SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

The application of near infrared spectroscopy under different circumstances

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UNIVERSITY OF DEBRECEN

DOCTORAL SCHOOL OF NEUROSCIENCES

DEBRECEN, 2021

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The Examination takes place at the library of Department of Pulmonology, Faculty of Medicine, University of Debrecen, 09th of June 2021 at 11:00.

Head of the **Defense Committee**:	Miklós Antal, MD, PhD, DsC
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Members of the Defense Committee:	Endre Nagy, MD, PhD, DsC
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The PhD Defense takes place at the Lecture Hall of Department of Pulmonology, Faculty of Medicine, University of Debrecen, 09th of June 2021 at 13:00.

Abbreviations

NIRS: near-infrared spectroscopy

CW NIRS: continuous-wave NIRS

SRS: spatial resolution spectrometry

MCW NIRS: multi-channel continuous-wave NIRS

TD NIRS: time domain NIRS

FD NIRS: frequency domain NIRS

TCD: Transcranial Doppler Ultrasound

ACCP/SCCM: American College of Chest Physicians/Society of Critical Care Medicine

PaO2: partial arterial oxigen pressure

PaCO2: partial arterial carbon dioxid pressure

FiO2: oxygen concentration of inhaled air

GPT: glutamic pyruvic transaminase

γ-GT: gamma-glutamyltransferase

AP: alkaline phosphatase

LDH: lactate-dehydrogenase

RASS: Richmond Agitation and Sedation Score

rSO2: regional tissue oxygen saturation

AZ: acetazolamid

CBF: cerebral blood flow

CBV: cerebral blood volume

CMRO2: cerebral metabolic rate

Introduction

Advances in medicine are solving more and more problems as well as discovering new ones. The evolving instrumentation makes it possible to study the functioning of the human body more and more accurately. The basic research of the previous centuries now allows the application of modern examination methods that we could not have dreamed of before, and this creates an opportunity to clarify the cause of the diseases and then to cure them.

In recent decades, an ever-widening array of methods for studying the blood supply, oxygen supply, and metabolism of the brain have been introduced. In addition to functional imaging procedures, electrophysiological methods, and ultrasound examinations, bedside non-invasive methods are becoming increasingly important. In critical conditions and during diagnostic or therapeutic interventions that potentially cause brain perfusion and oxygen supply disruption, it is important to obtain regular information about brain blood flow and oxygen saturation of brain tissue.

Nowadays, one of the important tools for non-invasive examination of cerebral oxygen supply is near-infrared spectroscopy (NIRS). Although there are many limitations of NIRS, its positive features include easy accessibility, low cost, portability, real-time measurement, and the fact that it does not require special skills from its user. The aim of our studies was to investigate the application of NIRS in some situations that occur in everyday clinical practice and have not been studied in the literature so far. In my dissertation, I present first the physical basis of the NIRS method, the limitations of its application, and then summarize the experience gained during its clinical application. The second half of the dissertation is the presentation and discussion of the results of our own research using the method.

Clinical applications of NIRS

NIRS is a non-invasive test method, easy to carry due to the size and construction of the instrument, and has become more widespread in clinical practice in the last decade.

The light source and sensors mounted on the head allow it to be used on a moving patient, as well as on infants and inpatients. It can also be useful in neurology, cardiology, psychology, and in anesthesiological aspects of various surgical procedures. Although there are potentially several methods available to monitor cerebral oxygen saturation in anesthetized patients, in 10% of cases, transcranial Doppler ultrasound is not feasible due to the lack of temporal bone window, while EEG and somatosensory evoked potential are affected by anesthetics, and the

intraoperative use of these methods is technically difficult to perform. In the following I summarize the most common areas of clinical application of NIRS.

