IMPACT OF THE INSPIRATORY CORTICAL CONTROL ON THE OUTCOME OF THE VENTILATORY WEANING TEST IN PATIENTS INTUBATED IN RESUSCITATION

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BRAIN-WEAN

N° 2016-A01814-47

NCT03372252

03/07/2017

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PROTOCOL SIGNING PAGE
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Le 20/12/2016
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RESUME

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Version n°1 du 20/12/2016
2016-A01814-47

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TITLE	Impact of the inspiratory cortical control on the outcome of the ventilatory weaning test in patients intubated in resuscitation.
JUSTIFICATION / BACKGROUND	In cases of severe acute respiratory distress, the insertion of an endotracheal tube (intubation) allows the patient to be connected to a ventilator in order to rest the respiratory muscles and ensure gas exchange. However, the duration of artificial ventilation must be as short as possible to avoid complications. To speed up extubation, i.e., the removal of the endotracheal tube, daily assessment of the criteria for weaning from the ventilator is a priority. Once these criteria are met, a spontaneous breathing trial is performed before extubation to check the patient's ability to breathe on their own without the ventilator. Despite these precautions, 20% of extubated patients must be reintubated within 7 days. Ventilator weaning requires minimal inspiratory endurance with intact neuromuscular control. Our team recently showed in healthy subjects deprived of a night's sleep that inspiratory endurance is positively correlated with the amplitude of cortical inspiratory motor control. It therefore seems essential to verify whether this cortical inspiratory control is associated with the outcome of weaning from mechanical ventilation and whether its simple and non-invasive monitoring would allow earlier identification of patients at risk of weaning failure. Hypothesis: Strong inspiratory brain control is associated with successful spontaneous breathing trials and extubation.

OBJECTIVES	Primary Compare inspiratory brain control during the first spontaneous breathing trial between patients who passed this test and patients who failed it. Secondary 1- Compare inspiratory brain control during the successful spontaneous breathing trial between patients who were not reintubated on day 7 and patients who were reintubated before day 7. 2- Compare inspiratory brain control during the first and last spontaneous breathing trial in patients who failed one or more times and then passed this test.
JUDGING CRITERIA	Primary Microvolt amplitude of inspiratory premotor potentials measured during the first 15 minutes of the first spontaneous ventilation trial in patients who passed this test and in patients who failed this test. Secondary 1- Amplitude in microvolts of inspiratory premotor potentials measured during the first 15 minutes of the successful spontaneous breathing trial in patients not reintubated on day 7 and in patients reintubated before day 7. 2- Amplitude in microvolts of inspiratory premotor potentials measured during the first 15 minutes of the first and last spontaneous breathing trial in patients who failed one or more times and then passed this test.
RESEARCH DESIGN	This is a prospective, physiological, routine care, comparative, single-center study in intubated and ventilated intensive care patients.
INCLUSION CRITERIA	All intubated and ventilated patients who are eligible for a spontaneous breathing trial, according to the attending physician, in accordance with the medical intensive care unit protocol and good clinical practice, may be included. Patients must meet the following criteria: - be at least 18 years of age; - have been intubated and ventilated for at least 24 hours; - be covered by Social Security or by a third party; - express consent given by patients/their “relatives” after clear and honest information about the study.
EXCLUSION CRITERIA	Patients must not meet the following criteria: - Age < 18 years; - Peripheral or central neuromuscular disorder leading to intubation (such as myopathy or myasthenia gravis); - Known psychiatric illness; - Agitation preventing electroencephalographic measurements from being performed; - Patients who have been deemed non-intubatable at the time of extubation;

