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Near-Infrared Spectroscopy Usefulness in Validation of Hyperventilation Test

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Abstract: *Background*: The hyperventilation test is used in clinical practice for diagnosis and therapeutic purposes; however, in the absence of a standardized protocol, the procedure varies significantly, predisposing tested subjects to risks such as cerebral hypoxia and ischemia. Near-infrared spectroscopy (NIRS), a noninvasive technique performed for cerebral oximetry monitoring, was used in the present study to identify the minimum decrease in the end-tidal CO_2 ($ETCO_2$) during hyperventilation necessary to induce changes on NIRS. *Materials and Methods*: We recruited 46 volunteers with no preexisting medical conditions. Each subject was asked to breathe at a baseline rate (8–14 breaths/min) for 2 min and then to hyperventilate at a double respiratory rate for the next 4 min. The parameters recorded during the procedure were the regional cerebral oxyhemoglobin and deoxyhemoglobin concentrations via NIRS, $ETCO_2$, and the respiratory rate. *Results*: During hyperventilation, $ETCO_2$ values dropped (31.4 ± 12.2%) vs. baseline in all subjects. Changes in cerebral oximetry were observed only in those subjects (n = 30) who registered a decrease (%) in $ETCO_2$ of 37.58 ± 10.34%, but not in the subjects (n = 16) for which the decrease in $ETCO_2$ was 20.31 ± 5.6%. According to AUC-ROC analysis, a cutoff value of $ETCO_2$ decrease >26% was found to predict changes in oximetry (AUC-ROC = 0.93, $p < 0.0001$). Seven subjects reported symptoms, such as dizziness, vertigo, and numbness, throughout the procedure. *Conclusions*: The rise in the respiratory rate alone cannot effectively predict the occurrence of a cerebral vasoconstrictor response induced by hyperventilation, and synchronous $ETCO_2$ and cerebral oximetry monitoring could be used to validate this clinical test. NIRS seems to be a useful tool in predicting vasoconstriction following hyperventilation.

Keywords: NIRS; hyperventilation; hypocapnia; cerebral blood flow

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1. Introduction

The hyperventilation procedure was first described 50 years ago by Major Meyer Friedman with the intent of providing a diagnostic tool for approaching patients with dyspnea [1]. While initially designed to differentiate between organic and psychosomatic etiologies of dyspnea, currently, the hyperventilation test is widely used in clinical practice for the evaluation of vestibular abnormalities or for the assessment of the vascular reactivity. From a physiological point of view, the changes that occur during hyperventilation are mediated by the reduction in the partial pressure of arterial carbon dioxide ($PaCO_2$),

which, in turn, interferes with the cerebrovascular autoregulatory functions and leads to vasoconstriction [2]. Vasoconstriction is accompanied by a lower regional blood flow, which results in a reduced oxygen supply and an increased risk of ischemic phenomena [3,4].

At present, there are few indications for the use of the hyperventilation procedure in clinical practice, whether by voluntary control of the breathing or by using mechanical ventilation devices. Some of these are the diagnosis and the study of epileptic seizures, the reduction in elevated intracranial pressure in neurosurgery (e.g., for the control of post-traumatic intracranial hypertension), and the coronary artery vasospasm test in patients with suspected or documented vasospastic angina [5–7]. A special indication of the use of the hyperventilation test is the training of pilots in aero-spatial medicine. Flight pilots are prone to hyperventilation in emergencies or during rapid decompressions of the cabin; accordingly, they need to have a good tolerance to hyperventilation [8]. Thus, they should pass a correctly performed hyperventilation test to avoid seizures or angina during the hypocapnia-induced cerebral vasoconstriction.

Classically, during a hyperventilation test, subjects are asked to hyperventilate vigorously for a few minutes at a respiratory rate that is higher than normal [9]. A physiological response in the form of angina, tinnitus, or dizziness is recorded thereafter. To date, there have been limited attempts to standardize the test in terms of ventilatory rate or duration. A quick survey of the current medical literature identified significant variations in the procedure's methodology from study to study, both in terms of test duration, with ranges from 3 and 5 min up to 20 and 60 min, and in terms of the prescribed respiratory frequency [10,11]. It is also well known that humans have large variability in terms of respiratory depth and rate during hyperventilation, which limits the applicability of standardization based on clinical criteria only [12].