Carotid endarterectomy has more than 2% stroke risk associated with the procedure. Shunt implantation, induced hypertension, and supplemental oxygen therapy can be used to prevent potential cerebral ischemia during surgery. There are several methods that can be used to detect cerebral hypoxia that develops during surgery. If surgery is performed under regional anesthesia, the change in the patient's mental state is the best alarming signal for us. In the case of general anesthesia, we have a more difficult task, in this case the EEG, transcranial Doppler ultrasound (TCD), or the evaluation of the somatosensory evoked potential can be used to detect the risk of cerebral ischemia, but due to the previously mentioned difficulties, NIRS can be used. Several studies have been conducted examining the possibilities of NIRS, based on these results NIRS does not appear to be significantly better than other methods in detecting cerebral ischemia. This is mainly due to the variability of the threshold used during NIRS. However, in terms of clinical applicability, NIRS is easy to handle, has good time resolution, and is not operator-dependent in use. In the case of bilateral registration, the change in cerebral oxygen saturation on both sides during the cross-clamp period can be easily compared. In general, a reduction in oxygen saturation of more than 20% on the affected side is considered significant after the cross-clamp period. Several studies have attempted to define an oxygen saturation limit indicating shunt insertion based on a comparison of the saturation values on both sides, but the results of the studies are inconsistent in this regard.

Perioperative stroke occurs in 1-3% of patients during *heart surgery*, and in more than 50% of patients develop cognitive dysfunction in the postoperative period. These problems can be caused by embolization and cerebral hypoperfusion. Various protocols have been developed to minimize these problems, including procedures to optimize NIRS-controlled brain oxygen delivery. Although the study data are not convincing enough, NIRS is still used by more and more people due to the cost-effectiveness and lack of risks of noninvasivity. In addition, some results suggest that not only surgery but also comorbidities may play a role in the neurocognitive decline following cardiac surgery.

The literature of NIRS used in *thoracic surgery* anesthesia is even less detailed today. The possibility of cerebral desaturation should also be considered in this patient population, as it may occur in greater numbers during one-lung ventilation, than in cardiac surgery. A study by Kazan et al. examined 50 patients who had undergone thoracic surgery and found that 87% of the patients had a cerebral oxygen desaturation of more than 15% from baseline. There may be

several causes of cerebral hypoxia during surgery: systemic desaturation due to one-lung ventilation, mediastinal displacement and decreased cardiac output, pulmonary arteriovenous shunt, increased central venous pressure and decreased cerebral perfusion pressure. This desaturation can be avoided by using normocapnia-drived pulmonary protective one-lung ventilation. However, further investigation of the association between postoperative cognitive dysfunction and cerebral hypoxia is required.

Other intraoperative applications and use of NIRS: The position of patients with hyperextension of head and neck during thyroidectomy decreases carotid artery blood flow and can worsen cerebral oxygen saturation. During prostatectomy, hemodilution and hypotension can cause the same thing. During abdominal surgery, cerebral desaturation was observed in 26% of patients. In spinal anesthesia, hypotension can also decrease the cerebral oxygen levels. These studies were more sporadic observations and generally did not cover how to prevent or treat a decrease in cerebral oxygen saturation during the intraoperative period.

Intensive therapy: Although continuous development of intensive care has resulted in significant reductions in mortality, cognitive impairment is seen in 25-75% of critically ill patients. Patients with delirium have permanent memory impairment and verbal disturbances. Studies using NIRS have demonstrated that low cerebral oxygen saturation is an independent risk factor for the development of delirium. Septic patients represent a large proportion of cases of intensive care. Sepsis-related encephalopathy is a multifactorial process that can be caused by damage of the blood-brain barrier and cerebral macro- and microcirculatory and metabolic disorders. NIRS can also provide important information for this patient population. The most important pathophysiological process in acute brain damage is cellular ischemia, which can lead to secondary damage, and NIRS can also be a good choice. There have been only few studies on this topic that have examined disease outcome under NIRS control, or there is no clear definition of the ischemic threshold in the brain, so an appropriate and comparable therapeutic algorithm cannot be established. An additional problem may be that the presence of intracranial hematoma, subarachnoid blood, and cerebral edema may affect our assumptions underlying the NIRS algorithms.

Other applications: In addition to the study of cerebral ischemia, NIRS is also capable of detecting cerebral metabolic and hemodynamic changes in other diseases, thus providing information on neuronal functions and dysfunctions. For example, in Alzheimer's disease, a deficient or abnormal hemodynamic response to functional activation can be observed using NIRS. In epilepsy surgery, the speech area in brain, the epileptic focal point, and the type of

seizure can be localized preoperative by NIRS. In addition, various NIRS techniques give us more information about post-stroke pathophysiological processes and perfusion changes.

