Study protocol

BRAIN VENT- Relation between lung protective ventilation, intracranial pressure, autoregulation and brain oxygenation in neurointensive care patients

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List of Abbreviations

ABI	acute brain injuries
ARDS	acute respiratory distress syndrome
BMI	Body mass index
PbtO2	brain tissue oxygen tension
RAP	Compensatory Reserve Index
CPP	cerebral perfusion pressure
CT	Computer tomography
etCO2	end-tidal CO2
VT_{exp}	expiratory tidal volume
EVLWI	Extravascular lung water index
NEM	Health research Ethics
ICM	intensive care monitoring
ICU	Intensive Care Unit
I:E	inspiratory: expiratory
FiO2	inspiratory oxygen fraction
VT_{insp}	inspiratory tidal volume
ICP	intracranial pressure
AMP	Pulse Wave Amplitude
MV	mechanical ventilation
NIRS	near infrared spectroscopy
PBW	Predicted body weight
PaCO2	partial pressure of carbon dioxide
PaO2	partial pressure of oxygen
Paw_{Endexp}	end-expiratory airway pressure
$P_{plateau}$	end-inspiratory plateau pressure
P_{eso}	esophageal pressure
P_{peak}	peak airway pressure
PEEP	positive end-expiratory pressure
P_{TP}	transpulmonary pressure
PrX	pressure reactivity index
PICCO	Pulse Contour Continuous Cardiac Output
SpO2	oxygen saturation measured by pulsoximetry
TCD	transcranial Doppler
TV	tidal volumes
UNN	University hospital of North Norway
VC	Volume Control
Vf	ventilatory frequency
VILI	ventilator-induced lung injury

1. Background

Background, status of knowledge and expected benefit

Acute brain injury (ABI) including traumatic brain injury and stroke, are important causes of disability and death[1,2]. It is of outmost importance to prevent secondary brain injury after the first hit. Respiratory failure frequently occurs in neurocritical care patients both in the prehospital phase and in-hospital[3]. In the context of ABI and respiratory failure, mechanical ventilation (MV) is crucial. Firstly, ABI with a poor Glasgow coma scale is an important indication for tracheal intubation and MV. Secondly, hypoxia and hypoventilation evolving from respiratory failure and inadequate MV are among the main causes of secondary brain injury[4]. Thirdly, MV, if wrongly used, can result in lung injury on its own right, defined as ventilator-induced lung injury[5]. Consequently, it is important to manage MV optimally in order to prevent the emergence of or worsening of respiratory failure and secondary brain injury[6–8].

Many recent studies have focused on ventilator settings in intensive care patients in order to prevent ventilator-induced lung injury and reduce mortality[9,11]. One of the main challenges is to apply so-called protective lung ventilation (PLV), which is sufficiently high positive end-expiratory pressure (PEEP), to avoid airway collapse (atelectotrauma) and/or low tidal volumes (TV) to prevent volutrauma. In acute respiratory distress syndrome (ARDS), PLV has evolved to become the « gold standard » of MV after year 2000[11]. Recently, researchers have shown increased interest in measuring transpulmonary pressure (P_{TP}), as a guide for more optimal PEEP settings in PLV[12]. P_{TP} can be determined by measuring the pressure difference between airway pressure and intrapleural pressure, as represented by the pressure changes during MV determined by means of an inflated balloon in the esophagus.

A few years ago, a leading investigator suggested the application of PLV for all ICU patients[13]. However, unfortunately, randomized trials of MV in acute lung injury/ARDS have excluded patients suffering from ABI, and specific data regarding PLV in these patients are limited. The ventilator settings in patients with ABI are often different to those applied in patients at risk of,–or suffering from ARDS[3,15]. The main concern is that PLV with high PEEP and low TV might cause high intrathoracic pressures, which might give rise to reduced venous return, hypercapnia and increased ICP which might be deleterious. Therefore, a tradition has evolved in neurocritical care to apply conventional ventilation with, in particular, low PEEP and high tidal volumes[14,15]. So far, studies dealing with the influence of various types of MV and associated PEEP levels on ICP remain inconclusive [16–18]. In addition, measurements of P_{tp} to individualize PEEP settings in this group of patients are lacking.