	- Patients who are not covered by Social Security or who are not covered through a third party; - Patients under guardianship, conservatorship, or subordination; - Pregnant or breastfeeding women, women of childbearing age who do not use effective contraception (hormonal/mechanical: oral, injectable, transcutaneous, implantable, intrauterine device, or surgical: tubal ligation, hysterectomy, total ovariectomy) - benefiting from enhanced protection, namely minors, persons deprived of their liberty by judicial or administrative decision, persons staying in a health or social institution, adults under legal protection, patients in emergency situations.
RESEARCH TREATMENTS/STRATEGIES/PROCEDURES	Functional neurophysiological and respiratory explorations during weaning from mechanical ventilation.
STUDY SIZE	70 patients
RESEARCH DURATION	Duration of inclusion: 6 months. Total duration of patient participation in the study: the entire weaning period, from the first spontaneous breathing trial until 7 days post-extubation or until death if extubation is not possible. Estimated total duration of the study, including the analysis period: 12 months (6 months of inclusion and 6 months of analysis). Duration of analysis: 6 months. Theoretical start date: 4th quarter of 2016. Theoretical end date, including the analysis period: 4th quarter of 2017.
EXPECTED IMPACTS	Improved understanding of the mechanisms involved in inspiratory endurance deficit and development of a new technique for predicting failure to wean from mechanical ventilation in intensive care patients.

Procédures

1) Installation of measurement sensors:

1.1) Electroencephalogram (EEG) recording electrodes:

EEG activity will be recorded using a cup electrode (Ag/AGCL Ø10mm pierced capsulex electrode; ZI Toulon Est, La Farlède, France) attached to the scalp at Cz (international 10-20 system) after skin abrasion, with a reference electrode at A2 (right mastoid) and a ground electrode at Fp2. The impedance of the EEG electrodes will be checked before the test and must be between 2 and 5 kΩ. These electrodes will be connected to an EEG amplifier (gain: 20,000 times; bandwidth frequencies 0.05–500 Hz; Biopac® Systems MP150, Inc. USA).

The signal will then be processed by an analog-to-digital converter, digitized at a sampling frequency of 2000 Hz (Biopac® Systems MP150, Inc. USA), and stored in a computer for further analysis.

1.2) Electrodes for recording the electrooculogram (EOG):
EOG activity will be recorded by two electrodes: one attached to the upper right part of the right eye and the other placed on the lower left part of the left eye.
The reference electrode will be the one placed on the right mastoid at A2 (international 10-20 system).

1.3) Electrodes for recording the electromyogram (EMG) of the right scalene muscle:
The EMG activity of the right scalene muscle will be collected by two electrodes attached to the muscle.

1.4) Pressure sensor:
The patient will breathe through their endotracheal tube. An artificial nose will be placed at the end of this endotracheal tube during the spontaneous ventilation weaning test.
A pressure sensor (Pneumotach Amplifier-1 Series 1110, Hans Rudolph, Inc., USA) will measure pressure variations during respiratory cycles and accurately identify the start of each inspiration (defined as the negativization of pressure at the tube).
This pressure sensor will be connected to the endotracheal tube by a small plastic device (Straight T-Connector, single use, Nonin Medical, Inc. Plymouth, MN, USA), adding very little dead space and having no effect on respiratory resistance.

1.5) Data acquisition:
All of these signal measurement systems will be connected to a simultaneous data acquisition system (Biopac® Systems MP150, Inc. USA) via signal collection, filtering, and amplification boxes specific to each parameter (EEG, EMG, ECG).
A connector will receive the analog pressure signal.
The Biopac® acquisition system will be coupled with AcqKnowledge 4.4 signal processing software installed on a computer.

2) Calibrations:
Before each test, the pressure sensor at the outlet of the intubation probe will be calibrated using a vertical U-tube manometer (Prolabo).

3) Measurement of occlusion pressure (P0.1):
To measure P0.1, the patient must be on mechanical ventilation and initiate their own breaths (spontaneous ventilation).
Thus, before each spontaneous breathing trial (SBT) through an artificial nose, the ventilator's inspiratory support will be set to a minimum inspiratory support of 7 cmH2O with positive expiratory pressure at 0 cmH2O, which is equivalent to spontaneous breathing without a ventilator.
Then, at the investigator's request, airway pressure will be measured during a very brief 100 ms occlusion using the ventilator's pressure transducer.
After the measurement, the patient will receive the set support.

4) Measurement of dyspnea sensation:
As soon as spontaneous ventilation is initiated and at the end of the SBT, patients will self-assess their degree of dyspnea (breathing discomfort) by completing a visual analogic scale (VAS) where 0 represents “no breathing discomfort” and 10 represents “choking, suffocation.”