The purpose of the present study was to evaluate objectively and in a noninvasive manner the changes that occur in the cerebral blood flow during the hyperventilation procedure. We used end-tidal CO_2 in non-intubated patients to quantify the extent of hypocapnia in subjects whose cerebral perfusion was estimated using near-infrared spectroscopy (NIRS) technology. NIRS technology noninvasively measures the concentration of oxygenated and deoxygenated hemoglobin, as well as derived parameters, in the target tissues, offering information about the perfusion and the oxygen supply of the tissue [13,14]. NIRS is used in clinical practice for the assessment of the cerebral oximetry during various states as traumatic brain injury, carotid endarterectomy, stroke, epilepsy, cardiac surgery, migraine, and mild cognitive impairment, and it has the advantage of providing real-time values of oxygenated an deoxygenated hemoglobin, in addition to being a noninvasive technique with no contraindications [15,16]. Another advantage of this technique is represented by the high reproducibility of the experiments. As a result, we assessed the degree of hypocapnia required to induce changes in the cerebral blood flow. NIRS was previously used successfully to assess the cerebral autoregulation [17]. Additionally, we assessed the objective changes at different timepoints to establish the minimal duration of hypocapnia compatible with an accurate hyperventilation test.

2. Materials and Methods

For this study, 46 healthy volunteers, 31 men and 15 women, aged between 18 and 38 years old (with a median age of 22 years) have been recruited. Exclusion criteria for participating in the study were as follows: history of epilepsy, seizure(s), stroke, vertigo, anxiety, myocardial infarction, cardiac arrhythmias, congenital heart diseases, asthma, severe pulmonary fibrosis, chronic obstructive pulmonary disease, tuberculosis, current upper respiratory tract infection, and peripheral artery disease. Prior to being enrolled in the study, each volunteer was informed regarding the methodology of the procedure. An anamnestic evaluation of the candidates was carried out to identify and exclude potential subjects with medical conditions that could suffer decompensation in the context of hyperventilation. Afterward, the selected candidates considered appropriate for the test signed an informed consent form. The procedure was conducted in baseline conditions, at rest, in

the morning, with no prior consumption of tobacco, caffeine, or other medications for the previous 12 h.

The parameters monitored during the hyperventilation procedure were (1) the variation of oxyhemoglobin and deoxyhemoglobin using near-infrared spectroscopy technology (NIRS) (PortaLite, Artinis Medical Systems, Einsteinweg, The Netherlands), which is an indirect parameter for estimating cerebral perfusion [18], and (2) the partial pressure of carbon dioxide in the expired air ($ETCO_2$) and the respiratory rate (RR) using a Vamos gas monitor (Dräger, Germany) [19]. NIRS-driven oximetry allowed the monitoring of cerebral blood oxyhemoglobin and deoxyhemoglobin concentrations by placing a NIRS oximeter sensor on the subject's forehead. Preparing for the procedure, the NIRS oximeter sensor was applied to the subject's forehead (on the right side), and they were offered a facial mask connected to the capnograph device through which they breathed, thus allowing for full data acquisition. If any artefact motion was identified on the NIRS trace, we asked to subjects to repeat the test after 1 h. Fortunately, with many of them being medical students, we had to repeat the test in just two cases.

Before beginning to hyperventilate, the subject was instructed to breathe with a respiratory rate in a relaxed state for 2 min, after which each subject was instructed to double their respiratory rate (following the respiratory rate displayed by the capnograph) for the next 4 min. The values for each of the monitored parameters were registered at 2 min with respect to 4 min after hyperventilation started. Oximetry analysis was performed continuously over the course of the procedure, preceding the initiation of hyperventilation, and during hyperventilation. At the end of the 4 min of hyperventilating, the subjects were instructed to return to their basal respiratory rates, while oximetry monitoring continued to objectivize post-hyperventilation oximetry changes. We considered that a patient was responsive to hyperventilation if the oxyhemoglobin decreased during hyperventilation by more than 50% of its basal value.

Statistical analysis. Our data are presented as the average values ± standard deviation. Student's t-test was performed for mean comparison and determination of area under the receiver operator's characteristics curve (AUC-ROC). AUC-ROC analysis was used to evaluate the performance of $ETCO_2$ in predicting NIRS change during hyperventilation. The results were considered statistically significant for $p < 0.05$. NCSS 2022 Statistical Software (NCSS 2022, LLC, Kaysville, UT, USA) was used for data analysis. All patients provided written informed consent, and the study was approved by the Clinical Emergency Hospital for Plastic, Reconstructive, and Burns Surgery Ethics Committee (No. 2/19.06.2020).

3. Results

Analyzing the data acquired during the procedure, we observed that the partial pressure of carbon dioxide in the expired air (measured through capnography as $ETCO_2$) diminished in all subjects as a result of hyperventilation (%$ETCO_2$ decreased on average by 31.4 ± 12.2%). The values of the respiratory rate and end-tidal CO_2 are presented in Table 1. There was no statistically significant difference between the value of $ETCO_2$ measured at 2 min and the value of $ETCO_2$ measured at 4 min (25.89 ± 4.95% and 24.6 ± 5.85%, respectively; $p = 0.24$). This observation is an argument in favor of limiting the duration of the hyperventilation procedure to 4 min.

Table 1. Values of respiratory rate and end-tidal CO_2 during basal state and after 2 and 4 min of hyperventilation.