It is generally accepted that monitoring and treatment of ICP as the single cerebral parameter is of limited use [19]. Therefore, multimodal monitoring of autoregulation, brain metabolism and oxygenation is rapidly emerging as part of treatment protocols for ABI[20,21]. Over more than two decades, co-workers at the University of Cambridge have developed a neuro-intensive care monitoring (ICM+) software[22]. The system continuously registers arterial blood pressure and intracranial pressure, and the difference between them, the cerebral perfusion pressure (CPP). The system also, has options to include hemodynamic variables. By means of ICP waveform analysis, the system estimates blood pressure reactivity index (PrX), which might be used therapeutically as a guide to optimize CPP. PrX is described as an indirect measurement of cerebrovascular autoregulation and correlates positively with patient outcome[23]. Negative mean arterial pressure-ICP correlation indicates pressure reactive vessels (negative PrX) and preserved autoregulation. In contrast, positive correlation indicates pressure- passive vessels and impaired autoregulation. ICM+ also provides the opportunity to study other clinically relevant ICP indices, as well which might be used to guide clinical management[24]. The relationships between ventilator changes and intracranial waveform analysis/autoregulation have not been explored. Since recent data suggest benefits from

individualizing ICP/CPP treatment with the use of ICP indices such as autoregulation and PrX, the relationship between this parameter and variables of ventilator mechanics needs elucidation[20,25]. In addition, the associations between MV and brain oxygenation and cerebral blood flow, all need further investigation.

Expected benefit

Better understanding of the influence of MV on multimodal neuromonitoring parameters might provide evidence for the best MV strategy to guide the clinical management of brain injury, while avoiding respiratory complications that may delay recovery and start of rehabilitation. The data gained by this project might lead to new treatment recommendations for patients with ABI focusing on outcome measures such as safety and effectiveness of care. The project will also identify respiratory and cerebral variables that should be included in a national or international multicenter study where the main outcome measures would relate to mortality and number of ICU days.
The ICM+ software is a research tool that is used in more than 50 neurosurgery centers worldwide and the ICP curve analysis has gained international recognition. Nevertheless, there is a lack of research on ventilator settings and ICP waveform analysis and this project will be the first to integrate the ventilator parameters in ICM+ and study its clinical use. All centers using ICM+ will be able to use the new integration that will be developed and tested in this project, should it prove to be effective.
Measurement of P_{tp} is a well-recognized research and clinical tool to better manage respiratory failure. But, there is little competence in the use of this method in Norway. We will develop a high level of experience with this methodology, which can then be applied for other patients with respiratory failure and the knowledge can also easily be transferred to other hospitals in Norway.

Study objectives

The proposed study is an exploratory analysis of the relationship between cerebral blood perfusion and oxygenation and lung mechanical variables at different ventilator settings. The primary approach will be to carry out baseline measurements to enable conclusions concerning the safety of PLV on normal ICP before extending the study to patients with more severe brain or lung injury in future studies.
The primary objective of Brain Vent is to investigate if PLV (higher PEEP and lower TV) as compared with conventional settings (lower PEEP and higher TV)
a. increase ICP.
b. diminish cerebral vasoreactive autoregulation as assessed by PrX, ie PrX will turn positive, which means that it will change the state from intact to impaired autoregulation.
The secondary objective is an exploratory analysis of the relationship between ventilator settings and other well defined respiratory, cerebral, and cardiovascular variables. The endpoints are described below.
There is also a third objective, which is described in the sub-project at the end of this document, which is to investigate the role of next of kin in research with ICU patients.

The study will also lead to increased knowledge in this area, which will serve to:

2. Improve ventilator settings for the lungs that at the same time are safe for the perfusion of the brain.
3. Identify important ventilator variables that affect the ICP curve analysis and evaluation of brain compliance and autoregulation, going from basic science to clinical integration.
4. Individualize mechanical ventilation based on airway pressure, transpulmonary pressure and severity of brain injury.
5. Develop the ICM+ monitoring software with incorporation of relevant ventilator signals.

Methodology

Study design
Brain Vent is a single center, blinded, randomized, cross-over clinical trial in a tertiary trauma, neurosurgery center, which will be conducted at the ICU, UNN Tromsø.

Study population
All consecutive admitted tracheally intubated adult patients with ICP monitoring (independent of the study) will be considered for inclusion within 12 hours by the principal investigator through the duration of the study, which is expected to require approximately 18 months to achieve the necessary sample size (see below).
A screening log will be used for participation or non-participation. Reason for non-participation will be recorded.

Inclusion criteria

- Any tracheally intubated or tracheotomized adult patient with ABI with GCS< 10 or Hunt-Hess grade>3 on controlled ventilation requiring continuous ICP measurement.
- Admission within 24 h after ABI.
- Proxy informed consent from relatives.

