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# BMJ Open

## 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.

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

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3 examination, neuromonitoring if available, ventilator settings and arterial blood  
4 gases will be recorded at admission and daily for the first 7 days from admission and  
5 then at day 10 and 14. The Glasgow Outcome Scale Data on mortality and  
6 neurological outcome (as for extended (GOSE)) will be collected at discharge from  
7 ICU, hospital and at 6 months follow-up.  
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### 10 11 12 **Ethics and dissemination**

13  
14 The study has been approved by the Ethic committee of Brianza at the Azienda Socio  
15 Sanitaria Territoriale (ASST)-Monza. Data will be disseminated to the scientific  
16 community by abstracts submitted to the European Society of Intensive Care  
17 Medicine annual conference and by original articles submitted to peer-reviewed  
18 journals.  
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25 **Trial registration number:** NCT04459884  
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30 **Keywords:** mechanical ventilation; brain injury; ventilator settings; outcome;  
31 Glasgow coma scale  
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### 34 35 36 37 **Strengths and limitations of the study**

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- 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

PaO<sub>2</sub> Arterial Partial Pressure of Carbon DioxidePaO<sub>2</sub> Arterial Partial Pressure of OxygenPbO<sub>2</sub> 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.<sup>1</sup> Paradoxically, ventilation itself has the potential to cause further pulmonary and cerebral damage and can increase mortality and morbidity.<sup>2</sup> Several experimental and clinical studies have shown how brain injury can cause secondary lung injury.<sup>2-4</sup> 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.<sup>5</sup>

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).<sup>6,7</sup> In particular, the use of low tidal volume seems to have the greater importance,<sup>8-11</sup> and it is recommended in critically ill patients with ARDS.<sup>12</sup>

Results from one multicenter randomized controlled trial suggest that also intensive care unit (ICU) patients without ARDS could benefit from '*protective lung ventilation strategies*'.<sup>13</sup> 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.<sup>14</sup>

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

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2  
3 beneficial effect on patients with healthy lungs and in the perioperative settings.  
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5 However, these recommendations often come into conflict with the management of  
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7 patients affected by acute brain injury, because low tidal volumes, high PEEP and  
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9 RMs can increase carbon dioxide levels (CO<sub>2</sub>) and increase intrathoracic pressure,  
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11 thus having detrimental effects on intracranial pressure (ICP) and cerebral perfusion  
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13 pressure (CPP).<sup>15-17</sup> Because of this, brain injured patients have been traditionally  
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15 excluded from the major trials regarding mechanical ventilation. There is therefore  
16  
17 still uncertainty regarding the use of protective ventilation in brain injured ill  
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19 patients, and, as suggested by a recent consensus of experts,<sup>18</sup> a multicenter  
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21 international study on mechanical ventilation strategies in brain injured patients is  
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23 currently missing.

## 24 25 **METHODS**

### 26 27 **Study design**

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29 We designed a large international multicenter prospective observational cohort  
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31 study including mechanically ventilated brain injured patients and planned 6-month  
32  
33 follow-up.

### 34 35 36 **Objectives**

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

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42 Secondary objectives are:

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44 - To describe the differences in ventilator settings among different countries.
- 45  
46 - To evaluate the association of ventilator settings with pulmonary complications  
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48 (including pneumonia, ARDS, neurogenic pulmonary edema)
- 49  
50 -To describe differences in the ventilator settings in presence/absence of high  
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52 intracranial pressure.
- 53  
54 - To evaluate the association of ventilator settings with outcomes

### 55 56 57 **Study population**

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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  $\geq$  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.

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3 -Hospital length of stay (LOS).  
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5 - Duration of mechanical ventilation (in days), ventilator free days (days) at ICU  
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7 discharge.  
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### 10 **Study procedures and settings**

11 The protocol has been endorsed by the European Society of Intensive Care (ESICM):  
12 Worldwide, more than 200 centers from 56 countries have been contacted to  
13 participate in the VENTIBRAIN study (more information at  
14 <https://www.esicm.org/research/trials/endorsed-trials/ongoing-projects->  
15 [endorsed/](https://www.esicm.org/research/trials/endorsed-trials/ongoing-projects-)).  
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18 The established recruitment window will open at the beginning of 2021. The  
19 inclusion period will be flexible for participating centers and determined at a later  
20 stage together with the study–coordinator. Centers will enroll consecutive patients  
21 for a minimum period of 3 months to a maximum period of 6 months.  
22

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

29 The following data will be collected at admission, and daily until day 7, and then at  
30 day 10 and 14:  
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- 32 • Demographic data and baseline clinical data, including neurological,  
33 neuroradiological and respiratory severity scores (Table 1-4), neuromonitoring  
34 data, and the occurrence of neurological and systemic complications
  - 35 • Ventilation settings, gas exchange variables and vital parameters
  - 36 • Chest radiography data from available chest X–rays and/or Computed  
37 Tomography (i.e., no extra chest X–rays are obtained)
  - 38 • Therapy Intensity Levels (TILs) and predefined complications recorded from  
39 medical chart (Table 5)
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3 At ICU discharge data on mortality, length of stay (days) duration of mechanical  
4 ventilation (in days), ventilator free days (days) will be collected

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7 At 6-months mortality and neurological outcome (as for extended Glasgow Outcome  
8 Scale, GOSE, Table 6), length of stay (in days), in hospital mortality will be collected  
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12 The GOSE at 6 months follow-up will be collected via phone-structured interviews to  
13 the patients and/or family members using a validated questionnaire. <sup>19</sup>Data on the  
14 cause and date of death will be also collected.  
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### 17 18 19 20 **Data management**

21 Anonymized data will be collected in a web-based electronic Case-Report Form  
22 (eCRF) and protected by encryption software and password provided to single users.  
23 Each patient will be associated to a numeric code generated by the central database.  
24 Data will be checked for consistency and completeness by the study coordinator and  
25 the core Steering Committee, to ensure the high quality of the collected data before  
26 the analysis and to limit the rate of errors and missing data.  
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29 The data will be securely stored at the University Milano-Bicocca; all procedures will  
30 comply with the EU Regulation 2016/679 on the protection of natural persons  
31 regarding personal data processing and movement. A Data Transfer Agreement to  
32 confirm the terms for data transfer from the centers to the Sponsor will be finalized.  
33 Patients' demographic characteristics, co-morbidities, diagnosis, timing of acute  
34 events and clinical presentation of acute brain injury will be extracted from the  
35 patients' medical records.  
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## 47 **STATISTICAL ANALYSIS**

### 48 **Sample size calculation**

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

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3 following 4 criteria:

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5 • Substantial contributions to the conception or design of the work; or the  
6 acquisition, analysis, or interpretation of data for the work; AND  
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8 • Drafting the work or revising it critically for important intellectual content; AND  
9  
10 • Final approval of the version to be published; AND  
11  
12 • Agreement to be accountable for all aspects of the work in ensuring that questions  
13 related to the accuracy or integrity of any part of the work are appropriately  
14 investigated and resolved.  
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18 A writing committee composed by the Core Steering Committee, biostatisticians and  
19 selected members of the advisory board will draft the manuscript and will be author  
20 of the manuscript. National coordinators will be authors if they will fulfill the ICMJE  
21 criteria and if they will promote the enrolment of at least 300 patients in their  
22 country. All the participant centers will be granted in the group authorship,  
23 “VENTIBRAIN”. The corresponding author will specify the group name and will clearly  
24 identify the group members who can take credit and responsibility for the work as  
25 collaborators. For each center, a participant will be indicated in the  
26 group authorship list every 50 patients enrolled. The ESICM support will be  
27 acknowledged in each publication generated from the study. In the main  
28 manuscripts, CR and GC will share the first authorship, FST will be the third author,  
29 and PP will be the last author. After publication of the primary results, on request  
30 the pooled dataset will be available for all members of the VENTIBRAIN collaborators  
31 for preplanned substudies and secondary analysis, after judgement and approval of  
32 scientific quality and validity statement guidelines and checklists. Each secondary  
33 analysis or substudy approved will have to include the core Steering Committee as  
34 authors. Preplanned analysis include the evaluation of blood gas values (such as  
35 oxygen and carbon dioxide) and their association with patient’s outcome, and the  
36 assessment of mechanical power used in this cohort of patients and its effect on  
37 outcomes.  
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## 56 **DISCUSSION AND EXPECTED IMPACT OF THE STUDY**

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58 VENTIBRAIN is designed to obtain a detailed description of patient’s characteristics,  
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3 management strategies resource use and association with clinical outcomes across  
4 many centers/countries. In particular, the study will provide insights in relation to  
5 clinical management, monitoring and treatment, practice variation in neuro-  
6 intensive care units around the world, differences in the ventilator management of  
7 brain injured patients and their potential association with outcome.  
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13 VENTIBRAIN has several strengths. First, its prospective design will increase the  
14 accuracy of data collection with potential minimization of the chance of residual  
15 confounding by unmeasured variables, which is a common limitation of  
16 retrospective design. Second, we aim to obtain a large sample size, able to provide  
17 information on neurological and systemic complications in mechanically ventilated  
18 brain injured patients, and eventually evaluate potential associations between  
19 ventilator settings and ICU/ 6 months patients' outcomes. Third, the inclusion of a  
20 large number of patients from different centers (dedicated and not dedicated  
21 neuroICUs), and countries, including low-income countries will provide information  
22 on geoeconomic differences in epidemiology, management strategies and outcomes  
23 of mechanically ventilated brain injured patients.  
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35 The need to particularly focus on the mechanical ventilator settings in this group of  
36 patients is related to the specific ventilator needs of brain injured patients.<sup>18,20,21</sup>  
37 Brain injured patients have a high number of pulmonary complications, ventilator  
38 associated pneumonia (VAP), and a high rate of need of tracheostomy and  
39 extubation failure.<sup>22</sup>  
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44 The optimal oxygenation and carbon dioxide targets are not clear in this population.  
45 Hypoxia has been largely recognized as a major cause of secondary brain injury;  
46 recently, also hyperoxia has shown to have potential detrimental effects on patients'  
47 outcome.<sup>23,24</sup>  
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51 Similarly, hypercapnia can cause cerebral vasodilation and increase intracranial  
52 pressure and should therefore be avoided, but hypocapnia and cerebral  
53 vasoconstriction can lead to cerebral ischemia and currently it is suggested only in  
54 case of life-threatening intracranial hypertension and risk of brain herniation.<sup>25,26</sup>  
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All in it, ventilator targets are unclear in this group of patients.

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5 Moreover, the general principles and ventilator settings applied in the general  
6 population have not been established in brain injured patients.<sup>19</sup>

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8 Recent literature has highlighted the importance of protective ventilation in ARDS  
9 and non ARDS patients,<sup>27-32</sup> as well as weaning protocols. However, country-specific  
10 practices, the lack of clear guidelines in the neuroICU population or different  
11 resources among countries may affect the implementation of all these interventions.  
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18 Protective ventilator strategies such as high PEEP or recruitment maneuvers with  
19 increased intrathoracic pressure and consequent jugular outflow reduction and  
20 intracranial hypertension;<sup>33</sup> low tidal volume and permissive hypercapnia may be  
21 contraindicated in this group of patients, and rescue therapies used in ARDS patients  
22 such as prone position can be contraindicated for the risk of increased ICP and  
23 neuromonitoring tools displacement and extracorporeal membrane oxygenation  
24 (ECMO) can be contraindicated for the risk of haemorrhage.<sup>34</sup> However, although  
25 these patients have been traditionally ventilated with high tidal volumes and low  
26 PEEP,<sup>29</sup> recent evidence suggests that the concept of protective ventilation is gaining  
27 interest even in the brain injured population.<sup>19</sup>  
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38 Results from the VENTIBRAIN study will allow to clarify the current status of the  
39 ventilator management of these patients, and in particular to discriminate the  
40 effects of tidal volume, PEEP and driving pressure on outcomes in brain injured  
41 patients with, at risk of, or without ARDS (using predefined scores), and the use of  
42 specific settings in case of intracranial hypertension. The VENTIBRAIN study offers a  
43 unique opportunity to globally uniform clinical guidelines regarding ventilator  
44 strategies in brain injured patients and eventually improving their outcome.  
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52 The VENTIBRAIN study has also several limitations that need to be addressed. First,  
53 we cannot exclude that ventilator settings and targets used by clinicians might be  
54 biased by the participation in the study, thus reducing the ability of VENTIBRAIN to  
55 represent the real ICU care of these patients. Second, the CRF designed for  
56 VENTIBRAIN was aimed to not cause excessive workload for the participating  
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3 centres. Therefore, some data regarding systemic complications will be potentially  
4 missing, while continuous data on respiratory and neuromonitoring might be  
5 incomplete. Similarly, due to the limited number of daily arterial blood gases and  
6 ventilator settings data collection, we will have a limited dataset that might not  
7 reflect completely real clinical practice.  
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13 Finally, the observational nature of VENTIBRAIN makes impossible to draw causal  
14 inferences between ventilator management and outcome in this group of patients.  
15 However, VENTIBRAIN is aimed to generate hypothesis for treatment effects and  
16 pave the way to design future randomized controlled trials of ventilation in these  
17 settings to draw causal inferences and improve clinical outcomes in ventilated brain  
18 injured patients.  
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## 26 **CONCLUSIONS**

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

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42 Figure 1. Timetable of the study.  
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54  
55 **Contributors:** CR, GC, FST, PP were equally responsible for writing of  
56 the manuscript and participated in study design. CR drafted the first version of the  
57 manuscript. FST, PP, GC, SG, PR reviewed the manuscript and agreed with  
58  
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3 submission.

