

# BMJ Open Cerebral cortex and respiratory muscles perfusion during spontaneous breathing attempts in ventilated patients and its relation to weaning outcomes: a protocol for a prospective observational study

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## ABSTRACT

**Introduction** In addition to the well-documented factors that contribute to weaning failure, increased energy demands of the respiratory muscles during spontaneous breathing trials (SBTs) might not be met by sufficient increases in energy supplies. This discrepancy may deprive blood and oxygen of other tissues. In this context, restrictions in perfusion of splanchnic organs and non-working muscles during SBT have been associated with weaning failure. However, alterations in perfusion of the brain during the weaning process are less well understood.

**Objective and hypothesis** To investigate whether cerebral cortex perfusion evolves differentially during the transition from mechanical ventilation (MV) to spontaneous breathing between patients failing or succeeding the SBT. We hypothesise that patients failing the SBT will exhibit reduced cerebral cortex perfusion during the transition from MV to spontaneous breathing as compared with patients succeeding the SBT.

**Methods and analysis** This single-centre, prospective, observational study will be conducted in a medical Intensive Care unit of University Hospital Leuven, Belgium in ready to wean patients. Blood flow index in the cerebral cortex (prefrontal area), inspiratory (scalene) and expiratory muscle (upper rectus abdominis) and a non-working muscle (thenar eminence) will be simultaneously assessed by near-infrared spectroscopy (NIRS) using the tracer indocyanine green dye. Measurements will be performed on the same day during MV and during SBT. NIRS-derived tissue oxygenation index and cardiac output (by pulse contour analyses) will be recorded continuously. Twenty patients failing an SBT are estimated to be sufficient for detecting a significant difference in the change of cerebral cortex perfusion from MV to SBT (primary outcome) between SBT failure and success patients.

**Ethics and dissemination** Ethics approval was obtained from the local ethical committee (Ethische Commissie Onderzoek UZ/KU Leuven protocol ID: S60516). Results from this study will be presented at scientific meetings and congresses and published in peer-reviewed journals.

**Trial registration number** NCT03240263; Pre-results.

## Strengths and limitations of this study

- The study constitutes the first attempt to investigate the role of cerebral cortex and respiratory muscles perfusion during spontaneous breathing trial in the pathophysiology of weaning failure.
- Repeated measurements of cerebral cortex perfusion will be performed by near-infrared spectroscopy (NIRS)-indocyanine green (ICG), a validated, practical and non-invasive method.
- Cardiac output, cerebral cortex, inspiratory and expiratory muscles and non-working muscle perfusion will be assessed simultaneously during mechanical ventilation and spontaneous breathing trial.
- A limitation of this study is that NIRS-ICG method cannot be used for measuring diaphragmatic perfusion and thus to provide a more complete picture of perfusion regulation of the main inspiratory muscle.
- The single-centre design may limit the external validity of the collected data.

## INTRODUCTION

### Background and rationale

Weaning failure is associated with complications including increased morbidity and hospital mortality.<sup>1</sup> The aetiology of weaning failure is often multifactorial including compromised respiratory mechanics, respiratory muscle dysfunction, heart failure, metabolic and endocrine disorders and cognitive dysfunction,<sup>2 3</sup> that by their interplay can contribute to excessive increase in respiratory muscle energy demands during the weaning process.<sup>4</sup>

Studies measuring the oxygen cost of breathing ( $VO_{2,resp}$ ) during the weaning process, have demonstrated that  $VO_{2,resp}$  of weaning failure patients may account for up to 59% of their total  $VO_{2,}$ <sup>5 6</sup> These studies

provided the first evidence that during the transition from mechanical ventilation (MV) to spontaneous breathing trial (SBT), the intensely working respiratory muscles might compete with other organs for the energy available. In this context, it has been suggested that the respiratory muscles may deprive blood and oxygen supplies of the brain, contributing to weaning failure.<sup>4</sup>

In support of this relationship, studies have demonstrated an association between splanchnic area hypoperfusion during SBT (assessed by tonometry and by laser-Doppler flow) and weaning failure.<sup>7–9</sup> Recently, it was shown that peripheral muscle oxygenation (ie, thenar eminence and vastus medialis muscle) measured by near-infrared spectroscopy (NIRS) during SBT was significantly lower in patients who failed liberation as compared with patients who were successfully liberated from MV.<sup>10–12</sup> Interestingly, whether during the weaning process cerebral cortex perfusion is affected by the increased respiratory muscle metabolic demands is less well understood in weaning patients.