Parameter	Basal	Hyperventilation 2 Min	Hyperventilation 4 Min
Respiratory Rate	10.45 ± 1.54	21.87 ± 3.58	22.08 ± 3.58
$ETCO_2$ (mmHg)	36.04 ± 4.49	25.89 ± 4.95	24.6 ± 5.85

In Figure 1, we can observe that, during basal ventilation, there anywhere no differences between the groups (35.96 ± 4.72 vs. 36.18 ± 4.16; $p = 0.87$) in end-tidal CO_2, whereas, at 2 min (23.86 ± 4.2 vs. 29.68 ± 4.01) and 4 min (22.4 ± 4.58 vs. 28.75 ± 4.97), there were significant differences between the group which presented changes in oximetry (blue bars) and group which did not (red bars) ($p < 0.01$).

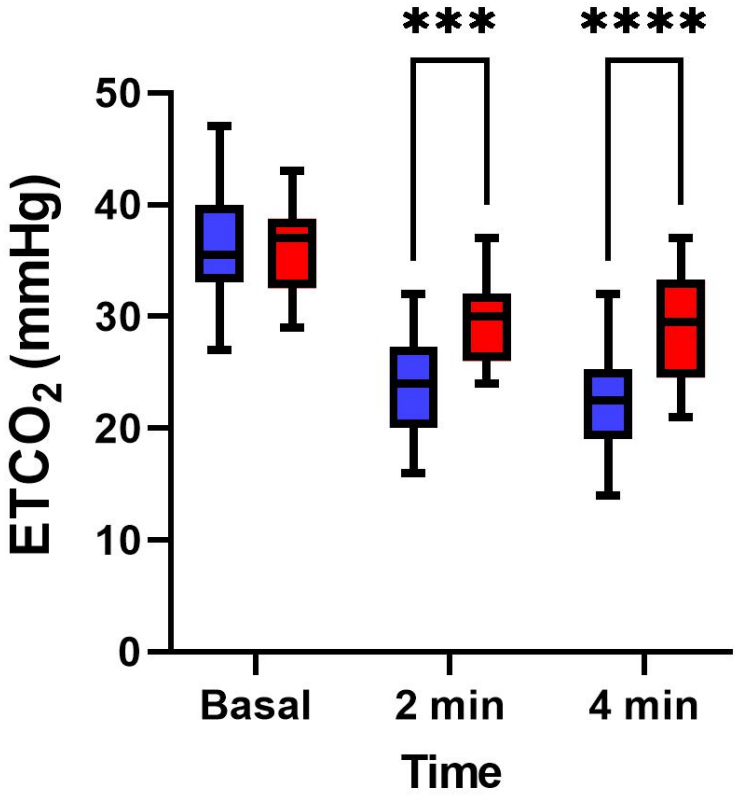

Figure 1. Mean values of end-tidal CO_2 ($ETCO_2$) in group presenting changes in the cerebral oximetry (blue) and in group not presenting any change in cerebral oximetry (red) at baseline and during hyperventilation at 2 min and 4 min. *** $p < 0.001$; **** $p < 0.0001$.

Seven subjects of the 46 (15%) described the occurrence of symptoms such as dizziness, vertigo, and sensations of paresthesia in the extremities.

However, oximetry changes were seen only in those subjects ($n = 30$) who registered a reduction in $ETCO_2$ (%) of 37.58 ± 10.34 compared with 20.31 ± 5.6 in subjects ($n = 16$) who did not present any signs on NIRS (Table A2). Figures 2–5 are charts representing the oximetry and end-tidal CO_2 data collected from one subject that participated in the study. The decrease in total hemoglobin resembles the decrease in oxyhemoglobin compared with deoxyhemoglobin (Figures 3 and 4). The recording of a subject who did not show any sign of change on NIRS during the hyperventilation test is revealed in Figure 5.