4  
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For peer review only

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## 14 Tables

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17 Table 1. The Berlin Definition of ARDS. Abbreviations: ARDS, acute respiratory  
18 distress syndrome; CPAP, continuous positive airway pressure; FiO<sub>2</sub>, fractional  
19 inspired oxygen; PaO<sub>2</sub>, arterial oxygen tension; PEEP, positive end-expiratory  
20 pressure.  
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23 Criteria	24 Definition		
25 Cause	26 Respiratory failure not fully explained by cardiac failure or fluid overload; 27 need objective assessment to exclude hydrostatic oedema if no risk factors 28 present (eg, echocardiography).		
29 Timing	30 Within 1 week of a known clinical insult or new/worsening respiratory 31 symptoms.		
32 Chest imaging (Rx or CTscan)	33 Bilateral opacities not fully explained by effusions, lobar/lung collapse or 34 nodules.		
35 Oxygenation	36 Mild 37 200 < PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 300 38 PEEP or CPAP ≥ 5 cm 39 H <sub>2</sub> O	40 Moderate 41 100 < PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 200 42 PEEP ≥ 5 cm H <sub>2</sub> O	43 Severe 44 PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 100 45 PEEP ≥ 5 cm H <sub>2</sub> O



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

<b>Diffuse injury I (no visible pathology)</b>	<ul style="list-style-type: none"> <li>no visible intracranial pathology</li> </ul>
<b>Diffuse injury II (swelling)</b>	<ul style="list-style-type: none"> <li>midline shift of 0 to 5 mm</li> <li>basal cisterns remain visible</li> <li>no high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> </ul>
<b>Diffuse injury III</b>	<ul style="list-style-type: none"> <li>midline shift of 0 to 5 mm</li> <li>basal cisterns compressed or completely effaced</li> <li>no high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> </ul>
<b>Diffuse injury IV (shift)</b>	<ul style="list-style-type: none"> <li>midline shift <math>&gt;5 \text{ mm}</math></li> <li>no high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> </ul>
<b>Evacuated mass lesion V</b>	<ul style="list-style-type: none"> <li>any lesion evacuated surgically</li> </ul>
<b>Non-evacuated mass lesion VI</b>	<ul style="list-style-type: none"> <li>high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> <li>not surgically evacuated</li> </ul>

Table 4. Fisher scale.

<b>Grade 1</b>	<ul style="list-style-type: none"> <li>• no subarachnoid (SAH) or intraventricular hemorrhage (IVH) detected</li> <li>• incidence of symptomatic vasospasm: 21%</li> </ul>
<b>Grade 2</b>	<ul style="list-style-type: none"> <li>• diffuse thin (&lt;1 mm) SAH</li> <li>• no clots</li> <li>• incidence of symptomatic vasospasm: 25%</li> </ul>
<b>Grade 3</b>	<ul style="list-style-type: none"> <li>• localized clots and/or layers of blood &gt;1 mm in thickness</li> <li>• no IVH</li> <li>• incidence of symptomatic vasospasm: 37%</li> </ul>
<b>Grade 4</b>	<ul style="list-style-type: none"> <li>• diffuse or no SAH</li> <li>• ICH or IVH present</li> <li>• incidence of symptomatic vasospasm: 31%</li> </ul>

Table 5. Therapy intensity Level Scale

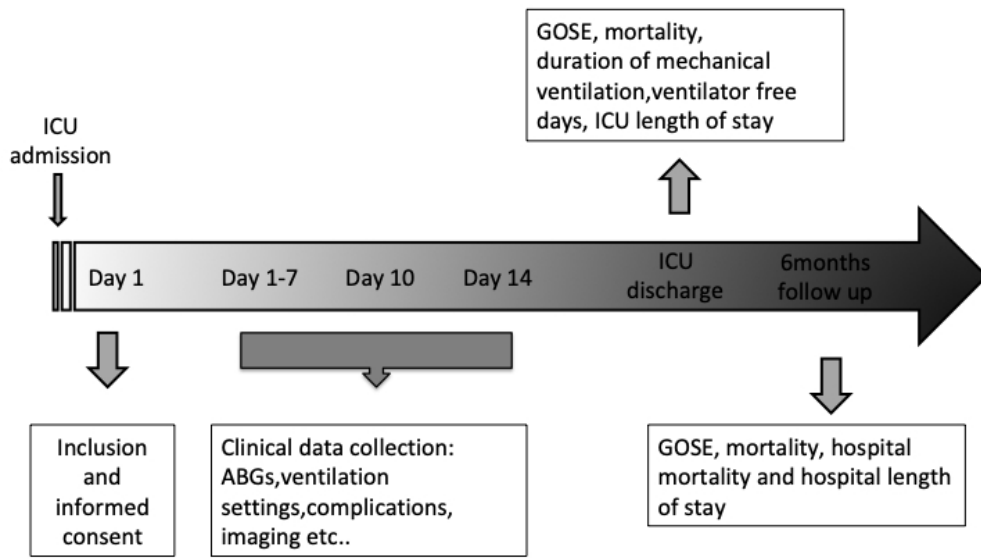
ITEM	DETAILS	SPECIFICS	SCORE	MAX
Positioning	head elevation for ICP control		1	1
	nursed flat (180°) for CPP management		1	
Sedation and neuromuscular blockade	low dose sedation (as required for mechanical ventilation)		1	8
	higher dose sedation for ICP control (but not aiming for burst suppression)		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 CO <sub>2</sub> 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 ( $T > 38^{\circ}\text{C}$ or spontaneous $T < 34.5^{\circ}\text{C}$ )		1	
	cooling for ICP control, $\geq 35^{\circ}\text{C}$		2	
	hypothermia $< 35^{\circ}\text{C}$		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	<b>Good recovery</b>	resumption of normal life (minor neurological or psychological deficits)
4	<b>Moderate disability</b>	disabled but independent for daily life; work capacity is reduced
3	<b>Sever disability</b>	conscious but dependent for daily life; unable to travel or go shopping without assistance
2	<b>Persistent vegetative state</b>	unresponsive and speechless
1	<b>Death</b>	

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# BMJ Open

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

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<b>Primary Subject Heading</b>:	Intensive care
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3 Multicenter observational study on practice of ventilation in brain injured patients:  
4 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.