A key feature of this project is the simultaneous assessment of perfusion and oxygenation in critical organs such as cerebral cortex, scalene muscle, rectus abdominis and thenar muscle (non-working muscle) along with measurements of central haemodynamic responses in weaning patients. These aforementioned measures are essential for comprehensively investigating whether respiratory muscles compete for energy supplies with other organs and particular with an organ (ie, cerebral cortex) that might play a pivotal role during the weaning process. The advantage of simultaneously measuring cardiac output, as well as cerebral cortex, respiratory and peripheral muscle perfusion is that it will allow evaluation of changes in local tissue perfusion relative to changes in total energy supplies (ie, central haemodynamic responses) for each patient.

Furthermore, restrictions in blood and oxygen supplies to the cerebral cortex might affect the output of the respiratory centre. In animal models, it has been demonstrated that after a reduction in carotid blood flow, a gradual decline in both electrical activation and pressure generation of the diaphragm developed.<sup>13</sup> This insufficient ‘drive’ from the respiratory centre might reduce neuromuscular competence leading to weaning failure.<sup>4</sup> In addition, stress and anxiety responses, which have been shown to be associated with weaning failure,<sup>14</sup> are regulated by the cerebral cortex.<sup>15</sup> Limitations in cerebral cortex blood flow during the weaning process might exaggerate stress and anxiety symptoms, which in turn could contribute to uncoordinated breathing and tachypnea,<sup>16</sup> further increasing energy demands of the respiratory muscles. Furthermore, during SBT, inspiratory neck muscles recruitment pattern has been identified as a sign of respiratory distress.<sup>17</sup> Evidence shows that patients who fail a weaning trial present greater electromyographic (EMG) activity of the inspiratory neck muscles that reached near maximal levels within the first 4 min of the SBT trial.<sup>18</sup> Lately, a study investigated the contribution of

the expiratory muscles to total respiratory muscles effort in weaning patients and demonstrated an increased EMG activity of the expiratory muscles from the onset to the end of SBT in the weaning failure group (from 13%±9% at the onset to 24%±10% at the end).<sup>19</sup>

The study is registered in a publicly accessible clinical trial database (clinicaltrials.gov) under the title: Inspiratory Muscle Training in Difficult to Wean Patients (see Study approval and registration section for more details).

### Objective and hypothesis

The primary objective of this project is to assess changes in cerebral cortex perfusion during the transition from MV to spontaneous breathing and to determine whether these changes differ in patients who fail or succeed the SBT. We hypothesise that patients failing the SBT will exhibit reduced cerebral cortex perfusion during the transition from MV to SBT as compared with patients succeeding the SBT.

## METHODS AND ANALYSIS

### Patient and public involvement

No patient involved.

### Study approval and registration

This single-centre, prospective observational study will be conducted in a 16-bed medical ICU of University Hospital Leuven, Belgium in consecutive weaning patients. This study covers the first step in which candidates are identified for an interventional study entitled “Inspiratory Muscle Training in Difficult to Wean Patients” that has been registered to clinicaltrials.gov. This interventional study aims to evaluate the effects of high-intensity inspiratory muscle strength training in comparison with sham endurance training on weaning outcomes in difficult-to-wean patients in the ICU. Patients who are not extubated shortly after the first SBT, during which this observational study collects data, will at a later stage be considered as potential candidates for the interventional study. As such, the intervention will not overlap with the here presented, preceding observational study. Written informed consent will be obtained from all patients. Unconscious patients and patients unable to follow the study information and thus to express their willingness will be excluded from the study (see online supplementary). All procedures will be performed in accordance with the ethical standards of the institutional review board of the UZ/KU Leuven and with the 1964 Helsinki declaration and its later amendments. The protocol is reported according to Strengthening the Reporting of Observational Studies in Epidemiology (see checklist in the online supplementary).

