generated by the central database. Data will be checked for consistency and completeness by the study coordinator and the core Steering Committee, to ensure the high quality of the collected data before the analysis and to limit the rate of errors and missing data. Also, a strict monitoring of data quality during the study will be performed.

The data will be securely stored at the University Milano-Bicocca; all procedures will comply with the EU Regulation 2016/679 on the protection of natural persons regarding personal data processing and movement. A Data Transfer Agreement to confirm the terms for data transfer from the centers to the Sponsor will be finalized. Patients' demographic characteristics, co-morbidities, diagnosis, timing of acute events and clinical presentation of acute brain injury will be extracted from the patients' medical records.

STATISTICAL ANALYSIS

Sample size calculation

Since the hypotheses of the study are exploratory, no formal sample size calculation has been performed. This international prospective observational study aims to recruit more than 3000 patients after acute brain damage. Recruitment will last 3-6 months at each center, aiming to enroll an average of 30 consecutive patients/center. This timeframe has been set according to a previous study[20] similar

to VENTIBRAIN, and including a similar network of centers. The number of enrolled patients and ICUs is considered adequate to capture the range of variation in ventilator settings observed in the clinical practice. We aim to include also low-middle income countries, in order to have a representation of the variability worldwide.

Plan of analysis

Patient and ventilation characteristics will be described by means (standard deviation), medians (I-III quartiles) and proportions, as appropriate. The different ventilator settings will be described according to type of brain injury (i.e. TBI, AIS and SAH), presence and severity of lung damage and countries. The association between daily ventilator settings and outcomes will be evaluated by appropriate multivariable models adjusting for relevant confounders at baseline (such as age, sex, cardiovascular and neurological history, primary diagnosis, Glasgow Coma Scale (GCS), pupillary reactivity and the severity of pulmonary and neurological conditions). We will explore the role of currently known thresholds for other ICU populations of ventilator settings; however, as in this population no specific thresholds have been defined, we will aim to assess the distribution of these settings and eventually define new thresholds for the brain injured population.

Cause specific Cox model will be applied to time to event outcomes (i.e., mortality, pulmonary complications) and logistic regression to dichotomous outcomes (i.e. poor neurological outcome at 6 month, GOSE <5). Multilevel regression models will be applied to account for repeated measurements on patients and heterogeneity induced by centers and, if residual variation is present, by countries.

The cumulative incidence in time of pulmonary complications during hospital stay will be estimated along with 95% confidence intervals accounting for mortality and discharge as competing events by the Aalen-Johansen estimator.

The occurrence of raised intracranial pressure value lasting more than 5 minutes >20 mmHg will be described daily together with the earlier ventilator settings. A multilevel longitudinal model on daily raised intracranial pressure will be also applied to evaluate the possible impact of ventilator settings adjusting for relevant confounders (as defined before); this model will include only ICP monitored patients.

A sensitivity analysis excluding data from centers that recruited less than 20 patients will be performed. Multiple imputation on covariates will be performed if missing data will exceed 10%. Statistical analyses will be conducted using R and SAS.

Patient and Public Involvement

No patient involved.

ETHICAL CONSIDERATIONS

Ethical standards

The PI and Steering Committee will ensure that this study is conducted in full conformity with the Declaration of Helsinki and Good Clinical Practices.

Ethics committee

Each NC/PI will notify the relevant ethics committee, in compliance with the local legislation and rules. The national coordinators will facilitate this process. The approval of the protocol (if required by local authorities) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the SC before the changes are implemented to the study.

Lack of capacity and Delayed Consent

Informed consent will be obtained from patients with no lack of capacity. For patients not able to provide informed consent at the time of recruitment, the responsible clinical/research staff will act as Consulter and consent eligible patients after discussion with the next of kin. If the patient has a Power of Attorney or a Legal tutor or an, he/she will act as Consultee and will be asked to consent/decline participation to the study on legal behalf of the patient.

In presence of patients' Advance Decision Plan, including participation in research studies, the Plan will be respected and recruitment pursued/abandoned accordingly.

At follow-up, patients who have regained capacity will be asked to provide Informed Consent and will be given the possibility to:

- Provide Informed Consent for the acute data and follow-up.
- Deny research participation and request destruction of acute data collected.