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5 **Trial registration number:** NCT04459884  
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10 **Keywords:** mechanical ventilation; brain injury; ventilator settings; outcome;  
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12 Glasgow coma scale  
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17 **Strengths and limitations of the study**

- 18  
19 - Results from this large multicenter study including mechanically ventilated  
20 acute brain injury patients admitted to the intensive care unit will provide a  
21 detailed description of the patients' characteristics, ventilator strategies, and  
22 their association to clinical outcomes.  
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24 - The main strength of this study relies on the global approach, since it allows  
25 to explore clinical practice in a wide number of geographical regions with  
26 different public health issues, including low- and middle-income countries.  
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28 - The main limitation of this study relies on the observational design with  
29 consequent difficulty to draw causal inferences.  
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31 - The results from this study will generate hypotheses for respiratory  
32 management of acute brain injured patients and help in better study design  
33 plans for future randomized controlled trials.  
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**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<sub>2</sub> Arterial Partial Pressure of Carbon DioxidePaO<sub>2</sub> Arterial Partial Pressure of OxygenPbO<sub>2</sub> 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.<sup>1</sup> Paradoxically, ventilation itself has the potential to cause further pulmonary and cerebral damage and can increase mortality and morbidity.<sup>2</sup> Several experimental and clinical studies have shown how brain injury can cause secondary lung injury.<sup>2-4</sup> 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.<sup>5</sup>

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).<sup>6,7</sup> In particular, the use of low tidal volume seems to have the greater importance,<sup>8-11</sup> and it is recommended in critically ill patients with ARDS.<sup>12</sup>

Results from one multicenter randomized controlled trial suggest that intensive care unit (ICU) patients without ARDS could also benefit from '*protective lung ventilation strategies*'.<sup>13</sup> 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.<sup>14</sup>

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<sub>2</sub>) and increase intrathoracic pressure, thus having detrimental effects on intracranial pressure (ICP) and cerebral perfusion pressure (CPP).<sup>15-17</sup> 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

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3 experts,<sup>18</sup> a multicenter international study on mechanical ventilation strategies in  
4 brain injured patients is currently needed.  
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## 8 **METHODS**

### 9 **Study design**

10 We designed a large international multicenter prospective observational cohort  
11 study including mechanically ventilated brain injured patients and planned 6-month  
12 follow-up.  
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### 18 **Objectives**

19 Primary objective is to describe ventilation settings of intubated and mechanically  
20 ventilated neurocritically ill patients admitted to the ICU.  
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23 Secondary objectives are:  
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- 25 - To describe the differences in ventilator settings among different countries.
- 26 - To evaluate the association of ventilator settings with pulmonary complications  
27 (including pneumonia, acute distress respiratory failure, neurogenic pulmonary  
28 edema).
- 29 -To describe differences in the ventilator settings in presence/absence of high  
30 intracranial pressure.
- 31 - To evaluate the association of ventilator settings with outcomes (i.e. 6-months  
32 mortality and neurological outcome, in-hospital and ICU mortality, hospital length of  
33 stay, duration of mechanical ventilation, ventilator free days at ICU discharge).  
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### 47 **Study population**

48 We will collect data of consecutive patients with acute brain injury requiring  
49 endotracheal intubation and mechanical ventilation, who are admitted to the  
50 intensive care unit (ICU).  
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### 56 **Inclusion criteria will be:**



- Age  $\geq$  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.

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3 At 6-months, mortality and neurological outcome (as for extended Glasgow  
4 Outcome Scale, GOSE, Table 6) will be collected.  
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9 The GOSE at 6 months follow-up will be collected via phone-structured interviews to  
10 the patients and/or family members using a validated questionnaire.<sup>19</sup>Data on the  
11 cause and date of death will be also collected.  
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## 15 16 **Data management**

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19 Anonymized data will be collected in a web-based electronic Case-Report Form  
20 (eCRF) and protected by encryption software and password provided to single users.  
21 Each patient will be associated to a numeric code generated by the central database.  
22 Data will be checked for consistency and completeness by the study coordinator and  
23 the core Steering Committee, to ensure the high quality of the collected data before  
24 the analysis and to limit the rate of errors and missing data. Also, a strict monitoring  
25 of data quality during the study will be performed.  
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33 The data will be securely stored at the University Milano-Bicocca; all procedures will  
34 comply with the EU Regulation 2016/679 on the protection of natural persons  
35 regarding personal data processing and movement. A Data Transfer Agreement to  
36 confirm the terms for data transfer from the centers to the Sponsor will be finalized.  
37 Patients' demographic characteristics, co-morbidities, diagnosis, timing of acute  
38 events and clinical presentation of acute brain injury will be extracted from the  
39 patients' medical records.  
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## 48 **STATISTICAL ANALYSIS**

### 49 **Sample size calculation**

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51 Since the hypotheses of the study are exploratory, no formal sample size calculation  
52 has been performed. This international prospective observational study aims to  
53 recruit more than 3000 patients after acute brain damage. Recruitment will last 3-6  
54 months at each center, aiming to enroll an average of 30 consecutive  
55 patients/center. This timeframe has been set according to a previous study<sup>20</sup> similar  
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3 to VENTIBRAIN, and including a similar network of centers. The number of enrolled  
4 patients and ICUs is considered adequate to capture the range of variation in  
5 ventilator settings observed in the clinical practice. We aim to include also low-  
6 middle income countries, in order to have a representation of the variability  
7 worldwide.  
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### 13 **Plan of analysis**

14 Patient and ventilation characteristics will be described by means (standard  
15 deviation), medians (I-III quartiles) and proportions, as appropriate. The different  
16 ventilator settings will be described according to type of brain injury (i.e. TBI, AIS and  
17 SAH), presence and severity of lung damage and countries. The association between  
18 daily ventilator settings and outcomes will be evaluated by appropriate multivariable  
19 models adjusting for relevant confounders at baseline (such as age, sex,  
20 cardiovascular and neurological history, primary diagnosis, GCS, pupillary reactivity  
21 and the severity of pulmonary and neurological conditions). We will explore the role  
22 of currently known threshold for other ICU populations of ventilator settings;  
23 however, as in this population no specific thresholds have been defined, we will aim  
24 to assess the distribution of these settings and eventually define new thresholds for  
25 the brain injured population.  
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38 Cause specific Cox model will be applied to time to event outcomes (i.e., mortality,  
39 pulmonary complications) and logistic regression to dichotomous outcomes (i.e.  
40 poor neurological outcome at 6 month, GOSE <5). Multilevel regression models will  
41 be applied to account for repeated measurements on patients and heterogeneity  
42 induced by centers and, if residual variation will be present, by countries  
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47 The cumulative incidence in time of pulmonary complications during hospital stay  
48 will be estimated along with 95% confidence intervals accounting for mortality and  
49 discharge as competing events by the Aalen-Johansen estimator.  
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52 The occurrence of raised intracranial pressure value lasting more than 5 minutes >20  
53 mmHg will be described daily together with the earlier ventilator settings. A  
54 multilevel longitudinal model on daily raised intracranial pressure will be also applied  
55 to evaluate the possible impact of ventilator settings adjusting for relevant  
56 confounders (as defined before); this model will include only ICP monitored patients.  
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3 A sensitivity analysis excluding data from centers that recruited less than 20 patients  
4 will be performed. Multiple imputation on covariates will be performed if missing  
5 will exceed 10%. Statistical analyses will be conducted using R and SAS.  
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### 10 **Patient and Public Involvement**