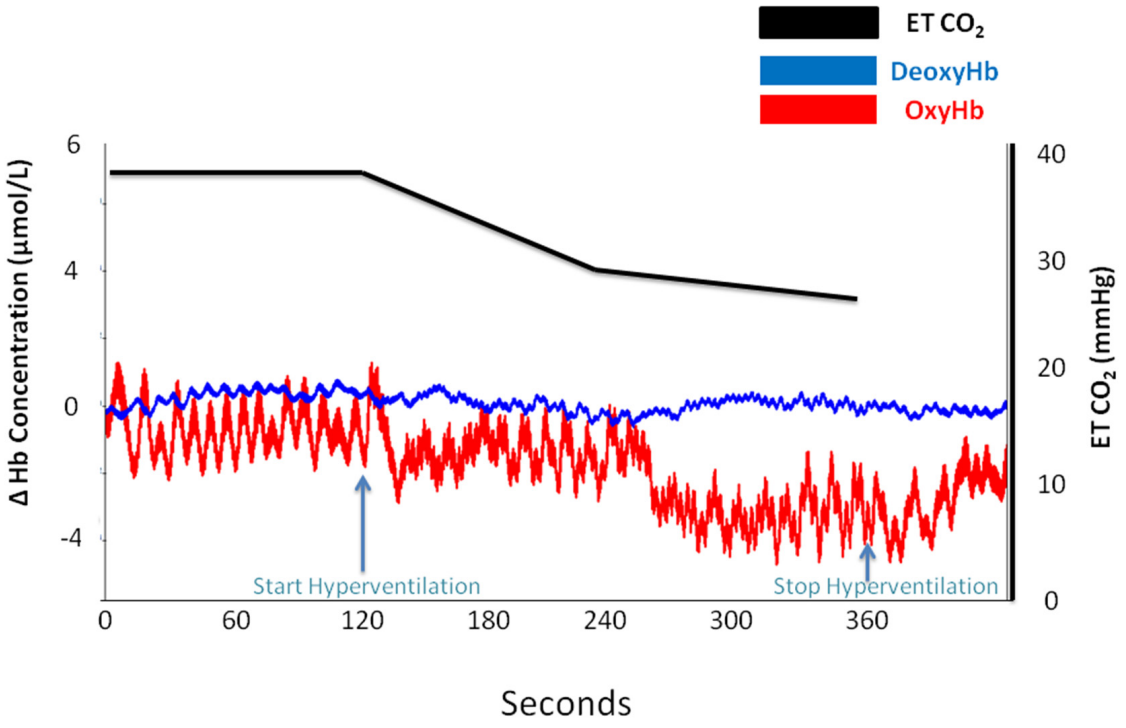

Figure 2. Oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) and end-tidal CO_2 changes at baseline and during hyperventilation and post-hyperventilation periods in the case of a subject who presented a drop in oxyhemoglobin.

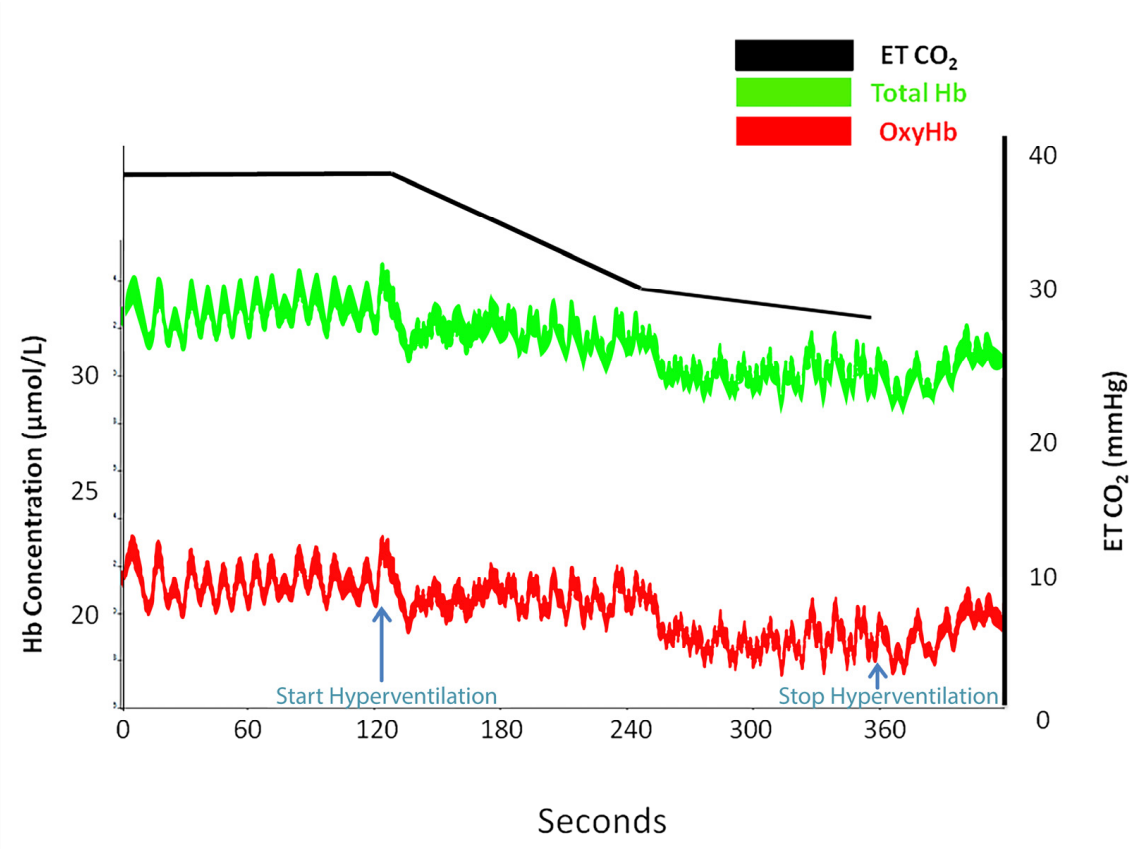

Figure 3. Total hemoglobin (tHb) trace (green), oxyhemoglobin trace (red), and end-tidal CO_2 trace (black) at baseline and during hyperventilation in the subject presented in Figure 2.