5) Measurement of inspiratory control by premotor potentials:
EEG signal analysis will be performed using the methodology developed by Raux et al. (Raux, 2007a; Raux, 2010).
The start of each inspiration will be identified on the inspiratory pressure signal. The EEG signal

will be divided into segments, starting 2.5 seconds before and ending 1 second after each inspiratory start (Figure 1).
The EEG signal will be cleaned of eye movements and blinks using the "EOG denoising" function of the AcqKnowledge 4.4 software.
Each segment will then be examined visually. EEG segments will be rejected if there are not at least 3.5 seconds between two inspirations, or in the event of artifacts related to excessive body or eye movements masking EEG variations.
The segments, contained in the first 15 minutes of the test, will be averaged point by point and the onset of the inspiratory premotor potential will be sought in the area of interest (0.5 to 2 seconds before inspiration).
The onset of the PPM will be defined as the lowest point of the averaged signal (Figure 2). A PPM will be considered present if the slope between this lowest point and the inspiratory onset is negative (upward deviation on the EEG signal).
The amplitude of the PPM will be measured in TI, the start of inspiration (negative pressure at the intubation probe).
The measurement of inspiratory motor potentials will be performed offline, after the end of the SBT, and will be done blind: the analyst will not know whether the test was successful or unsuccessful, nor which patient it concerns, thanks to the anonymization of the computer files.
Signal analysis will be performed in collaboration with Prof. T. Similowski's Experimental and Clinical Respiratory Neurophysiology team.

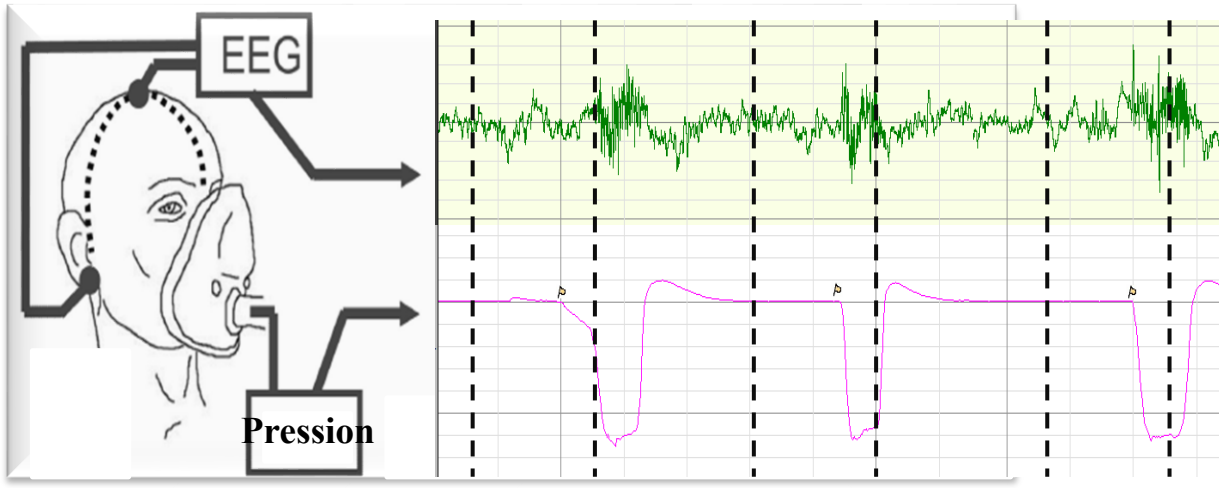

Figure 1 : Explanatory diagram of the EEG signal averaging method adapted from the study by Tremoureux et al. (Tremoureux, 2010). The start of each inspiration is marked on the oral pressure signal (yellow flags). The EEG signal is divided into segments starting 2.5 seconds before the start of inspiration and ending 1 second after. The segments obtained are then averaged point by point.