It should be mentioned that NIRS can be used in experimental anesthesiology to test different breathing modes and anesthetics, as well as in aeronautics and space medicine.

Objectives

In my dissertation, I would like to present my own research results in different applications of NIRS. We have mainly selected applications for which no literature data are available so far, but which are also of clinical significance.

1. First we aimed to study cerebral vasoreactivity in a septic patient population. We examined whether the cerebral vasoreactivity of patients with septic encephalopathy differs compared to healthy individuals.
2. In our second examination we studied how systemic and cerebral oxygen saturation change during diagnostic bronchoscopy with varying degrees of oxygen supplementation. Secondary endpoints of our study were the number and duration of desaturation episodes occurring during the intervention and its risk factors.

Patients, methods

First study: Assessment of cerebral tissue oxygen saturation in septic encephalopathy during acetazolamide provocation

Patients

Patients suffering from severe sepsis were selected from the perioperative intensive care unit at the Clinic of Anesthesiology and Intensive Care of the Clinical Center of the University of Debrecen. Only patients fulfilling the criteria of severe sepsis according to the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee were enrolled in our study. Severe sepsis was defined according to recent internationally accepted guidelines if hypoperfusion or dysfunction of at least one organ system was present in the patients. Only those with at least two organ manifestations related to the septic process entered the present study. Lung manifestation was considered if the ratio between the partial pressure of oxygen measured in arterial blood (PaO_2) and the fraction of inspired oxygen (FiO_2) was below 200. Kidney manifestation was considered if daily diuresis was < 500 ml along with an increased level of creatinine. Liver manifestation was diagnosed if the concentration of serum bilirubin and the liver enzymes (GPT = glutamic pyruvic transaminase; γ-GT = gamma-glutamyltransferase; AP = alkaline phosphatase; LDH = lactate dehydrogenase) were elevated.

Sepsis-related encephalopathy was defined as a combination of the following: patients had to meet the criteria of clinical sepsis and had to show disturbance of consciousness or alertness of any severity. A certified neurologist (BF) performed a detailed neurological assessment of all the patients in order to exclude direct infectious involvement of the central nervous system (such as meningitis or encephalitis). Sedative drugs were not administered before the neurological assessment. Consciousness disturbance was graded numerically according to the Richmond Agitation and Sedation Score (RASS).

Cerebral vasoreactivity testing

To assess cerebral vasoreactivity, 15 mg/kg BW acetazolamide (Diamox, Lederle Pharmaceuticals, Carolina, Puerto Rico, USA) was injected intravenously. Before starting the acetazolamide test, a cerebral oxymetry probe was placed on the forehead of both the patients

and the healthy subjects on both sides. INVOS 5100C Cerebral Oxymeter System (Somanetics Corporation, Troy, MI, USA) was used to monitor cerebral oxygen saturation. Readings of cerebral oxygen saturation were registered at rest and 5, 10, 15 and 20 minutes after injecting acetazolamide, which is in line with the methodology proposed in previous vasoreactivity tests. Parallel to cerebral oxygen saturation measurements, arterial blood was taken from a radial artery catheter in septic patients to perfom blood gas analysis. As it was considered that placement of an arterial catheter in healthy persons would be unethical, serial blood gas analysis in controls was omitted.

Statistical analysis

Before analysing the data, normality tests were performed. Means and standard deviations are shown for all values, if the samples were not normally distributed, median and 95% confidence intervals were used for district analysis and non-parametric tests were used for comparison. Repeated measure analysis of variance was used to detect differences in cerebral oxygen saturation values after acetazolamide administration. Pairwise comparisons were also performed between the groups using the Mann–Whitney U test. A P value of less than 0.05 was intended to be accepted as statistically significant.

Ethical considerations

The study was approved by the local Medical Ethics Committee of the University of Debrecen Clinical Center. The patients' nearest relatives gave written informed consent in all cases. In controls, the subjects gave informed consent.