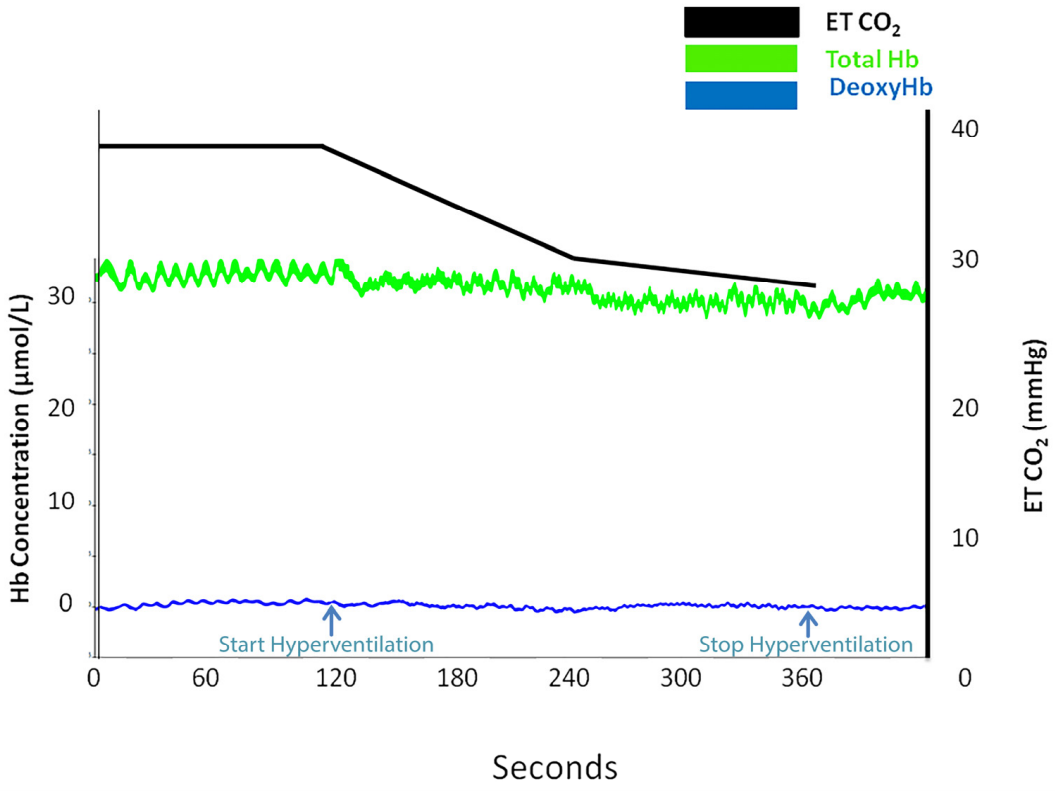

Figure 4. Total hemoglobin (tHb) trace (green), deoxyhemoglobin trace (blue), and end-tidal CO_2 trace (black) at baseline and during hyperventilation in the subject presented in Figure 2.