Exclusion criteria

- ICP > 22 mmHg before treatment of high ICP
- Acute respiratory failure defined as partial pressure of oxygen/ inspiratory oxygen fraction (PaO2/FiO2) ratio < 40 kPa and X ray pathology
- History of pulmonary disese: Chronic respiratory failure diagnosis stage III and IV in the GOLD classification, pulmectomy, lobectomy or restrictive lung disease.
- Body mass index (BMI) > 35.
- Known right or biventricular cardiac failure with cardiac index < 2,5 L/min/m^2 or ejection fracture < 40 %.
- Refractory hypovolemia as diagnosed with pulse pressure variation > 12 % with tidal volume 8 ml/predicted bodyweight (intubated on controlled ventilation) or passive leg rise test with > 10 % increase in stroke volume measured by VTI echocardiography or PICCO.
- Medulla lesion that affect the autonomic nervous system.
- Patients who has undergone decompressive craniectomy.

Planned number of participants and statistical analysis

In this study setting, we aim to show that LPV is non-inferior to conventional ventilator setting, with regards to ICP increase or change of PrX> 0.3 (diminished autoregulation).
Sample size calculation is based on the primary outcome and the cross-over study design. Assuming a difference of zero, a standard deviation of 4 mmHg and a non-inferiority margin of 3mmHg, power of 80% and a significance level of 0.025, a total of 28 patients will be included [16]. We will recruit 30 patients to Brain Vent to take account of technical issues or dropouts. The non-inferiority margin is chosen to be lower than the minimal clinical important difference of 5 mmHg. It is assumed that there will be no missing data in the period 2 measurements due to the short time interval between the two different interventions. The sample size calculation is done with STATA 15.1 and the main analysis will be done in SPSS.

Descriptive statistics will be presented with mean and standard deviations or median and interquartile range as appropriate for continuous variables. Categorical variables will be presented as proportion of patients in the different categories. Subject level profiles for each group (AB, BA) will be plotted to visualize the results. The hypothesis of non-inferiority will be tested based on the

lower confidence limits of the difference. Period effect, sequence effect and secondary outcomes will be analysed with linear mixed models.

Procedure
Patients will be ventilated with Servo U®ventilators (Maquet, Rastatt, Germany). Treatment will follow local procedures.

Intervention
PLV include change in two parameters, PEEP and TV. In order to analyse whether a change in TV affects the patient, we will test TV and PEEP changes in two different ventilation protocols, called intervention 1 and intervention 2 (Table 1). One of these will have lower TV, and the other will have lower TV and higher PEEP. We are not testing higher PEEP without lower TV to minimize risk of overdistending the lungs. Baseline is standard ventilator settings as described in Table 1. Each patient will receive the two interventions using a cross-over design, in which they will be randomly allocated to either have intervention 1 first followed by intervention 2, or vice versa. This will boost the power of the analysis because each patient's outcomes on intervention 1 will be compared with her/his outcomes on intervention 2. The basic model, as described in Table 2, is chosen because being a complex ICU patient, within-patient variability in respiration and brain damage is less than between patient variability. Because the patient's study time is short, all patients should reach the second period of their randomization and receive both interventions. Therefore, this is a powerful design in this study setting.
The randomization will be done with dedicated software at the research department of the study hospital and her/his randomized order will be concealed until the patient has entered the study. Subsequently, the analysis will be blinded for which intervention is which. The treatment responsible physician (not the researcher who makes the recordings) will change the ventilator settings in accordance with the randomised order and will interrupt the intervention if ICP rises above 22 over 5 minutes, for safety reasons.

Table 1. Study procedure (for those patients randomly allocated to the intervention 1 followed by intervention 2 sequence. Group A). Group B will have the reverse order with Intervention 2 first.