11 No patient involved.  
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## 14 **ETHICAL CONSIDERATIONS**

### 15 **Ethical standards**

16 The PI and Steering Committee will ensure that this study is conducted in full  
17 conformity with the Declaration of Helsinki and Good Clinical Practices.  
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### 20 **Ethics committee**

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

35 Informed consent will be obtained from patients with no lack of capacity. For  
36 patients not able to provide informed consent at the time of recruitment, the  
37 responsible clinical/research staff will act as Consulter and consent eligible patients  
38 after discussion with the next of kin. If the patient has a Power of Attorney or a Legal  
39 tutor or an, he/she will act as Consultee and will be asked to consent/decline  
40 participation to the study on legal behalf of the patient.  
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48 In presence of patients' Advance Decision Plan, including participation in research  
49 studies, the Plan will be respected and recruitment pursued/abandoned accordingly.  
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51 At follow-up, patients who have regained capacity will be asked to provide Informed  
52 Consent and will be given the possibility to:  
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- 54 • Provide Informed Consent for the acute data and follow-up.
- 55 • Deny research participation and request destruction of acute data collected.
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## 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

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

## 25 26 27 **DISCUSSION AND EXPECTED IMPACT OF THE STUDY**

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

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

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3 The need to particularly focus on the mechanical ventilator settings in this group of  
4 patients is related to the specific ventilator needs of brain injured patients.<sup>18,21</sup> Brain  
5 injured patients have a high number of pulmonary complications, ventilator  
6 associated pneumonia, and a high rate of need of tracheostomy and extubation  
7 failure.<sup>22</sup>

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

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20 Similarly, hypercapnia can cause cerebral vasodilation and increase intracranial  
21 pressure and should therefore be avoided, but hypocapnia and cerebral  
22 vasoconstriction can lead to cerebral ischemia and currently it is suggested only in  
23 case of life-threatening intracranial hypertension and risk of brain herniation.<sup>25,26</sup>

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

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29 Moreover, the general principles and ventilator settings applied in the general  
30 population have not been established in brain injured patients.<sup>19</sup>

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

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



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3 Results from the VENTIBRAIN study will allow to clarify the current status of the  
4 ventilator management of these patients, and in particular to discriminate the  
5 effects of tidal volume, positive end expiratory pressure and driving pressure on  
6 outcomes in brain injured patients with, at risk of, or without acute distress  
7 respiratory pressure (using predefined scores), and the use of specific settings in  
8 case of intracranial hypertension. The VENTIBRAIN study offers a unique opportunity  
9 to globally uniform clinical guidelines regarding ventilator strategies in brain injured  
10 patients and eventually improving their outcome.  
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19 The VENTIBRAIN study has also several limitations that need to be addressed. First,  
20 we cannot exclude that ventilator settings and targets used by clinicians might be  
21 biased by the participation in the study, thus reducing the ability of VENTIBRAIN to  
22 represent the real ICU care of these patients. Second, the CRF designed for  
23 VENTIBRAIN was aimed to not cause excessive workload for the participating  
24 centres. Therefore, some data regarding systemic complications will be potentially  
25 missing, while continuous data on respiratory and neuromonitoring might be  
26 incomplete. Similarly, due to the limited number of daily arterial blood gases and  
27 ventilator settings data collection, we will have a limited view that might not reflect  
28 completely real clinical practice.  
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38 Finally, the observational nature of VENTIBRAIN makes impossible to draw causal  
39 inferences between ventilator management and outcome in this group of patients.  
40 However, VENTIBRAIN is aimed to generate hypotheses for treatment effects and  
41 pave the way to design future randomized controlled trials of ventilation in these  
42 settings to draw causal inferences and improve clinical outcomes in ventilated brain  
43 injured patients.  
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49 VENTIBRAIN is designed to assess and describe the clinical practice in ventilator  
50 strategies in critically ill brain injured patients in a large number of different  
51 countries/centers worldwide. Results from this study will help to identify differences  
52 in clinical practices and could be used to plan new trials on mechanical ventilation in  
53 this specific subgroup of patients.  
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7 **Contributors:** CR, GC, FST, PP were equally responsible for writing of  
8 the manuscript and participated in study design. CR drafted the first version of the  
9 manuscript. FST, PP, GC, SG, PR, AV reviewed the manuscript and agreed with  
10 submission.  
11  
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13

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15 public, commercial or not-for profit sectors.  
16  
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18 **Competing interests:** None declared.  
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20 Patient consent: Not required.  
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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; FiO<sub>2</sub>, fractional inspired oxygen; PaO<sub>2</sub>, 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 < PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 300 PEEP or CPAP ≥ 5 cm H <sub>2</sub> O	Moderate 100 < PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 200 PEEP ≥ 5 cm H <sub>2</sub> O	Severe PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 100 PEEP ≥ 5 cm H <sub>2</sub> O

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

<b>Diffuse injury I (no visible pathology)</b>	<ul style="list-style-type: none"> <li>no visible intracranial pathology</li> </ul>
<b>Diffuse injury II (swelling)</b>	<ul style="list-style-type: none"> <li>midline shift of 0 to 5 mm</li> <li>basal cisterns remain visible</li> <li>no high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> </ul>
<b>Diffuse injury III</b>	<ul style="list-style-type: none"> <li>midline shift of 0 to 5 mm</li> <li>basal cisterns compressed or completely effaced</li> <li>no high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> </ul>
<b>Diffuse injury IV (shift)</b>	<ul style="list-style-type: none"> <li>midline shift <math>&gt;5 \text{ mm}</math></li> <li>no high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> </ul>
<b>Evacuated mass lesion V</b>	<ul style="list-style-type: none"> <li>any lesion evacuated surgically</li> </ul>
<b>Non-evacuated mass lesion VI</b>	<ul style="list-style-type: none"> <li>high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> <li>not surgically evacuated</li> </ul>



Table 4. Fisher scale.