### Methods of selection and monitoring of participants

The study will include patients during the first SBT. The decision to start an SBT will be made by the clinical team caring for the patient.<sup>20</sup> The clinical team will evaluate patients’ ‘readiness to wean’ on a daily basis. Monitoring

of the patients before, during and following the SBT will be facilitated by using an electronic record platform (MetaVision, iMD-Soft, Needham, Massachusetts, USA) of the patients SBTs and ventilation status completed by nurses and the clinical team as previously described.<sup>20</sup>

### Assessing readiness to wean

Readiness to wean will be performed according to a local protocol as has been described elsewhere.<sup>20</sup> Specifically, this evaluation will include the assessments of: (1) resolution of the acute phase of the disease for which the patient was intubated, (2) adequate oxygenation ( $\text{PaO}_2$  arterial oxygen/inspiratory oxygen fraction ( $\text{PaO}_2/\text{F}_1\text{O}_2\%$ ) of 150–200 requiring positive end-expiratory pressure (PEEP)  $\leq 5$  to 8  $\text{cmH}_2\text{O}$  and  $\text{F}_1\text{O}_2 \leq 0.4$  to 0.5), (3) absence of fever (temperature  $< 38^\circ\text{C}$ ), (4) haemodynamic stability (eg, heart rate  $\leq 140$  beats/min), (5) stable blood pressure, no or minimal vasopressors (dobutamine  $\leq 5$   $\mu\text{g}/\text{kg}/\text{min}$ , norepinephrine  $\leq 0.1$   $\mu\text{g}/\text{kg}/\text{min}$ ), (6) absence of myocardial ischaemia, (7) adequate haemoglobin (eg, haemoglobin  $> 70$ – $80$  g/L), (8) adequate mentation and (9) adequate cough.<sup>21</sup> These criteria may be individualised by treating clinicians.

### SBT evaluation

The SBT will be performed either with the use of a T-tube, low-level pressure support ventilation ( $\leq 8$   $\text{cmH}_2\text{O}$ ) or continuous positive airway pressure ( $\leq 5$   $\text{cmH}_2\text{O}$ ). The SBT will be performed for at least 30 min before being considered successful. The duration can be prolonged up to a maximum of 120 min. Patients will be in a semi-recumbent position, and the  $\text{F}_1\text{O}_2\%$  will be kept constant during the trial. The following criteria will be assessed for evaluating the success of the SBT: (1) adequate gas exchange ( $\text{SpO}_2 \geq 85\%$ – $90\%$ ,  $\text{PaO}_2 \geq 55$ – $60$  mm Hg,  $\text{pH} \geq 7.32$  and increase  $\text{PaCO}_2 \leq 10$  mm Hg), (2) adequate ventilatory pattern (respiratory rate  $\leq 30$ – $35$ /min, change during SBT in respiratory rate  $< 50\%$ ), (3) haemodynamically stable (heart rate  $< 120$ – $140$  beats/min, changes during SBT in heart rate  $< 20\%$ , systolic blood pressure  $< 180$ – $200$  and  $> 90$  mm Hg and change during SBT in blood pressure  $< 20\%$ ) and (4) subjective clinical signs (no changes in mental well-being and comfortable, no sweating, no paradoxical breathing).<sup>1</sup> These criteria can be individualised by the treating clinician who will decide whether or not to extubate the patient. The SBT will be immediately interrupted in case of poor tolerance. The reason(s) for an SBT failure will also be recorded.