Procedure Observation time	Baseline (run-in period) 2 h	Intervention 1 1.5 h	Baseline (wash-out) 1,5 h	Intervention 2 1,5 h
PEEP (mmHg)	5	5	5	12
TV (ml/kg PBW)	9	6	9	6

Table 2. The basic design model[26]. Each patient is treated for 2 periods of time. Patients are randomly allocated to receive treatments in this order (intervention 1 first, followed by intervention 2) or the reverse order (intervention 2 first, followed by intervention 1)

	Group A	*Group B*
Period 1	**Intervention 1**	**Intervention 2**
Period 2	**Intervention 2**	**Intervention 1**

Ventilatory settings in detail:
a. Conventional settings- Volume control (VC), inspiratory: expiratory (I:E) ratio 1:2, Tinsp 10 %, PEEP 5 cm H_2O, VT 9 ml/predicted bodyweight, ventilator frequency (Vf) needed to give partial pressure of carbon dioxide (PaCO2) 4.5-5 kPa, oxygen saturation (SpO2) > 96. Plateau pressure< 30 cm H_2O
b. Intervention 1- VC, I:E ratio 1:2, Tinsp 10 %, PEEP 5, TV 6 ml/predicted bodyweight, Vf (<30/min) will be increased to the same minute ventilation as in a. Plateau pressure< 30 cm H_2O
c. Intervention 2- VC, I:E ratio 1:2, Tinsp 10 %, PEEP 12, TV 6 ml/PBW, Vf (<30/min) will be increased to the same minute ventilation as in a., SpO2> 96. Plateau pressure< 30 cm H_2O

Age (>= 70, < 70) and type of damage (TBI or SAB) will be stratified in the two groups in the randomisation.

Observations and outcome measurements during the study:
All primary and secondary outcome measurements will be recorded from minimum 2 hours before to 1 hours after intervention. ICM + will record monitoring signals for 3 h during the start setting for calibration of the PrX signal.

Respiratory component
Respiratory settings and changes will be measured by

- Blood gases: PaO2/FiO2 ratio.
- Pressure transducer in esophagus: Esophageal pressure (P_{eso}). Continously and end-insp/end-exp just.
- Ventilator: Oxygenation index, end-tidal CO2 (etCO2), inspiratory oxygen fraction (FiO2), Peak airway pressure (P_{peak}), $P_{plateau}$, PEEP, End-expiratory airway pressure (Paw_{Endexp}), Vf, tidal volume inspiratory (VT_{insp}), tidal volume expiratory (VT_{exp}) at each breath, Total PEEP (end expiratory occlusion), from Paw and P_{eso} and hence from P_{tp}.
- Pulse Contour Continuous Cardiac Output (PICCO) thermodilution: Extravascular lung water index (EVLWI) as a determinant of fluids in the lungs.

Cerebral component:
ICP will be measured by:

- Invasive- ICP probe placed intraparenchymal or in the ventricular space
- Non-invasive ICP with transcranial Doppler (TCD) measurement of optic nerve sheath diameter and straight systolic flow velocity or flow velocity of MCA bilaterally.

Intracranial pressure indices, as a measure of compensatory reserve and autoregulation will be assessed by

- Intracranial and arterial pressure waveform analysis with ICM+® - PrX. Compensatory reserve index (RAP) index and mean pulse amplitude (AMP). Slow AMP. See further down for references.

Brain blood perfusion and oxygenation;

- Brain tissue oxygen tension (PbtO2). *Only for patients having a clinical indication for CT caput.*
- if clinically indicated.
- TCD measurement of flow velocity in arteria cerebri media.
- Computer tomography (CT) of brain perfusion for assessment of global and local cerebral perfusion during the first 24 h. *Only for patients having a clinical indication for CT caput.*
- Protein S100B is a new outcome prediction tool in brain injury, which is not thoroughly explored[27]. It will be analysed on admission as part of a description of the severity of ABI.

Cardiovascular component:
Positive pressure ventilation may hamper venous return, which might decrease cardiac index and cerebral blood flow. Therefore, data from the cardiovascular system also will be included.
A PICCO arterial catheter and a central venous catheter will be inserted for continuous measurement of the following intravascular pressures and cardiac index and derived variables by thermodilution once/hour:

- Cardiac output
- Stroke volume
- Arterial blood pressure
- Central venous pressure

- Intrathoracic blood volume index (ITBVI) as determinants of preload.
- The following treatment will be documented:
- Vasopressor dose
    - Inotropic support
- Any fluid transfusion, amount and constitution

Other patient data that will be registered
Background and baseline demographic data of the study population: Sex, Glasgow coma scale before intubation, diagnosis, age, PBW, BMI, type of ICP monitoring, CT Marshall score, extracranial injuries.
In hospital treatment data: Daily fluid administration, duration of invasive and non invasive ventilation, duration and dose of sedation, ICU days, duration of the hospital stay in days from admission to hospital to discharge to home or rehabilitation.