Second study: Assessment of systemic and cerebral oxygen saturation during diagnostic bronchoscopy

Consecutive patients admitted to the Bronchology Laboratory of the Department of Pulmonology, University of Debrecen Clinical Center for flexible bronchoscopy from January 2018 to June 30 were asked to participate in the study.

Te indication of flexible bronchoscopy was based in all cases on the results of medical history, physical examination, chest X-ray and/or chest CT scan, lung function tests, and laboratory parameters including hemoglobin concentration and hemostatic variables as well as blood gas analysis when necessary. Bronchoscopy was performed in all cases with suspected lung cancer for the purpose of cytological or histological sampling.

Bronchoscopy was performed using the PENTAX EB-1975K (Pentax Medical, Hamburg, Germany) device after a fasting period of at least 4 hours. The procedure was performed in the supine position after topical administration of lidocaine 2% solution. Routine monitoring consisted of ECG, noninvasive blood pressure measurement, and pulseoximetry (finger probe). As an additional monitoring tool, a near-infrared monitoring sensor was placed on the forehead of patients' dominant hemisphere for monitoring cerebral oxygen saturation. An INVOS 5100C cerebral oximeter (Covidien LLC, 15 Hampshire Street, Mansfield, MA 02048, USA) was used for cerebral near-infrared spectroscopy measurements.

Patient grouping: Patients undergoing bronchoscopy were randomly assigned (presealed envelope randomization) to three different groups as follows:

- Group A (N=31 patients): patients in this group did not receive any oxygen supplementation during the procedure. Rescue supplemental oxygen through nasal cannula was provided if clinically significant desaturation could be observed during bronchoscopy. Significant desaturation was defined as systemic oxygen saturation ≤90% on pulsoxymetry or a relative change of ≥4% lasting for ≥1 minute. Cerebral desaturation was defined as a more than 20% decrease in rSO_2 compared to baseline measured using near-infrared spectroscopy.
- Group B (*N* = 31 patients): supplemental oxygen was provided for the patients through a nasal cannula by a flow rate of 2 litre/min throughout the procedure.
- Group C (*N* = 30 patients): supplemental oxygen was administered through a nasal cannula by a flow rate of 4 litre/min throughout the procedure.

The following data were collected or calculated in all patients prior to bronchoscopy for the sake of later analysis:

- hemoglobin concentrations (g / L),
- FVC% (forced vital capacity %),
- FEV1% (forced expiratory volume for 1 second expressed as a percentage)
- FEV1/FVC (Tiffeneau-index).

Parameters registered or calculated during the bronchoscopy procedure are as follows:

- pulse rate,
- systemic oxygen saturation using finger probe pulsoxymetry,
- cerebral tissue oxygen saturation (NIRS).

Study End Points

- Primary end point was defined as the incidence of systemic and cerebral desaturation in the three groups.
- Secondary end points were factors influencing systemic and cerebral desaturation.

Statistical analysis

Power analysis: As a first step, we performed a power analysis for determining the sample size. Based on our pilot study performed among ten patients, we observed a 3.1±1.2 decrease in systemic oxygen saturation during bronchoscopy without oxygen administration. Based on this, we hypothesized that administration of 4 litre/min oxygen through a nasal cannula results in a less than 1% decrease in systemic oxygen saturation. Using an alpha of 0.05 and a power of 90%, the necessary number of patients to be included was calculated as 30 per group. With a further "Apriori" power analysis, the required sample size for a one-way independent ANOVA analysis of "systemicO_2" within the 3 study groups was calculated. Te effect size (ES) in this study was considered large using Cohen's criteria. With alpha=0.05, power =0.9, and ES=0.4, the projected sample size per group was approximately N=27.39 using the power calculator of Australia and New Zealand Melanoma Trial Group (106). Thus, our proposed total sample size of 92 for the 3 groups (30+ samples per group) can be considered adequate for the major objectives of our study. Furthermore, a "sensitivity" power analysis was also performed

with a total sample size of 92, an average "systemic O_2" of 97.23, and a relative variance of 2.6%. We obtained a very large actual effect size ES=0.506 in our analysis.

Before starting statistical analysis, parameters in all groups were checked for normality by the Kolmogorov–Smirnov test. For normally distributed data, the t-test was used, whereas in the case of nonnormal distribution, the ANOVA test was used. Pearson correlation was applied for testing the relationship between systemic and cerebral oxygen saturations.