<b>Grade 1</b>	<ul style="list-style-type: none"><li>• no subarachnoid (SAH) or intraventricular hemorrhage (IVH) detected</li><li>• incidence of symptomatic vasospasm: 21%</li></ul>
<b>Grade 2</b>	<ul style="list-style-type: none"><li>• diffuse thin (&lt;1 mm) SAH</li><li>• no clots</li><li>• incidence of symptomatic vasospasm: 25%</li></ul>
<b>Grade 3</b>	<ul style="list-style-type: none"><li>• localized clots and/or layers of blood &gt;1 mm in thickness</li><li>• no IVH</li><li>• incidence of symptomatic vasospasm: 37%</li></ul>
<b>Grade 4</b>	<ul style="list-style-type: none"><li>• diffuse or no SAH</li><li>• ICH or IVH present</li><li>• incidence of symptomatic vasospasm: 31%</li></ul>

Table 5. Therapy intensity Level Scale. Abbreviations: ICP, intracranial pressure; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CO<sub>2</sub>, carbon dioxide;

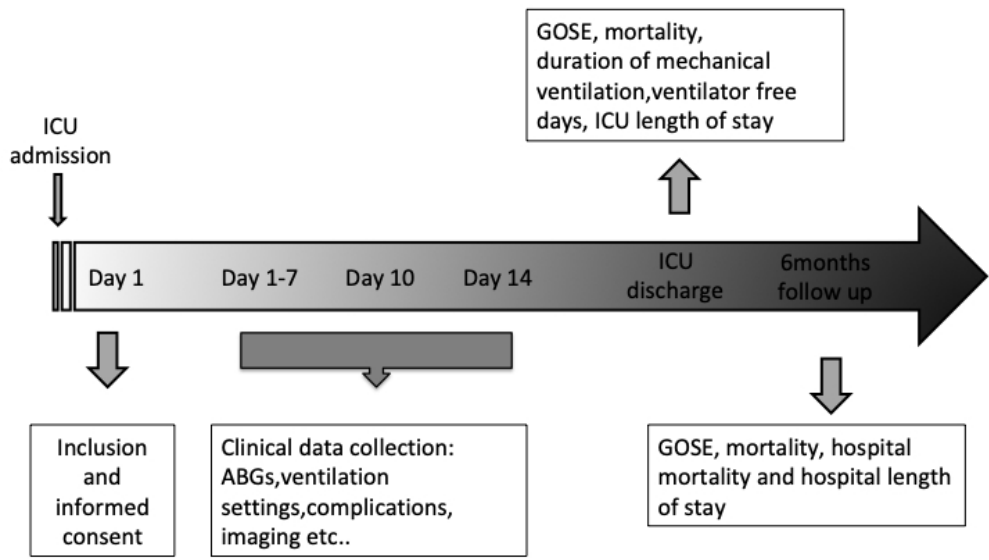
ITEM	DETAILS	SPECIFICS	SCORE	MAX
Positioning	head elevation for ICP control		1	1
	nursed flat (180°) for CPP management		1	
Sedation and neuromuscular blockade	low dose sedation (as required for mechanical ventilation)		1	8
	higher dose sedation for ICP control (but not aiming for burst suppression)		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 <sub>2</sub> 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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# BMJ Open

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

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3 Multicenter observational study on practice of ventilation in brain injured patients:  
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5 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.

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5 **Trial registration number:** NCT04459884  
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10 **Keywords:** mechanical ventilation; brain injury; ventilator settings; outcome;  
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12 Glasgow coma scale  
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17 **Strengths and limitations of the study**

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19 - Results from this large multicenter study including mechanically ventilated  
20 acute brain injury patients admitted to the intensive care unit will provide a  
21 detailed description of the patients' characteristics, ventilator strategies, and  
22 their association to clinical outcomes.  
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24 - The main strength of this study relies on the global approach, since it allows  
25 to explore clinical practice in a wide number of geographical regions with  
26 different public health issues, including low- and middle-income countries.  
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28 - The main limitation of this study relies on the observational design with  
29 consequent difficulty to draw causal inferences.  
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31 - The results from this study will generate hypotheses for respiratory  
32 management of acute brain injured patients and help in better study design  
33 plans for future randomized controlled trials.  
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**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<sub>2</sub> Arterial Partial Pressure of Carbon Dioxide

PaO<sub>2</sub> Arterial Partial Pressure of Oxygen

PbO<sub>2</sub> 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.<sup>1</sup> Paradoxically, ventilation itself has the potential to cause further pulmonary and cerebral damage and can increase mortality and morbidity.<sup>2</sup> Several experimental and clinical studies have shown how brain injury can cause secondary lung injury.<sup>2-4</sup> 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.<sup>5</sup>

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).<sup>6,7</sup> In particular, the use of low tidal volume seems to have the greater importance,<sup>8-11</sup> and it is recommended in critically ill patients with ARDS.<sup>12</sup>

Results from one multicenter randomized controlled trial suggest that intensive care unit (ICU) patients without ARDS could also benefit from '*protective lung ventilation strategies*'.<sup>13</sup> 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.<sup>14</sup>

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<sub>2</sub>) and increase intrathoracic pressure, thus having detrimental effects on intracranial pressure (ICP) and cerebral perfusion pressure (CPP).<sup>15-17</sup> 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

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3 experts,<sup>18</sup> a multicenter international study on mechanical ventilation strategies in  
4 brain injured patients is currently needed.  
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## 8 **METHODS**

### 9 **Study design**

10 We designed a large international multicenter prospective observational cohort  
11 study including mechanically ventilated brain injured patients and planned 6-month  
12 follow-up.  
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### 18 **Objectives**

19 Primary objective is to describe ventilation settings of intubated and mechanically  
20 ventilated neurocritically ill patients admitted to the ICU.  
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23 Secondary objectives are:  
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- 25 - To describe the differences in ventilator settings among different countries.
- 26 - To evaluate the association of ventilator settings with pulmonary complications  
27 (including pneumonia, acute distress respiratory failure, neurogenic pulmonary  
28 edema).
- 29 -To describe differences in the ventilator settings in presence/absence of high  
30 intracranial pressure.
- 31 - To evaluate the association of ventilator settings with outcomes (i.e. 6-months  
32 mortality and neurological outcome, in-hospital and ICU mortality, hospital length of  
33 stay, duration of mechanical ventilation, ventilator free days at ICU discharge).  
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### 47 **Study population**

48 We will collect data of consecutive patients with acute brain injury requiring  
49 endotracheal intubation and mechanical ventilation, who are admitted to the  
50 intensive care unit (ICU).  
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### 56 **Inclusion criteria will be:**

- Age  $\geq$  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.