### Weaning outcomes assessment

Weaning success will be defined as a patient remaining free of MV support for  $> 48$  hours after the successful SBT, including the use of non-invasive ventilation following the extubation.<sup>21</sup> Weaning failure will be defined as either failure to pass the SBT or reinstatement of MV within 48 hours of extubation.<sup>21</sup>

### Exclusion criteria

The following exclusion criteria have been defined: pre-existing neuromuscular disease, head or spinal cord injury above T8, any skeletal pathology that impairs chest wall movements such as severe kyphoscoliosis, congenital deformities or contractures, liver cirrhosis, patients with allergic reactions to iodine, oedema, trauma or haematoma skin lesions at the sites of NIRS measurements that could hinder placement of NIRS sensor probes, poor general prognosis or anticipated fatal outcome.

### Study design, procedures, measurements and data collection

Diagnosis and comorbidities will be recorded on inclusion in the study. The list of comorbidities considered includes cardiovascular diseases, chronic respiratory diseases, chronic renal failure, hypertension, diabetes, cancer and obesity.<sup>22</sup> Measurements will be performed on the day clinicians will judge that the patient is ready to wean during two conditions: (1) on MV, immediately preceding the planned SBT, for a period of 30 min and (2) during the SBT for a maximum period of 120 min. The trial time schedule of the assessments that will be performed are presented in table 1. Specifically, T0 represents baseline assessment, T1 indicates the last minute of the 30 min period on MV prior to the start of SBT, T2 indicates the last minute of SBT if prematurely terminated ( $< 30$  min). T3 represents the last minute of the first 30 min of SBT and T4 indicates the last minute of the SBT if prolonged ( $> 30$  and  $\leq 120$  min). Day x corresponds to the day T0 +48 hours.

### Study methodologies and procedures

#### Peripheral blood flow measured by NIRS

Blood flow index (BFI) of the brain, working respiratory and non-respiratory muscles will be measured by NIRS (HAMAMATSU Photonics KK) in combination with injections from venous of the tracer indocyanine green (ICG) dye<sup>23</sup> (NIRS-ICG) (see online supplementary). Three sets of NIRS optodes will be transcutaneously positioned as follows: for the brain over the prefrontal cortex area (at an adequate distance to avoid interference with the midline sinus),<sup>24</sup> on the scalene muscles and on the upper rectus abdominis. An additional probe (fourth) will be placed on thenar eminence muscle representing a non-working muscle site<sup>11 12</sup> (see online supplementary).

NIRS-ICG-derived BFI, is valid and reproducible in detecting relative perfusion differences in the cerebral cortex during bedside assessment<sup>25–27</sup> and inspiratory and expiratory muscles at rest and during progressively increase in respiratory muscle effort.<sup>28</sup> This non-invasive monitoring of BFI is based on recording the changing levels of chromophores in the muscles and brain tissue, namely, oxygenated, deoxygenated and total haemoglobin.<sup>25</sup> NIRS also enables detection of other chromophore tracers with absorption properties in the near-infrared spectrum.<sup>25</sup> ICG is completely excreted by the liver and is cleared from the human circulation with a half-time of  $3.2 \pm 0.6$  to  $3.4 \pm 0.7$  min thus making ICG a