Dissemination

Data will be disseminated to the scientific community by abstracts submitted to the European Society of Intensive Care Medicine annual conference and by original articles submitted to peer-reviewed journals.

Publication and data sharing policy

Data sharing policy

After the publication of the main papers, any requests for the use of the data will be made to the VENTIBRAIN Core Steering Committee (CR, GC, PP, FST), and decisions will be made in relation to these requests. The VENTIBRAIN investigators will have priority in requests to use the data set for subsequent studies.

Publication and Authorship

Data will be made available to the scientific community by means of abstract by scientific papers submitted to peer-reviewed journals. Authorship of the main manuscript will follow the ICMJE recommendations that base authorship on the following 4 criteria:

• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

• Drafting the work or revising it critically for important intellectual content; AND

• Final approval of the version to be published; AND

• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A writing committee composed by the members of the core steering committee and biostatisticians and a part of the enlarged steering committee will draft the manuscript and will be author of the manuscript. National coordinators will be authors if they will fulfill the ICMJE criteria and if they will promote the enrolment of at least 300 patients in their country. All the participant centers will be granted in the group authorship, “VENTIBRAIN”. The corresponding author will specify the group name and will clearly identify the group members who can take credit and responsibility for the work as collaborators. For each center, a participant will be

indicated in the group authorship list every 10 patients enrolled. The ESICM support will be acknowledged in each publication generated from the study. In the main manuscripts, CR will have the first authorship, and PP will be the last author. After publication of the primary results, on request the pooled dataset will be available for all members of the VENTIBRAIN collaborators for preplanned substudies and secondary analysis, after judgement and approval of scientific quality and validity statement guidelines and checklists. Each secondary analysis or substudy approved will have to include part of the core Steering Committee as authors. Preplanned analyses include the evaluation of blood gas values (such as oxygen and carbon dioxide) and their association with patient's outcome, and the assessment of mechanical power used in this cohort of patients and its effect on outcomes.

DISCUSSION AND EXPECTED IMPACT OF THE STUDY

VENTIBRAIN is designed to obtain a detailed description of patient's characteristics, management strategies resource use and association with clinical outcomes across many centers/countries. In particular, the study will provide insights in relation to clinical management, monitoring and treatment, practice variation in neuro-intensive care units around the world, differences in the ventilator management of brain injured patients and their potential association with outcome.

VENTIBRAIN has several strengths. First, its prospective design will increase the accuracy of data collection with potential minimization of the chance of residual confounding by unmeasured variables, which is a common limitation of retrospective design. Second, we aim to obtain a large sample size, able to provide information on neurological and systemic complications in mechanically ventilated brain injured patients, and eventually evaluate potential associations between ventilator settings and ICU/ 6 months patients' outcomes. Third, the inclusion of a large number of patients from different centers (dedicated and not dedicated neuroICUs), and countries, including low-income countries will provide information on geoeconomics differences in epidemiology, management strategies and outcomes of mechanically ventilated brain injured patients.

The need to particularly focus on the mechanical ventilator settings in this group of patients is related to the specific ventilator needs of brain injured patients.[18,21] Brain injured patients have a high number of pulmonary complications, ventilator associated pneumonia, and a high rate of need of tracheostomy and extubation failure.[22]

The optimal oxygenation and carbon dioxide targets are not clear in this population.

Hypoxia has been largely recognized as a major cause of secondary brain injury; recently, also hyperoxia has shown to have potential detrimental effects on patients' outcome.[23,24]

Similarly, hypercapnia can cause cerebral vasodilation and increase intracranial pressure and should therefore be avoided, but hypocapnia and cerebral vasoconstriction can lead to cerebral ischemia and currently it is suggested only in case of life-threatening intracranial hypertension and risk of brain herniation.[25,26]

All in it, ventilator targets are unclear in this group of patients.

Moreover, the general principles and ventilator settings applied in the general population have not been established in brain injured patients.[19]

Recent literature has highlighted the importance of protective ventilation in ARDS and non-ARDS patients,[27-32] as well as weaning protocols. However, country-specific practices, the lack of clear guidelines in the neuroICU population or different resources among countries may affect the implementation of all these interventions.