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3 At 6-months, mortality and neurological outcome (as for extended Glasgow  
4 Outcome Scale, GOSE, Table 6) will be collected.  
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9 The GOSE at 6 months follow-up will be collected via phone-structured interviews to  
10 the patients and/or family members using a validated questionnaire.<sup>19</sup>Data on the  
11 cause and date of death will be also collected.  
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## 15 16 **Data management**

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19 Anonymized data will be collected in a web-based electronic Case-Report Form  
20 (eCRF) and protected by encryption software and password provided to single users.  
21 Each patient will be associated to a numeric code generated by the central database.  
22 Data will be checked for consistency and completeness by the study coordinator and  
23 the core Steering Committee, to ensure the high quality of the collected data before  
24 the analysis and to limit the rate of errors and missing data. Also, a strict monitoring  
25 of data quality during the study will be performed.  
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33 The data will be securely stored at the University Milano-Bicocca; all procedures will  
34 comply with the EU Regulation 2016/679 on the protection of natural persons  
35 regarding personal data processing and movement. A Data Transfer Agreement to  
36 confirm the terms for data transfer from the centers to the Sponsor will be finalized.  
37 Patients' demographic characteristics, co-morbidities, diagnosis, timing of acute  
38 events and clinical presentation of acute brain injury will be extracted from the  
39 patients' medical records.  
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## 48 **STATISTICAL ANALYSIS**

### 49 **Sample size calculation**

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51 Since the hypotheses of the study are exploratory, no formal sample size calculation  
52 has been performed. This international prospective observational study aims to  
53 recruit more than 3000 patients after acute brain damage. Recruitment will last 3-6  
54 months at each center, aiming to enroll an average of 30 consecutive  
55 patients/center. This timeframe has been set according to a previous study<sup>20</sup> similar  
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3 to VENTIBRAIN, and including a similar network of centers. The number of enrolled  
4 patients and ICUs is considered adequate to capture the range of variation in  
5 ventilator settings observed in the clinical practice. We aim to include also low-  
6 middle income countries, in order to have a representation of the variability  
7 worldwide.  
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### 13 **Plan of analysis**

14 Patient and ventilation characteristics will be described by means (standard  
15 deviation), medians (I-III quartiles) and proportions, as appropriate. The different  
16 ventilator settings will be described according to type of brain injury (i.e. TBI, AIS and  
17 SAH), presence and severity of lung damage and countries. The association between  
18 daily ventilator settings and outcomes will be evaluated by appropriate multivariable  
19 models adjusting for relevant confounders at baseline (such as age, sex,  
20 cardiovascular and neurological history, primary diagnosis, Glasgow Coma Scale  
21 (GCS), pupillary reactivity and the severity of pulmonary and neurological  
22 conditions). We will explore the role of currently known thresholds for other ICU  
23 populations of ventilator settings; however, as in this population no specific  
24 thresholds have been defined, we will aim to assess the distribution of these settings  
25 and eventually define new thresholds for the brain injured population.  
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38 Cause specific Cox model will be applied to time to event outcomes (i.e., mortality,  
39 pulmonary complications) and logistic regression to dichotomous outcomes (i.e.  
40 poor neurological outcome at 6 month, GOSE <5). Multilevel regression models will  
41 be applied to account for repeated measurements on patients and heterogeneity  
42 induced by centers and, if residual variation is present, by countries.  
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47 The cumulative incidence in time of pulmonary complications during hospital stay  
48 will be estimated along with 95% confidence intervals accounting for mortality and  
49 discharge as competing events by the Aalen-Johansen estimator.  
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52 The occurrence of raised intracranial pressure value lasting more than 5 minutes >20  
53 mmHg will be described daily together with the earlier ventilator settings. A  
54 multilevel longitudinal model on daily raised intracranial pressure will be also applied  
55 to evaluate the possible impact of ventilator settings adjusting for relevant  
56 confounders (as defined before); this model will include only ICP monitored patients.  
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3 A sensitivity analysis excluding data from centers that recruited less than 20 patients  
4 will be performed. Multiple imputation on covariates will be performed if missing  
5 data will exceed 10%. Statistical analyses will be conducted using R and SAS.  
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#### 10 **Patient and Public Involvement**

11 No patient involved.  
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### 14 **ETHICAL CONSIDERATIONS**

#### 15 **Ethical standards**

16 The PI and Steering Committee will ensure that this study is conducted in full  
17 conformity with the Declaration of Helsinki and Good Clinical Practices.  
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#### 20 **Ethics committee**

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

35 Informed consent will be obtained from patients with no lack of capacity. For  
36 patients not able to provide informed consent at the time of recruitment, the  
37 responsible clinical/research staff will act as Consulter and consent eligible patients  
38 after discussion with the next of kin. If the patient has a Power of Attorney or a Legal  
39 tutor or an, he/she will act as Consultee and will be asked to consent/decline  
40 participation to the study on legal behalf of the patient.  
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48 In presence of patients' Advance Decision Plan, including participation in research  
49 studies, the Plan will be respected and recruitment pursued/abandoned accordingly.  
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51 At follow-up, patients who have regained capacity will be asked to provide Informed  
52 Consent and will be given the possibility to:  
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- 54 • Provide Informed Consent for the acute data and follow-up.
- 55 • Deny research participation and request destruction of acute data collected.
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## 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

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

26 VENTIBRAIN is designed to obtain a detailed description of patient's characteristics,  
27 management strategies resource use and association with clinical outcomes across  
28 many centers/countries. In particular, the study will provide insights in relation to  
29 clinical management, monitoring and treatment, practice variation in neuro-  
30 intensive care units around the world, differences in the ventilator management of  
31 brain injured patients and their potential association with outcome.  
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39 VENTIBRAIN has several strengths. First, its prospective design will increase the  
40 accuracy of data collection with potential minimization of the chance of residual  
41 confounding by unmeasured variables, which is a common limitation of  
42 retrospective design. Second, we aim to obtain a large sample size, able to provide  
43 information on neurological and systemic complications in mechanically ventilated  
44 brain injured patients, and eventually evaluate potential associations between  
45 ventilator settings and ICU/ 6 months patients' outcomes. Third, the inclusion of a  
46 large number of patients from different centers (dedicated and not dedicated  
47 neuroICUs), and countries, including low-income countries will provide information  
48 on geoeconomics differences in epidemiology, management strategies and  
49 outcomes of mechanically ventilated brain injured patients.  
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3 The need to particularly focus on the mechanical ventilator settings in this group of  
4 patients is related to the specific ventilator needs of brain injured patients.<sup>18,21</sup> Brain  
5 injured patients have a high number of pulmonary complications, ventilator  
6 associated pneumonia, and a high rate of need of tracheostomy and extubation  
7 failure.<sup>22</sup>

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

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18 Similarly, hypercapnia can cause cerebral vasodilation and increase intracranial  
19 pressure and should therefore be avoided, but hypocapnia and cerebral  
20 vasoconstriction can lead to cerebral ischemia and currently it is suggested only in  
21 case of life-threatening intracranial hypertension and risk of brain herniation.<sup>25,26</sup>

22  
23 All in it, ventilator targets are unclear in this group of patients.