**Table 1** Time schedule and assessments of the study

Timepoints	Baseline T0	MV T1	SBT T2	SBT T3	SBT T4	Day x T0+48 hours
<b>Enrolment</b>						
Eligibility screen	•					
Informed consent	•					
<b>Demographics—baseline characteristics</b>						
Age, years	•					
Gender, male/female	•					
Body mass index, kg/m <sup>2</sup>	•					
Diagnosis	•					
Comorbidities	•					
Duration on MV before SBT, days	•					
<b>Tissues blood flow and oxygenation parameters</b>						
Cerebral cortex BFI, nMol/s and TOI*, %		•	•	•	•	
Scalene muscles BFI, nMol/s and TOI*, %		•	•	•	•	
Abdominal muscle BFI, nMol/s and TOI*, %		•	•	•	•	
Thenar muscle BFI, nMol/s and TOI*, %		•	•	•	•	
Cerebral cortex DO <sub>2</sub> index, arbitrary units		•	•	•	•	
Scalene muscles DO <sub>2</sub> index, arbitrary units		•	•	•	•	
Abdominal muscle DO <sub>2</sub> index, arbitrary units		•	•	•	•	
Thenar muscle DO <sub>2</sub> index, arbitrary units		•	•	•	•	
Cerebral cortex VC index, arbitrary units		•	•	•	•	
Scalene muscles VC index, arbitrary units		•	•	•	•	
Abdominal muscle VC index, arbitrary units		•	•	•	•	
Thenar muscle VC index, arbitrary units		•	•	•	•	
<b>Haemodynamic parameters</b>						
Heart rate*, beats/min		•	•	•	•	
Mean arterial blood pressure*, mm Hg		•	•	•	•	
Cardiac output*, L/min		•	•	•	•	
Systemic vascular resistance*, dynes/s/cm <sup>-5</sup>		•	•	•	•	
Norepinephrine/epinephrine, yes/no and dose, µg/kg/min		•	•	•	•	
<b>Respiratory parameters and ventilatory settings</b>						
Respiratory rate*, breaths/min		•	•	•	•	
Tidal volume*, mL/min		•	•	•	•	
Minute ventilation*, L/min		•	•	•	•	
FIO <sub>2</sub> , inspiratory oxygen fraction*, %		•	•	•	•	
PS, pressure support*, cmH <sub>2</sub> O		•	•	•	•	
PEEP, positive end-expiratory pressure*, cmH <sub>2</sub> O		•	•	•	•	
Neuromuscular activation index of the respiratory system (P0.1), cmH <sub>2</sub> O			•	•	•	
<b>Blood gas values</b>						
PaO <sub>2</sub> , arterial O <sub>2</sub> partial pressure, mm Hg		•	•	•	•	
PaCO <sub>2</sub> , arterial CO <sub>2</sub> partial pressure, mm Hg		•	•	•	•	
SaO <sub>2</sub> , arterial O <sub>2</sub> saturation, %		•	•	•	•	
Systemic arterial O <sub>2</sub> content, mL O <sub>2</sub> /L		•	•	•	•	
Systemic DO <sub>2</sub> , L O <sub>2</sub> /min		•	•	•	•	

Continued

Table 1 Continued

Timepoints	Baseline T0	MV T1	SBT T2	SBT T3	SBT T4	Day x T0+48 hours
pH		•	•	•	•	
Hb, haemoglobin concentration, g/L		•	•	•	•	
SpO <sub>2</sub> , stands for peripheral capillary O <sub>2</sub> saturation*, %		•	•	•	•	
<b>Weaning outcomes</b>						
SBT outcomes, failure/success			•	•	•	
SBT duration, minutes			•	•	•	
Reason(s) for SBT failure			•	•	•	
Weaning outcome (failure/success)						•

Measurements will be performed on the day clinicians will judge that the patient is ready to wean.

Systemic vascular resistance would be calculated using the following formula:  $[80 \times (\text{mean arterial blood pressure} - \text{central venous pressure} / \text{cardiac output})]$ . Systemic arterial O<sub>2</sub> content will be calculated using the following formula:  $[(1.34 \times \text{Hb} \times \text{SaO}_2) + (0.003 \times \text{PaO}_2)]$ . Systemic DO<sub>2</sub> will be calculated by multiplying cardiac output to systemic arterial O<sub>2</sub> content. Tissues DO<sub>2</sub> index will be calculated by multiplying tissues BFI to systemic arterial O<sub>2</sub> content and will be presented in arbitrary units. Conductance to flow for each tissue will be calculated by dividing BFI with mean arterial blood pressure and will be presented in arbitrary units. Measurement of P0.1 -the negative airway pressure generated during the first 100 ms of an occluded inspiration- will be measured by the ventilator as an index of the neuromuscular activation of the respiratory system.<sup>39</sup> Development of stress and anxiety manifested by rapid and unexplained increase in physiological measures such as heart rate, blood pressure and respiratory rate will be evaluated during the transition from MV to SBT and throughout spontaneous breathing attempt will be evaluated in all patients.<sup>40</sup>

\*Asterisk denotes the parameters that will be assessed continuously on MV and during SBT period.