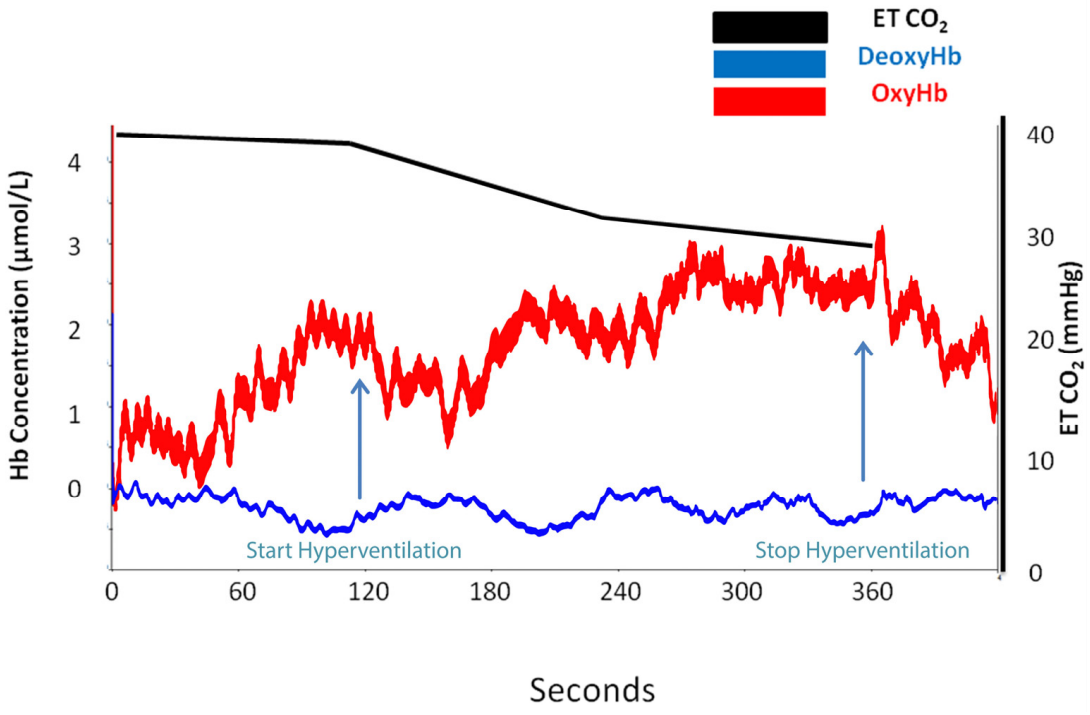

Figure 5. Oxyhemoglobin (oxyHb), deoxyhemoglobin (deoxyHb), and end-tidal CO_2 changes at baseline and during hyperventilation and post-hyperventilation periods in the case of a subject who did not present any drop in oxyhemoglobin.

We found that the cutoff value of $ETCO_2$ decrease predicting changes in NIRS was ≥26%, with AUC-ROC (CI 95%) = 0.93 (0.8212–0.9753) ($p < 0.0001$), a sensitivity of 0.8667, a specificity of 0.875, a positive predictive value of 0.8678, a negative predictive value of 0.8739, and a Youden Index of 0.7417 (Figure 6).

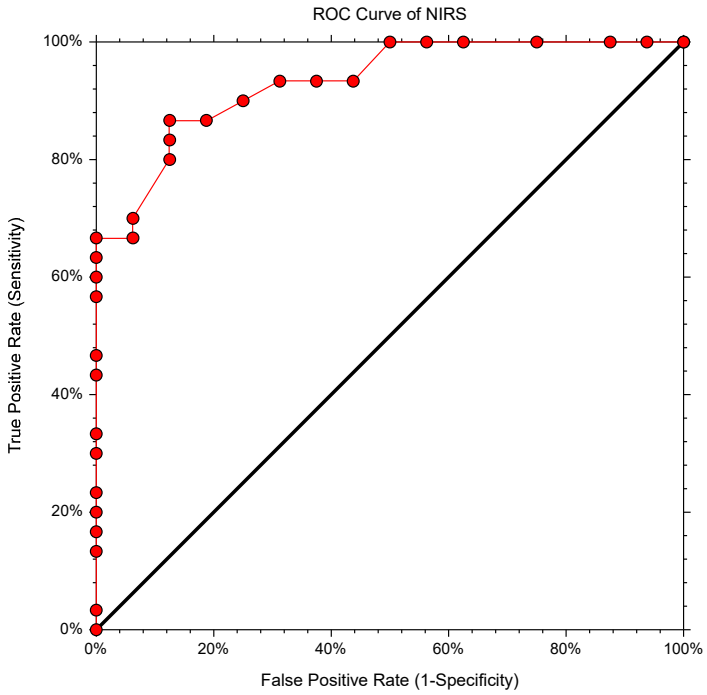

Figure 6. ROC curve analysis of $ETCO_2$ to predict oximetry changes (NIRS).

The oximetry changes consisted of a reduction in oxyhemoglobin concentration, whilst the deoxyhemoglobin level remained almost constant. These subjects presented a reduction of 26% or greater from the baseline levels of $ETCO_2$, along with oximetry changes, but an association between the percentage $ETCO_2$ decrease and clinical signs was not mandatory. There were also subjects with a greater reduction in $ETCO_2$ who did not report any signs.

4. Discussion

Our results showed that, during hyperventilation, reaching a certain prescribed respiratory rate (21.87 ± 3.58 breaths/min) higher than the initial baseline rate (10.45 ± 1.54 breath/min) was not necessarily followed by an equally significant rise in alveolar ventilation in a patient capable of sustaining a state of hypocapnia corresponding to changes in cerebral oximetry. $ETCO_2$ levels allow accurately estimating the $paCO_2$ values [20] and are conditioned by the tissue carbon dioxide production/alveolar ventilation ratio [21]. As such, $ETCO_2$ recording is necessary because the respiratory rate cannot accurately estimate the alveolar ventilation (the amplitude of the respiratory movements is variable among subjects).

Subjects maintained a constant $ETCO_2$ at 2 min and 4 min, but most of them reported fatigue; hence, further respiratory effort could have led to a decrease in alveolar ventilation.