Rationale for choice of monitoring
Cerebral monitoring:
ICP will be measured continously as part of routine monitoring by invasive ICP probe in the brain. It will also be assessed noninvasively with transcranial Doppler (TCD)[28]. . In the future, non-invasive ICP measurements will most likely be the gold standard. Therefore, it is important to find out if TCD changes reflect changes in ventilator settings as accurate as the invasively measured ICP changes.
Neurointensive treatment is guided by multimodal monitoring. Brain perfusion and oxygenation is crucial for cerebral metabolism. The latter will be monitored locally with with a probe measuring partial pressure of oxygen in brain and regionally with near infrared spectroscopy.
Protein S100B is a new outcome prediction tool in brain injury, which is not thoroughly explored[27]. It will be analysed on admission as part of a description of the severity of ABI. The analysis of S100B is part of the Scandinavian guidelines for traumatic brain injury.

ICM+® software for brain monitoring (University of Cambridge Enterprise, Cambridge, UK) is downloaded on a computer that is connected to a Philips monitor. The software monitors signals and performs waveform analysis and correlation analysis. ICP waveform analysis provides individualized information about the patient's intracranial compliance and pressure reactivity including calculation of PrX, AMP, RAP[29]. This helps the clinician to be alert on patients at risk of cerebral hypoperfusion. The pressure reactivity index (PrX), is the moving correlation analysis between mean arterial pressure (MAP) and mean ICP. When autoregulation is intact, the cerebral vasculature dilates or constricts dependent on the arterial blood pressure. This can be trended by the ICP monitoring online: Negative MAP-ICP correlation indicates pressure reactive vessels (negative PrX) and preserved autoregulation and positive correlation indicates pressure- passive vessels and impaired autoregulation. This correlation can be used to individualize CPP treatment to hold CPP in the negative PrX area.
For this study, in addition to waveform analysis, the ICM+ continuously monitors the ventilator signals: etCO2, FiO2, P_{peak}, $P_{plateau}$, PEEP, Paw_{Endexp}, Vf, VT_{insp}, VT_{exp} and P_{eso} of each breath.
Respiratory monitoring
Esophagus manometer (FluxMed):
This is a gastric tube equipped with an esophagus balloon connected to a manometer for P_{eso} monitoring. Proper placement of the balloon is assessed from Baydur test and optimal volume filling the balloon assessed from the balloon PV curve in vivo[30].
P_{eso} measurement enable calculation of tidal $P_{TP,}$ which is the pressure needed to insufflate the lung[12]. It can be determined by measuring the pressure difference in end inspiration and end expiration between airway pressure and intrapleural pressure, represented indirectly by the pressure changes determined in the esophagus. By calculating P_{tp} we will document if there is any relationship between the tidal P_{tp} and monitored cerebral parameters in the different procedures.

Even if we use the same TV and PEEP in lung protective ventilator settings in different patients, there might be a different change in tidal P_{tp} that need to be addressed in future studies.

PICCO monitoring system (Pulsion Medical Systems, Munich, Germany):
A thermistor catheter will be placed in a femoral or brachial artery. PICCO measurement will be used to monitor both preload, cardiac output and changes in EVLW. All these parameters might be affected by the lung protective settings and can be related to cerebral parameters, such as ICP, CPP, ICP indices and cerebral oxygenation and metabolism variables. Increased EVLW has been noticed, on the average, more than two days before the patients meet ARDS criteria [31]. Therefore, we suggest that measurement of EVLW and pulmonary vascular permeability index (PVPI) in ABI patients at risk might enhance our possibilities of diagnosing the condition at the stage of emerging or "mild ARDS". In addition, determining pre-load by means of changes in intra-thoracic blood volume index (ITBVI), might provide valuable information about fluid load [32].

Detailed conduct of the study
Pre- intervention phase:
1. A member of the research team will recruit the patient within the first 24 hours after the ABI after rigorous consideration of the exclusion criteria
2. The patient will receive standard care with deep sedation, fentanyl/propofol and elevated upper body by 20 degrees.
3. Pleural effusion > 2 cm will be excluded with ultrasound.
4. The ventilator settings will be conventional as described above and in Table 1.

Intervention phase with randomized order of intervention 1 and 2:
a. Intervention 1: Reduce tidal volume to 6 ml/kg predicted bodyweight, as a first step towards protective lungventilation. Maintain PEEP 5.
b. Monitor 1,5 h.
c. Go back to conventional ventilator settings for 1,5 hours.
d. Decrease TV to 6 ml/kg predicted bodyweight and increase PEEP to 12 cm H_2O as in LPV.
e. Monitor 1,5 h.
f. Go back to conventional settings or other settings on the discretion of the treating clinician.