BFI, blood flow index; DO<sub>2</sub>, oxygen delivery; MV, mechanical ventilation; pH, hydrogen ion concentration; SBT, spontaneous breathing trial; TOI, tissue oxygenation index; VC, vascular conductance.

suitable tracer for repetitive measurements even at short intervals without accumulation of dye.<sup>29</sup> The number of ICG injections that will be performed in each patient will not exceed the number of three (see table 1). Each injection will contain 5 mg of ICG dissolved in 1 mL of sterile water (5 mg/mL) followed by a rapid 10 mL flush of isotonic saline. NIRS-ICG-derived BFI as a relative measurement of local tissues perfusion will be calculated by dividing the muscle ICG peak concentration (assessed by NIRS-ICG curve) by the rise time from 10% to 90% of peak.<sup>28</sup> A representative example of BFI calculation is presented in figure 1. ICG concentration curves data will be exported by NIRS in document file format and stored on disk for off-line analysis (see online supplementary).

#### Peripheral oxygenation measured by NIRS

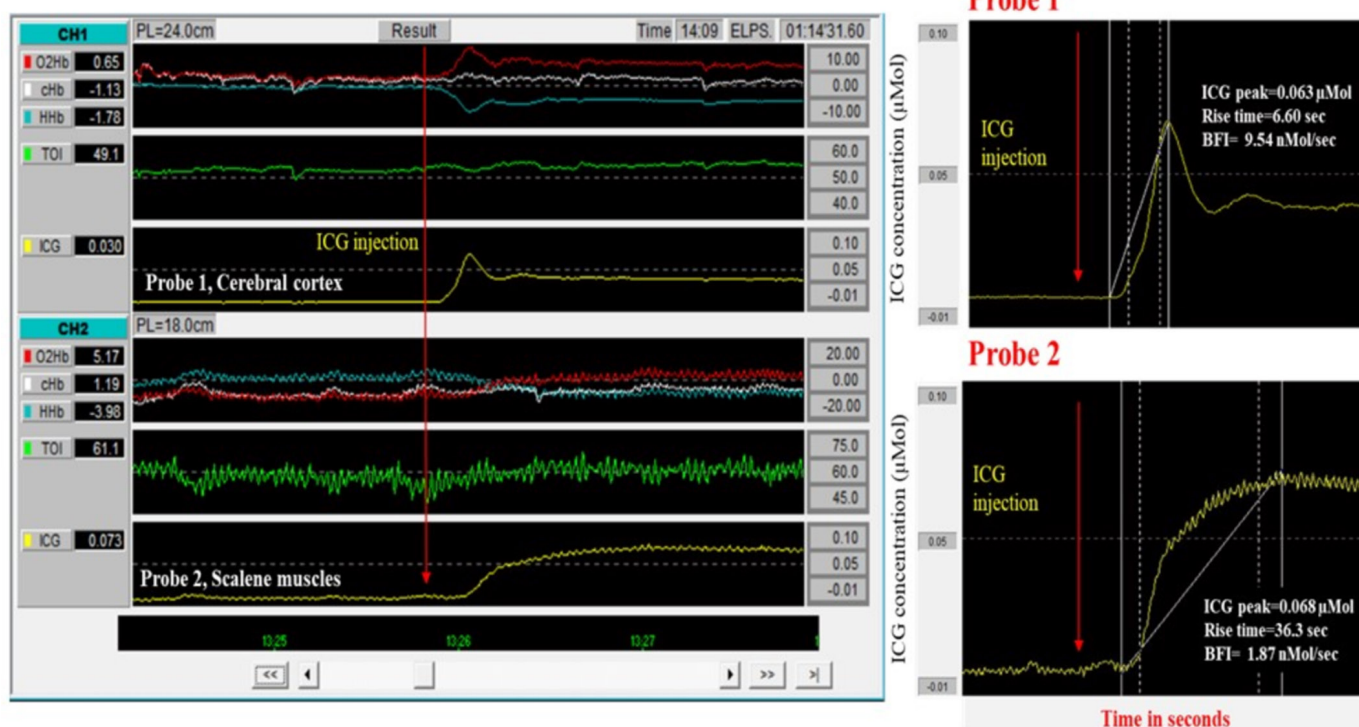
Measurements of tissues oxygenation index (TOI) will be performed continuously on MV and during SBT by the same NIRS device as used for the measurement of BFI (figure 1). NIRS-derived TOI is a real-time and rapidly responsive absolute index of fractional local tissue oxygenation. This non-invasive index is the ratio of microvascular oxygenated (HbO<sub>2</sub>) to total tissue haemoglobin concentration (tHbO<sub>2</sub>) expressed as percentage  $[(\text{HbO}_2 / \text{tHbO}_2) * 100]$  and reflects the dynamic balance between local tissue oxygen supply and utilisation<sup>30</sup> and therefore tissue capacity to match oxygen supplies relative to its metabolic demands.<sup>31</sup> TOI data will be averaged over 60s immediately before ICG injection (see online supplementary).