Assessment of hemodynamic cerebral changes during the hyperventilation test are essential in order to verify that the test is properly performed. There are many techniques used in humans that measure global or local cerebral blood flow, some invasive, based on brain pulsations recording through skull defects, and some less invasive or noninvasive, such as nitrous oxide dilution, transcranial Doppler ultrasound, magnetic resonance imaging, or NIRS [22–24]. In fact, NIRS is a modern technique that shows the tissue oxygenation index, the expression of the balance between oxygen delivered by the cerebral blood flow and local metabolic demands. It is known that hypocapnia secondary to hyperventilation

induces cerebral arterial vasoconstriction as proven by imagistic studies [25]. Arterial vasoconstriction decreases the number of erythrocytes crossing the vessel, thereby also decreasing the amount of hemoglobin. This then determines an increase in the oxygen extraction ratio and a drop in oxyhemoglobin if the cerebral metabolism remains constant.

We observed in our subjects a decrease in total hemoglobin (Figures 3 and 4), and this decrease was similar to the decrease in oxyhemoglobin (Figure 3), while deoxyhemoglobin concentration remained constant (Figure 4). We preferred to monitor oxyhemoglobin and deoxyhemoglobin continuously during the test rather than to monitor the changes in total hemoglobin because the decrease in oxyhemoglobin is easier to observe compared to deoxyhemoglobin level, which remains constant. Thus, a decrease in total hemoglobin and oxyhemoglobin corresponds to arterial vasoconstriction. Similarly, in a study that focused on the effects of hyper/hypoxia and hyper/hypocapnia on cerebral tissue oxygenation, subjects that hyperventilated in order to reduce $ETCO_2$ by 1.5 kPa below the baseline for 5 min had a reduced cerebral oxygenation index as a result of decreased cerebral blood flow and reduced cerebral blood volume [26]. Furthermore, a speech study revealed a decrease in ETCO2 by 4–10 mmHg during a 5 min recitation task, which was associated with oxyhemoglobin and total hemoglobin decrease [27]. The results were attributed to cerebral vasoconstriction secondary to hyperventilation, which prevailed over the neurovascular coupling mechanism associated with increased brain activity during the task.

Furthermore, we observed an association between the occurrence of cerebral arterial vasoconstriction, as established by NIRS cerebral oximetry, and the $ETCO_2$ variation from baseline; specifically, oximetry changes indicating the occurrence of vasoconstriction were produced only in those subjects who also presented a reduction in $ETCO_2$ level equal to or greater than 26% from baseline. Accordingly, we believe that $ETCO_2$ monitoring is required, to have a more precise, quantifiable method that allows estimating the effectiveness and adequacy of the hyperventilation procedure as it is being conducted.

Although $ETCO_2$ measurements are used in emergency departments and intensive care units to early detect respiratory depression or the level of sedation [28], $ETCO_2$ level is not always correlated with tissue oxygen saturation [29]. The NIRS-assisted oximetry readings raise the clinician's awareness of recognizing the hyperventilation-related cerebral arterial vasoconstriction. This technique requires, however, trained personnel and involves supplementary costs compared to $ETCO_2$ devices [30].

We must emphasize that there are systemic and brain variables that influence the measured cerebral saturation in oxygen. Confounding factors for brain oxygenation changes assessed by NIRS during hyperventilation test are the local neuronal activity and the neurovascular coupling reflex, vasomotricity of brain vessels in response to mean arterial pressure changes, muscle activity, and autonomic nervous system activation [31]. Recently, all these physiological systemic parameters have gained attention for fNIRS neuroimaging analysis, and a new method was developed, the systemic physiology augmented functional near-infrared spectroscopy (SPA-fNIRS), which allows a more comprehensive interpretation of the brain fNIRS signals [32].

Additionally, we observed that the presence of clinical symptoms described in many of the studies involving hyperventilation (e.g., dizziness, numbing of the extremities, or sensations of paresthesia) [33] was reported by seven of the subjects. All of them presented a reduction in $ETCO_2$ equal to or greater than 26% coupled with changes in oximetry readings consistent with the occurrence of cerebral vasoconstriction. The absence of symptoms does not preclude effective hyperventilation. During anamnesis, it is important to inquire about relaxation techniques based on hyperventilation that the subject might practice, as such breathing relaxation methods are becoming increasingly popular [34]. In such patients, we did not notice any change in the cerebral oximetry despite the hyperventilation.

We believe that the cerebral activation test based on eliciting brain blood flow changes through hyperventilation is still an important method of evaluating cerebral reactivity, even in the face of other alternative minimally invasive methods [35,36]. However, for it to

be adequately performed, the subject must be monitored with a cerebral oximeter and with a sensor capable of measuring $ETCO_2$.