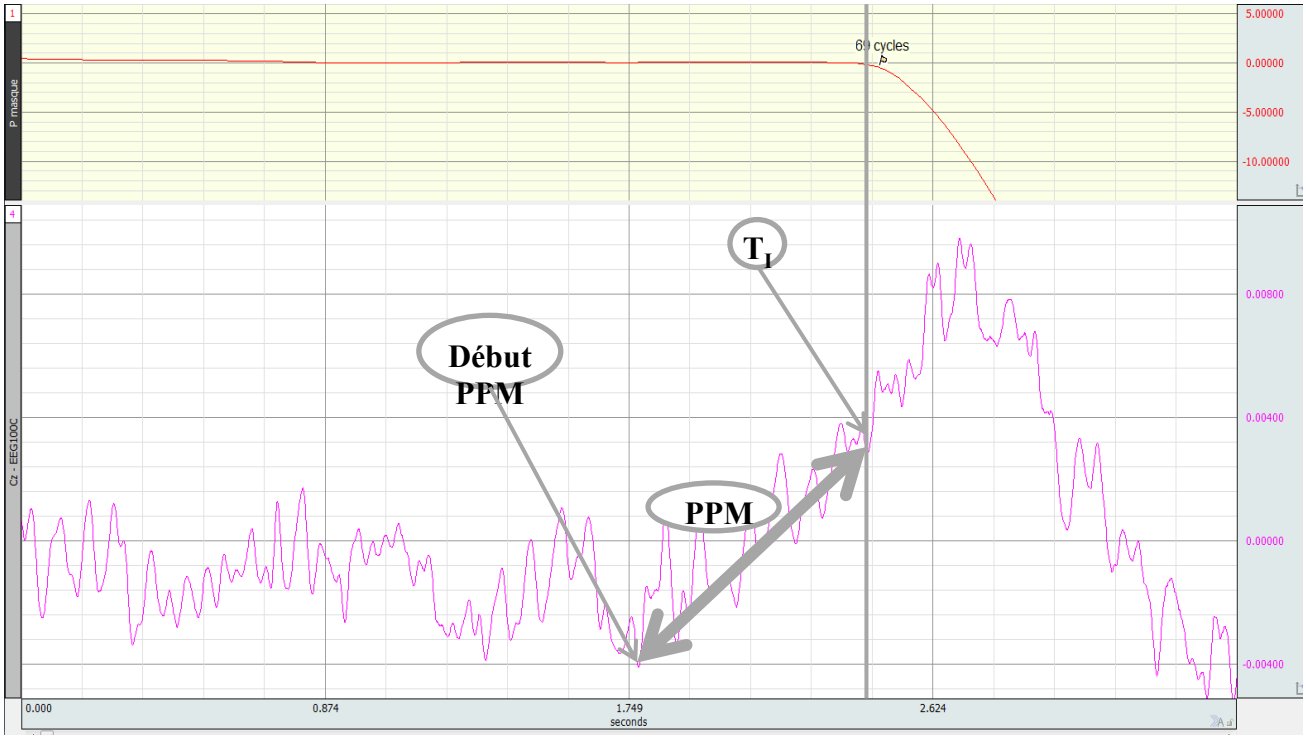

Figure 2 : Explanatory diagram of the method for measuring the amplitude of the averaged PPM. The start of the PPM is the lowest point of the averaged EEG signal. The PPM ends at the start of inspiration TI. A PPM is considered to be present if the slope between this lowest point and the start of inspiration is negative. The PPM amplitude is the difference between the TI point and the lowest point on the averaged EEG signal.

Participant tracking summary table

	Inclusion	Before the SBT	During the SBT	After the SBT
Information for patients/relatives	X			
Eligibility criteria	X			
Certificate of non-objection	X			
Placement of sensors: EEG, EOG, and EMG electrodes on the right scalene muscle pressure at the intubation tube		X		
Measurement of P0.1		X		
Dyspnea VAS			X	
Monitoring: EEG, EOG, EMG of the right scalene muscle pressure at the intubation tube			X	

Extubation if SBT is successful				**X**
7-day monitoring of progress after extubation				**X**

Inclusion and recording

1) Obtaining consent

Patients in intensive care are sometimes unable to give their consent to participate in clinical research. In this context, and in accordance with Article L.1122-1-2, express consent will be sought from “relatives” and, as soon as possible, from the patient once they have recovered sufficiently neurologically.

The investigating physician shall provide the patient with free and informed information and answer all their questions concerning the purpose, nature of the constraints, foreseeable risks, and expected benefits of the research. They shall also specify the participant's rights in the context of research and verify the eligibility criteria.
The information and consent form shall be given to patients and/or “close relatives.”