#### Haemodynamic status

Cardiac output will be assessed continuously by pulse contour analyses using a sensor (Pulsioflex Monitor, Pulsion Medical Systems SE) connected to an existing arterial catheter<sup>32</sup> (see online supplementary). The calculation of cardiac output is performed beat-by-beat by simply multiplying the stroke volume that is calculated by arterial pressure waveform analysis with the recorded heart rate<sup>32</sup> (see online supplementary). Pulse contour analyses method has been validated against cardiac output calculations using gold-standard methods.<sup>33–38</sup> The results show that this method can provide a clinically acceptable cardiac output trend assessment in haemodynamically stable ICU patients. Cardiac output and heart rate data will be averaged over 60s during each BFI determination (see online supplementary).

#### Respiratory parameters and ventilator settings

At the different time points (see table 1), blood gases will be obtained (ABL 625; Radiometer, Copenhagen, Denmark) in addition to ventilator settings, such as inspiratory oxygen fraction (F<sub>I</sub>O<sub>2</sub>), PEEP and amount of pressure (PS), and measured variables including respiratory rate, tidal volume and minute ventilation. The latter will be collected from the individual electronic patient records (MetaVision, iMD-Soft, Needham, Massachusetts, USA).



**Figure 1** Left panel: a typical screenshot from NIRS device of the output of one two-channel near-infrared spectrophotometer (NIRS), showing the indocyanine green (ICG) dye signal (yellow) following intravenous ICG injection marked by the red arrow. Green trace (tissue oxygenation index (TOI)) is oxygenation signal and O<sub>2</sub>Hb, oxyhemoglobin; cHb, total haemoglobin; HHb, deoxyhemoglobin signals are also presented. Right panel: upslope differences of ICG, indicating greater perfusion under the probe 1 (cerebral cortex, frontal area) than in probe 2 (scalene muscles). Solid lines represent the baseline and peak ICG concentration points while dotted lines represent the rise time from 10% to 90% of peak, respectively. Peak ICG concentration is converted from µMol to nMol (multiplied by 1000). The rise time expressed in seconds between 10% and 90% of ICG concentration peak is indicated, and probe 1 and probe 2 BFI results are shown. BFI, blood flow index.

### Primary and secondary outcomes

The primary outcome of the present study is the difference in changes in cerebral cortex BFI from MV to spontaneous breathing between SBT success and SBT failure patients. Secondary outcomes include the differences in changes in respiratory, and thenar muscle perfusion, changes in cerebral cortex, respiratory and thenar muscle TOI, ventilator settings, changes in breathing pattern parameters, haemodynamic parameters and blood gas parameters. Additionally, the difference in changes in cerebral cortex BFI from MV to spontaneous breathing between weaning success or failure will be studied.