5. Conclusions

The vasoconstriction process in the brain's circulatory system in response to hyperventilation is heterogeneous, with individual variations. The hyperventilation procedure utilized in clinical practice depends on many variables, and it should be backed by an $ETCO_2$ decrease of at least 26% (AUC-ROC = 0.93) from the baseline. This is necessary because a respiratory rate that is double compared to baseline does not automatically translate into a significant rise in actual alveolar ventilation. Cerebral oximetry monitoring (NIRS) could also be included in the clinical protocol as a measure to validate the procedure. NIRS has the advantage of being a noninvasive technique providing useful real time information about vascular status in the investigating area. In some special situations, such as holotropic respiration, NIRS is requested because these kinds of patients seem to have other cutoff values. Regarding the length of the procedure, it should be between 2 min and 4 min. Further studies involving imaging are needed to confirm the $ETCO_2$ cutoff for the hyperventilation test.

Author Contributions: Conceptualization B.P. and A.-M.Z.; methodology B.P. and S.I.; formal analysis, D.B., S.S., S.I., C.I.B. and B.P.; investigation D.B., S.S. and B.P.; writing—original draft preparation, D.B., S.S., B.P., C.D.M.Z. and A.M.P.; writing—review and editing, B.P., A.-M.Z., C.D.M.Z., A.S. and A.M.P. All authors read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Clinical Emergency Hospital of Plastic Surgery and Burns, Bucharest, Romania (No. 2/19.06.2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. The Recorded Parameters for All the Volunteers Enrolled in the Study: RR—Respiratory Rate, $ETCO_2$—End-Tidal CO_2.

Subject	Basal (RR)	RR at 2 Min	RR at 4 Min	Basal $ETCO_2$	$ETCO_2$ at 2 Min	$ETCO_2$ at 4 Min
II	10	22	23	36	30	29
VM	12	24	22	42	32	34
EC	13	22	20	47	29	25
CT	12	24	19	38	27	32
AA	10	21	22	43	34	36
PR	10	21	19	38	28	24
IA	10	22	22	40	32	30
BD	12	20	24	40	31	31
CD	10	20	20	37	25	26
MB	12	24	20	34	28	30
GM	10	20	20	35	25	25
NM	10	20	20	34	22	18
CZ	10	20	22	30	18	17

Table A1. *Cont.*

Subject	Basal (RR)	RR at 2 Min	RR at 4 Min	Basal $ETCO_2$	$ETCO_2$ at 2 Min	$ETCO_2$ at 4 Min
AG	10	20	21	41	25	24
AC	10	20	22	33	20	19
VM	10	22	22	34	26	21
AD	10	20	21	28	20	19
DF	11	20	20	42	37	37
CS	10	20	19	38	32	31
VLS	10	20	20	37	30	29
PB	10	20	21	40	23	19
MD	12	23	23	40	26	23
MM	10	25	26	35	22	22
NA	9	27	25	30	19	19
SD	9	17	18	33	19	14
PRI	8	23	21	39	23	23
DM	10	23	26	32	30	26
LC	11	23	25	34	19	16
PO	10	25	24	40	22	21
MA	9	20	21	42	26	24
PV	10	19	26	40	28	19
UA	15	34	35	37	32	31
BM	10	20	23	39	26	25
MP	10	22	20	29	24	22
AD	14	33	30	34	25	26
RB	11	25	25	36	32	30
TB	10	24	25	34	26	24
AN	12	22	23	39	35	34
ALI	8	18	19	39	28	26
AMIR	11	20	20	31	24	23
EF	9	22	20	33	20	17
CNI	11	19	20	31	26	26
DIL	14	28	30	30	16	26
CHT	10	20	20	30	20	19
CIC	9	18	18	37	28	21
RNS	7	14	14	27	21	19

Table A2. NIRS Changes and the Amount of End-Tidal CO_2 Variation for Each Subject.

Subject	NIRS Change	Delta CO_2 (%)
II	Yes	20
VM	No	20
EC	Yes	39
CT	Yes	29
AA	No	21
PR	Yes	27
IA	Yes	20
BD	Yes	23
CD	No	33
MB	No	18
GM	Yes	29
NM	Yes	35
CZ	Yes	40
AG	Yes	40
AC	Yes	40
VM	Yes	24
AD	Yes	29
DF	No	12
CS	No	16

Table A2. *Cont.*

Subject	NIRS Change	Delta CO_2 (%)
VLS	No	22
PB	Yes	53
MD	Yes	43
MM	Yes	37
NA	Yes	37
SD	Yes	57
PR	Yes	41
DM	No	19
LC	Yes	53
PO	Yes	48
MA	Yes	43
PV	Yes	53
UA	No	16
BM	Yes	36
MP	No	24
AD	Yes	26
RB	No	17
TB	No	29
AN	No	13
ALI	Yes	34
AMR	No	23
EFL	Yes	49
CNIC	No	17
DIL	Yes	47
CHTAS	Yes	37
CCIOT	No	25
RNS	Yes	30

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