2) Inclusion:

A reflection period of approximately 30 minutes will be allowed. Consent will be obtained after this reflection period.
After verifying the eligibility criteria, the investigator will obtain the express oral consent of the patient or “close relative” and will date and sign the consent form, noting that the patient or “close relative” has given their consent orally.
The investigator will keep a copy of the express consent in the center file and will give a duplicate to the patient or “close relative.”
The investigator will specify in the patient's medical file their participation in the research, the terms of consent collection, and the terms of information provision.

3) Procedure for the recording

Setup and procedure for SBT:

One hour before each SBT test, the patient will be fitted with measurement sensors (3 EEG electrodes, 2 EOG electrodes, 2 EMG electrodes on the right scalene muscle, and 1 pressure sensor at the outlet of the intubation tube).

The occlusion pressure P0.1 will then be measured by the ventilator.

The activity of the inspiratory cortical motor control will then be recorded for 30 minutes prior to the SBT test in order to study the patient's baseline condition under mechanical ventilation.

A dyspnea VAS will be presented to the patient at the beginning and end of the SBT.

The weaning test will be conducted according to the department's usual protocol under the supervision of the physician in charge of the patient.

Monitoring of cortical inspiratory control and pressure at the end of the endotracheal tube will continue throughout the SBT (≤ 1 hour).

Any treatments being administered at the time of the SBT will be recorded in order to establish a possible link between certain medications and cortical inspiratory motor control.
In fact, apart from one study of eight patients with Ondine's syndrome (Tremoureux, 2014), all studies on inspiratory PPMs have only involved healthy subjects, and we cannot predict the impact of resuscitation treatments (particularly sedatives) on their analysis.

Follow-up

At the end of the SBT test, patients will be divided into two groups:
- Group 1: patients who have passed their first SBT test and are extubated;
- Group 2: patients who have failed their first SBT test. The weaning test will be repeated daily until successful, in accordance with department procedures.

Patients in group 1 will be monitored for up to 7 days after extubation about their ventilatory status.

Rules for repeal a person's participation in the search

1) Repeal of a person's participation in the research:

Patients or their “relatives” may withdraw their consent and request to be removed from the study at any time and for any reason.

In the event of premature withdrawal, the investigator will document the reasons as fully as possible.

The investigator may temporarily or permanently discontinue a patient's participation in the study for any reason that is in the patient's best interests.

2) Discontinuation of part or all of the research:

The study may be discontinued prematurely in the event of unforeseen events or new information that makes it unlikely that the objectives of the study or clinical program will be achieved, which may lead the research sponsor to discontinue the study prematurely.
The Poitiers University Hospital reserves the right to terminate the study at any time if it appears that the inclusion objectives are not being met.

Statistical Aspects

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The software used will be Statview.

1) Calculation of study size

The number of patients included xill be **70**.
The number of patients was determined in agreement with the study methodologist.
The number of patients was calculated using the POWER procedure in SAS (version 9.4).

The expected failure rate during the first spontaneous ventilation test is 20%; the distribution between the groups to be compared (failure/success) will therefore be 1:5.

In a study conducted by our team, the mean amplitude of inspiratory premotor potentials in healthy subjects was 7.2µV under normal sleep conditions and 4.3µV after a night of sleep deprivation. The

intergroup variability in the amplitude of premotor potentials, as assessed by the standard deviation, was 3.1µV.
Taking into account the 1:5 distribution, to highlight a difference of 3 µV between the amplitude of the PPMs of patients in group 1 who passed their SBT test and the amplitude of the PPMs of patients in group 2 who failed the test, setting a type I risk of 5%, a power of 80%, and a bilateral situation, a total of 63 patients must be included, i.e., 50 patients in group 1 and 13 patients in group 2. To account for the usual 10% of unusable recordings, we plan to include 70 patients; 56 patients in group 1 and 14 patients in group 2.
Given that the intensive care unit performs an average of 400 intubations per year and 267 weans per year, or just over 5 per week, and that it is reasonable to assume that 3 patients per week can be included, a minimum inclusion period of 6 months will be necessary to recruit 70 patients.

2) Statistical methods used

Analysis of the primary endpoint:
The amplitude of the premotor potentials measured during the first 15 minutes of the first SBT test will be compared between patients in groups 1 and 2 using a nonparametric Mann-Whitney U test for unpaired series.

3) Expected degree of statistical significance:

A $p<0.05$ will be considered statistically significant.