For safety reasons, the intervention will be interrupted if ICP increases to over 22 over 5 minutes, or CPP decreases to below 50 mmHg.

Questionnaire to the next of kin and the patient
A questionnaire will be given to the patient´s next of kin at the start of the study and 6 months after the ICU stay. It will contain questions about:

- What does the next of kin feel about the request/inclusion of their relative in a research project?
    - Did the relative understand the information given about the study?
    - In what setting was the relative given information about the study?
    - Who was providing the information given to the relative? (ansvarlig lege, sykepleier, andre, prosjektleder?)
    - Did you as a relative feel confident that the study would not impact on the patients outcome in a negative way if you agreed/disagreed to participate on behalf of the patient?
- Is it necessary to consent on behalf of the relative before he or she regains the mental capacity to consent on his/her own behalf?
    - Did you as a relative think it was positive or negative to be asked to participate on behalf of the patient?
    - Did the relative have any difficulties taking decisions on behalf of the patient?

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Cooperation
The methodology presupposes cooperation with leading European scientific communities. The methodology learnt from these communities will be introduced in our hospital, not only for research purposes but also as a valuable tool for daily clinical work. The research team consists of neurophysiologists, anaesthesiologists, nurses and neurosurgeons from tertiary hospitals with several publications and PhD projects on the relevant methodologies. Professor Guerin at Hospital de la Croix Rousse in Lyon is a prominent researcher in lung mechanics and the treatment of patients with ARDS. The knowledge obtained through cooperation with the colleagues in Lyon will also be of use for other categories of patients. It is also a part of our ICU department´s strategic plan to incorporate P_{tp}.
The Department of Clinical Neurosciences in Cambridge, where the applicant will be working is a leading institution in neurointensive research, which hosts many visiting doctors and researchers. Apart from learning ICP wave analysis, the stay at the University hospital in Cambridge will contribute increased cooperation and knowledge transfer in monitoring and treatment of traumatic brain injury and cerebrovascular and neurological diseases. The technique with non-invasive ICP measurement will be useful for clinicians in other hospitals in North Norway as well. This will make it more easy for colleagues at remote local hospitals to discuss the status of the patient with the neurosurgeon via telephone or video conference equipment over distances corresponding to more than 2 ½ hours with an ambulance plane.
A multicenter study is already under discussion and will be further planned during the time course of the present study.

6. User involvement

1 former ICU patients and 2 next of kin have contributed to the information sheet and consent form. These users were contacted directly by the chief investigator. The protocol was also introduced to them in their native language (Norwegian) in order to get valuable inputs as regards the study design and inclusion criteria. We also consulted them with regard to the potential positive impact of the study on the patient group. Their opinion was also sought on identifying factors that could hamper or increase patient participation.
After the analysis, we will also ask the users and the patient's next of kin for advices on how the results can be transferred to patients, their next of kin and other forums.

4. Ethical and regulatory considerations

The study will be conducted according to Good Clinical Practice guidelines. The protocol, the information and the informed consent forms will undergo approval by the Regional Committee for Medical and Health Research Ethics (REC). Informed consent will be obtained from the next of kin at admission and later by the patient whenever it is appropriate. The current conventional ventilator management of patients with ABI appears to be suboptimal. Although the treatment protocol for mechanical ventilation will not automatically be changed during these studies, we believe that this research might elucidate the respiratory management of the included patients on individual basis The interventions will be performed during a limited time period and within clinically safe tidal volume and airway pressure limits. We do not anticipate that the monitoring, or the intervention, will impose any risk or burden to the patient. By studying previous studies on ventilator settings, care has been taken to choose settings that are within safe range and do not overdistend the lungs. Risks with high PEEP include low cardiac output due to reduced venous return caused by hypovolemia or right cardiac failure. These patients will be excluded from the study. Another consequence might be increased ICP. This is continuously monitored and if above a certain value, it

will be a trigger to finish the intervention. The risk for violating patient integrity is very low since data will be stored in accordance with Norwegian law requirements.

5. Publication

We will publish the results in an international peer-reviewed medical journal, and additionally in national and international congresses. Moreover, we will present the results in forums of interest groups for cerebrovascular diseases including previous patients and relatives.

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