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26 Moreover, the general principles and ventilator settings applied in the general  
27 population have not been established in brain injured patients.<sup>19</sup>

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

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Protective ventilator strategies such as high positive end expiratory pressure or recruitment maneuvers may increase intrathoracic pressure and consequently reduce jugular outflow;<sup>33</sup> 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.<sup>34</sup> However, although these patients have been traditionally ventilated with high tidal volumes and low positive end expiratory pressure,<sup>29</sup> recent evidence suggests that the concept of protective ventilation is gaining interest even in the brain injured population.<sup>19</sup>

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3 Results from the VENTIBRAIN study will allow to clarify the current status of the  
4 ventilator management of these patients, and in particular to discriminate the  
5 effects of tidal volume, positive end expiratory pressure and driving pressure on  
6 outcomes in brain injured patients with, at risk of, or without acute distress  
7 respiratory pressure (using predefined scores), and the use of specific settings in  
8 case of intracranial hypertension. The VENTIBRAIN study offers a unique opportunity  
9 to globally uniform clinical guidelines regarding ventilator strategies in brain injured  
10 patients and eventually improving their outcome.  
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19 The VENTIBRAIN study has also several limitations that need to be addressed. First,  
20 we cannot exclude that ventilator settings and targets used by clinicians might be  
21 biased by the participation in the study, thus reducing the ability of VENTIBRAIN to  
22 represent the real ICU care of these patients. Second, the CRF designed for  
23 VENTIBRAIN was aimed to not cause excessive workload for the participating  
24 centres. Therefore, some data regarding systemic complications will be potentially  
25 missing, while continuous data on respiratory and neuromonitoring might be  
26 incomplete. Similarly, due to the limited number of daily arterial blood gases and  
27 ventilator settings data collection, we will have a limited view that might not reflect  
28 completely real clinical practice.  
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39 Finally, the observational nature of VENTIBRAIN makes impossible to draw causal  
40 inferences between ventilator management and outcome in this group of patients.  
41 However, VENTIBRAIN is aimed to generate hypotheses for treatment effects and  
42 pave the way to design future randomized controlled trials of ventilation in these  
43 settings to draw causal inferences and improve clinical outcomes in ventilated brain  
44 injured patients.  
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49 VENTIBRAIN is designed to assess and describe the clinical practice in ventilator  
50 strategies in critically ill brain injured patients in a large number of different  
51 countries/centers worldwide. Results from this study will help to identify differences  
52 in clinical practices and could be used to plan new trials on mechanical ventilation in  
53 this specific subgroup of patients.  
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7 **Contributors:** CR, GC, FST, PP were equally responsible for writing of  
8 the manuscript and participated in study design. CR drafted the first version of the  
9 manuscript. FST, PP, GC, SG, PR, AV reviewed the manuscript and agreed with  
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20 Patient consent: Not required.  
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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; FiO<sub>2</sub>, fractional inspired oxygen; PaO<sub>2</sub>, 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 < PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 300 PEEP or CPAP ≥ 5 cm H <sub>2</sub> O	Moderate 100 < PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 200 PEEP ≥ 5 cm H <sub>2</sub> O	Severe PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 100 PEEP ≥ 5 cm H <sub>2</sub> O

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

<b>Diffuse injury I (no visible pathology)</b>	<ul style="list-style-type: none"> <li>no visible intracranial pathology</li> </ul>
<b>Diffuse injury II (swelling)</b>	<ul style="list-style-type: none"> <li>midline shift of 0 to 5 mm</li> <li>basal cisterns remain visible</li> <li>no high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> </ul>
<b>Diffuse injury III</b>	<ul style="list-style-type: none"> <li>midline shift of 0 to 5 mm</li> <li>basal cisterns compressed or completely effaced</li> <li>no high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> </ul>
<b>Diffuse injury IV (shift)</b>	<ul style="list-style-type: none"> <li>midline shift <math>&gt;5 \text{ mm}</math></li> <li>no high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> </ul>
<b>Evacuated mass lesion V</b>	<ul style="list-style-type: none"> <li>any lesion evacuated surgically</li> </ul>
<b>Non-evacuated mass lesion VI</b>	<ul style="list-style-type: none"> <li>high or mixed density lesions <math>&gt;25 \text{ cm}^3</math></li> <li>not surgically evacuated</li> </ul>

Table 4. Fisher scale.

<b>Grade 1</b>	<ul style="list-style-type: none"><li>• no subarachnoid (SAH) or intraventricular hemorrhage (IVH) detected</li><li>• incidence of symptomatic vasospasm: 21%</li></ul>
<b>Grade 2</b>	<ul style="list-style-type: none"><li>• diffuse thin (&lt;1 mm) SAH</li><li>• no clots</li><li>• incidence of symptomatic vasospasm: 25%</li></ul>
<b>Grade 3</b>	<ul style="list-style-type: none"><li>• localized clots and/or layers of blood &gt;1 mm in thickness</li><li>• no IVH</li><li>• incidence of symptomatic vasospasm: 37%</li></ul>
<b>Grade 4</b>	<ul style="list-style-type: none"><li>• diffuse or no SAH</li><li>• ICH or IVH present</li><li>• incidence of symptomatic vasospasm: 31%</li></ul>

Table 5. Therapy intensity Level Scale. Abbreviations: ICP, intracranial pressure; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CO<sub>2</sub>, 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 <sub>2</sub> 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	

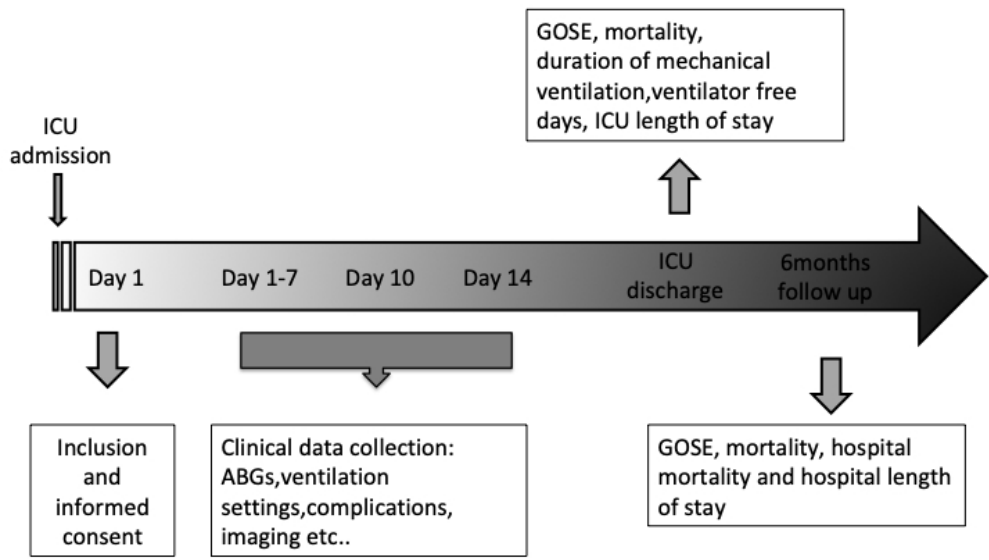


	treatment of fever (T > 38°C or spontaneous T < 34.5°C)		1	
	cooling for ICP control, ≥ 35°C		2	
	hypothermia < 35°C		5	
	intracranial operation for progressive mass lesion, NOT scheduled on admission		4	
	decompressive craniectomy		5	
	Maximum total possible score			38

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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