Protective ventilator strategies such as high positive end expiratory pressure or recruitment maneuvers may increase intrathoracic pressure and consequently reduce jugular outflow;[33] low tidal volume and permissive hypercapnia may be detrimental in this group of patients, and rescue therapies used in ARDS patients such as prone position can be contraindicated for the risk of increased ICP and neuromonitoring tools displacement. Finally, extracorporeal membrane oxygenation (ECMO) can be contraindicated for the risk of haemorrhage.[34]However, although these patients have been traditionally ventilated with high tidal volumes and low positive end expiratory pressure,[29] recent evidence suggests that the concept of protective ventilation is gaining interest even in the brain injured population.[19]

Results from the VENTIBRAIN study will allow to clarify the current status of the ventilator management of these patients, and in particular to discriminate the effects of tidal volume, positive end expiratory pressure and driving pressure on outcomes in brain injured patients with, at risk of, or without acute distress respiratory pressure (using predefined scores), and the use of specific settings in case of intracranial hypertension. The VENTIBRAIN study offers a unique opportunity to globally uniform clinical guidelines regarding ventilator strategies in brain injured patients and eventually improving their outcome.

The VENTIBRAIN study has also several limitations that need to be addressed. First, we cannot exclude that ventilator settings and targets used by clinicians might be biased by the participation in the study, thus reducing the ability of VENTIBRAIN to represent the real ICU care of these patients. Second, the CRF designed for VENTIBRAIN was aimed to not cause excessive workload for the participating centres. Therefore, some data regarding systemic complications will be potentially missing, while continuous data on respiratory and neuromonitoring might be incomplete. Similarly, due to the limited number of daily arterial blood gases and ventilator settings data collection, we will have a limited view that might not reflect completely real clinical practice.

Finally, the observational nature of VENTIBRAIN makes impossible to draw causal inferences between ventilator management and outcome in this group of patients. However, VENTIBRAIN is aimed to generate hypotheses for treatment effects and pave the way to design future randomized controlled trials of ventilation in these settings to draw causal inferences and improve clinical outcomes in ventilated brain injured patients.

VENTIBRAIN is designed to assess and describe the clinical practice in ventilator strategies in critically ill brain injured patients in a large number of different countries/centers worldwide. Results from this study will help to identify differences in clinical practices and could be used to plan new trials on mechanical ventilation in this specific subgroup of patients.

Contributors: CR, GC, FST, PP were equally responsible for writing of the manuscript and participated in study design. CR drafted the first version of the manuscript. FST, PP, GC, SG, PR, AV reviewed the manuscript and agreed with submission.

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Figures headings:

Figure 1.Timetable of the study. Abbreviations: ABGs, arterial blood gases; ICU, intensive care unit; GOSE, Glasgow outcome scale extended.

Tables

Table 1. The Berlin Definition of ARDS. Abbreviations: ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; FiO2, fractional inspired oxygen; PaO2, arterial oxygen tension; PEEP, positive end-expiratory pressure.

Criteria	**Definition**		
Cause	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic oedema if no risk factors present (eg, echocardiography).		
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms.		
Chest imaging (Rx or CTscan)	Characteristics of the lung images		
Oxygenation	Mild 200<PaO2/FiO2≤300 PEEP or CPAP≥5 cm H2O	Moderate 100<PaO2/FiO2≤200 PEEP ≥5 cm H2O	Severe PaO2/FiO2≤100 PEEP ≥5 cm H2O

Table 2. Glasgow Coma Scale

	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to pain	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Makes sounds	Words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion / Withdrawal to painful stimuli	Localizes to painful stimuli	Obeys commands

Table 3. Marshall classification of traumatic brain injury

Diffuse injury I (no visible pathology)	• no visible intracranial pathology
Diffuse injury II (swelling)	• midline shift of 0 to 5 mm • basal cisterns remain visible • no high or mixed density lesions >25 cm^3
Diffuse injury III	• midline shift of 0 to 5 mm • basal cisterns compressed or completely effaced • no high or mixed density lesions >25 cm^3
Diffuse injury IV (shift)	• midline shift >5 mm • no high or mixed density lesions >25 cm^3
Evacuated mass lesion V	• any lesion evacuated surgically
Non-evacuated mass lesion VI	• high or mixed density lesions >25 cm^3 • not surgically evacuated

Table 4. Fisher scale.