### Data management and sources of bias

Data will be collected in anonymously digital formats ensuring sharing on a collaborative basis, long-term access and preservation of the data. Only the researchers of this project will take care of the handling of the data during and after the end of the project. The treating clinician who decides on the duration of the SBT for each patient, and judges whether or not to extubate the patients will be blinded to the specific NIRS data obtained. Researchers who will perform the analysis of the NIRS-derived parameters will be blinded to weaning outcomes. Missing data will not be imputed. The distribution of the missing data

will be explored to identify the possible impact on the results of the study.

### Sample size calculation

Based on the hypothesis of the study, the sample size was calculated taking into account (1) previously reported change in cerebral cortex BFI during the transition from MV to SBT and (2) the prevalence of SBT failure. Specifically, an expected effect size (Cohens d) of 0.467 was calculated from the mean difference of cerebral cortex BFI (ie, 6.70 nMol/sec) and the corresponding pooled standard deviation (ie, 14.0 nMol/sec), from a previous study that investigated interhemispheric differences in cerebral cortex BFI in critically ill patients.<sup>27</sup> Accordingly, using this effect size, the critical sample size is calculated to be 20 SBT failure patients on the basis of using an analysis of variance (ANOVA) as the statistical analysis method. Anticipating that approximately only 1 out of 5 patients (20% rate)<sup>1</sup> is expected to fail the SBT, an estimated number of 100 (ie, 20\*5) patients in total is considered to be included in order to identify the 20 weaning failure patients.

### Statistical analysis

Continuous variables will be presented as mean values with SD if normally distributed or as a median with IQR

if not. Categorical values will be presented as numbers and proportion. For comparisons between SBT success or failure group, continuous variables will be compared using Student's t-test or Mann-Whitney U test based on the distribution of the variables. Categorical values will be compared using  $\chi^2$  or Fisher's exact test, as appropriate. Two-way ANOVA will be applied to examine the interaction among respiratory, haemodynamic, blood gases and peripheral circulation and oxygenation responses and different time points (ie, T1-T4, see [table 1](#)) between SBT success and SBT failure group. One-way ANOVA with repeated measures will be used for the comparison of the different time measurements (ie, T1-T4, see [table 1](#)) for each group. Independent association between changes in cerebral cortex BFI from MV to different time measurements during SBT and SBT outcomes (failure, success) will be explored by logistic regression analysis. Further exploration of independent associations between SBT outcomes (failure, success) and all respiratory, haemodynamic, blood gases and peripheral circulation and oxygenation variables will be also explored by logistic regression analysis. Finally, multiple logistic regression analysis including all significant independent predictors (after checking them for collinearity) will be performed to identify determinants of SBT outcomes. Data will be analysed using the SPSS Software, version 21. Statistical significance will be defined as  $p < 0.05$ . Additionally, analogous analyses will be performed for weaning outcomes (failure, success).

## ETHICS AND DISSEMINATION

The local Ethics Commission approved this study protocol (S60516) and the results will be submitted for publication in peer-reviewed journals and in research congresses scientific meetings as abstracts, posters or oral presentations. Any protocol amendments will be submitted to the same local Ethics Commission and communicated to the trial registry. Written informed consent will be obtained from all patients. There is no intention of using a professional writer and authorship will be based on the collaboration of each member of the research group.

## Trial status

After obtaining ethical approval from the local ethics committee pilot measurements were initiated in December 2018. Enrolment into the study was started in January 2019. Based on the number of patients have been enrolled in the study from January 2019, we expect to recruit 25-30 patients per year. Data collection and analyses are estimated to be completed in September 2023.

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**Contributors** ZL, MVH, RG, DL, GH, and AW are responsible for the overall development of an ethically sound protocol. ZL, MVH, AD, MV, PM, JW, RG, DL, GH and AW are involved in the conception and production of the study and the development of the initial protocol. All authors contributed to the drafting, critical revision and final approval of the document.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

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