Grade 1	• no subarachnoid (SAH) or intraventricular hemorrhage (IVH) detected • incidence of symptomatic vasospasm: 21%
Grade 2	• diffuse thin (<1 mm) SAH • no clots • incidence of symptomatic vasospasm: 25%
Grade 3	• localized clots and/or layers of blood >1 mm in thickness • no IVH • incidence of symptomatic vasospasm: 37%
Grade 4	• diffuse or no SAH • ICH or IVH present • incidence of symptomatic vasospasm: 31%

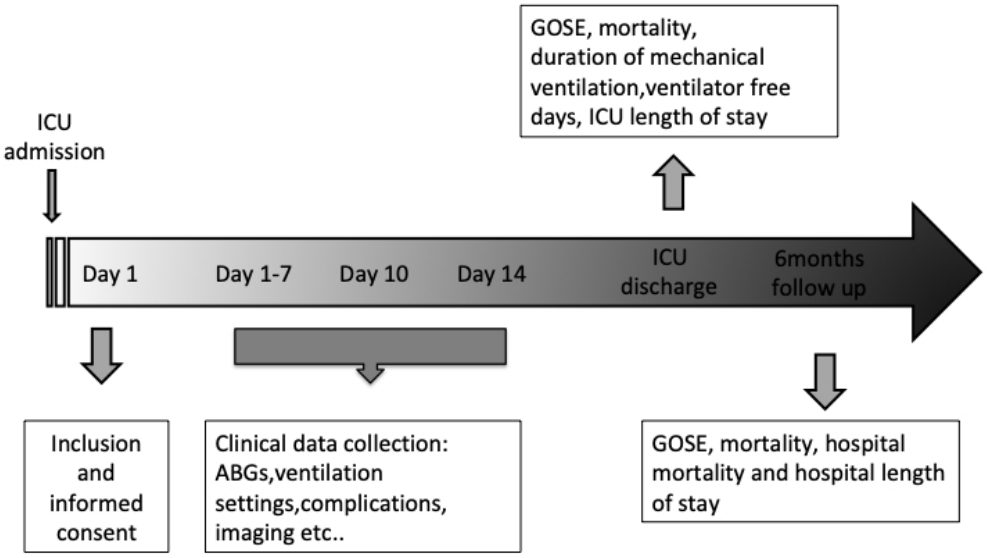
Table 5. Therapy intensity Level Scale. Abbreviations: ICP, intracranial pressure; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid;CO_2, carbon dioxide;

ITEM	DETAILS	SPECIFICS	SCORE	MAX
Positioning	head elevation for ICP control		1	1
	nursed flat (180°) for CPP management		1	
Sedation and neuromuscular blockade	low dose sedation (as required for mechanical ventilation)		1	8
	higher dose sedation for ICP control (but not aiming for burst suppression)		2	
	high dose propofol or barbiturates for ICP control (metabolic suppression)		5	
	neuromuscular blockade (paralysis)		3	
CSF drainage	CSF drainage – low volume	< 120ml/day (< 5ml/h)	2	3
	CSF drainage – high volume	≥ 120ml/day (≥ 5ml/h)	3	
CPP management	fluid loading for maintenance of cerebral perfusion		1	2
	vasopressor therapy required for management of cerebral perfusion		1	
Ventilatory management	mild hypocapnia for ICP control, based on arterial CO_2 in mmHg	≥ 35, < 40	1	4
	moderate hypocapnia for ICP control	≥ 30, < 35	2	
	intensive hypocapnia for ICP control	< 30	4	
Hyperosmolar therapy	mannitol	≤ 2g/kg/24h	2	6
	mannitol	> 2g/kg/24h	3	
	hypertonic saline	≤ 0.3g/kg/24h	2	
	hypertonic saline	> 0.3g/kg/24h	3	

	treatment of fever (T> 38°C or spontaneous T < 34.5°C)		1	
	cooling for ICP control, ≥ 35°C		2	
	hypothermia < 35°C		5	
	intracranial operation for progressive mass lesion, NOT scheduled on admission		4	
	decompressive craniectomy		5	
Maximum total possible score				38

Table 6. Extended Glasgow Outcome Scale

Category number	**Definition**
1	Upper good recovery
2	Lower good recovery
3	Upper moderate disability
4	Lower moderate disability
5	Upper severe disability
6	Lower severe disability
7	Vegetative State
8	Death



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