In order to check the changes in systemic and cerebral oxygen saturation during bronchoscopy, we applied the Hurst exponent calculations that indicate the probability of desaturation during the entire procedure. The more the Hurst exponent exceeds 0.5, the lower the probability of desaturation throughout the procedure is. In addition, higher values of the Hurst exponent refer to a stable trend of oxygen saturation.

Te Cox multiparametric proportional hazard model was used for assessing the underlying factors of systemic and cerebral desaturation. Te following parameters were considered as continuous parameters: gender, smoking, hemoglobin concentration, FVC%, FEV1%, and mean systemic O_2 saturation. A-C groups were considered as categorical variables in the multiparametric model.

Ethical considerations

Te study was approved by the Medical Ethics Committee of the University of Debrecen Clinical Center (registration number: 4989-2018) and was registered on Clinical Trials under the number of NCT04002609. After being given a detailed explanation of the procedure, all patients gave written informed consent.

Results

Assessment of cerebral tissue oxygen saturation in septic encephalopathy during acetazolamide provocation

Fifteen patients with severe sepsis and 10 age- and sex-matched control subjects entered the study. The most important clinical data of the septic patients are summarized in Table 1. 9 of the examined 15 septic individuals died in the later phase of intensive therapy.

Table 1. Clinical characteristics of septic patients

Patient Nr.	Age	Gender	Body temp (°C)	WBC (G/l)	CRP (mg/L)	PCT (µg/L)	PaO_2/FiO_2	Creatinine (µmol/L)	Bilirubin (µmol/L)	GPT (U/L)	Gamma-GT (U/L)	AP (U/L)	LDH (U/L)
1	66	N	37.2	16.4	228.2	73.5	162	167.0	20.6	12.0	76.0	287.0	452
2	65	F	37.9	10.6	28.3	42.8	405	226.0	20.1	5.0	255.0	602.0	536
3	77	N	37.5	18.0	199.6	124.2	387	53.0	8.6	42.0	399.0	277.0	677
4	51	N	37	13.3	101.2	23.8	355	473.0	10.0	11.0	63.0	353.0	480
5	78	F	37.7	15.0	306.5	2.5	217	99.0	32.0	82.0	154.0	408.0	540
6	62	F	37.7	10.2	262.8	9.2	163	143.0	39.0	75.0	63.0	197.0	459
7	88	F	38.6	4.2	173.7	11.7	437	80.0	11.0	32.0	48.0	178.0	410
8	65	F	37.8	13.0	391.6	62.8	178	143.0	16.0	21.0	27.0	121.0	367
9	86	N	38.1	3.4	245.5	13.3	265	106.0	43.3	68.0	151.0	492.0	388
10	63	F	36.9	22.4	223.0	21.9	380	129.0	7.8	93.0	71.0	254.0	1018
11	70	N	37.0	16.1	121.3	2.3	217	75.0	10.0	21.0	29.0	171.0	502
12	79	N	37.1	15.9	338.2	6.38	215	134.0	15.6	13.0	45.0	285.0	499
13	78	N	38	16.0	312.8	19.7	263	88.0	6.0	38.0	14.0	286.0	903
14	79	F	38.9	18.8	196.8	89.5	202	224.0	24.0	12.0	84.0	136.0	354
15	56	F	37.9	15.3	120.3	0.45	237	62.0	12.3	24.0	26.0	90.0	308

It is obvious from the presented data that all patients had at least one other organ manifestation due to the septic process besides the brain. The distribution RASS scores were in the septic group as follows: RASS –1 = 4 cases, RASS –2 = 7 cases, RASS –3 = 4 cases.

The effect of acetazolamide on PaO_2 and $PaCO_2$:

In septic patients serial arterial blood gas analysis measurements were performed before and after acetazolamide administration in order to assess changes in carbon dioxide and oxygen partial pressures. The results are summarized in figures 6 and 7. As shown, the administration of acetazolamide resulted in an increase of the partial pressure of CO_2, reaching a plateau at 10 minutes, then remained constant until the end of the study period (20 min) (figure 6).

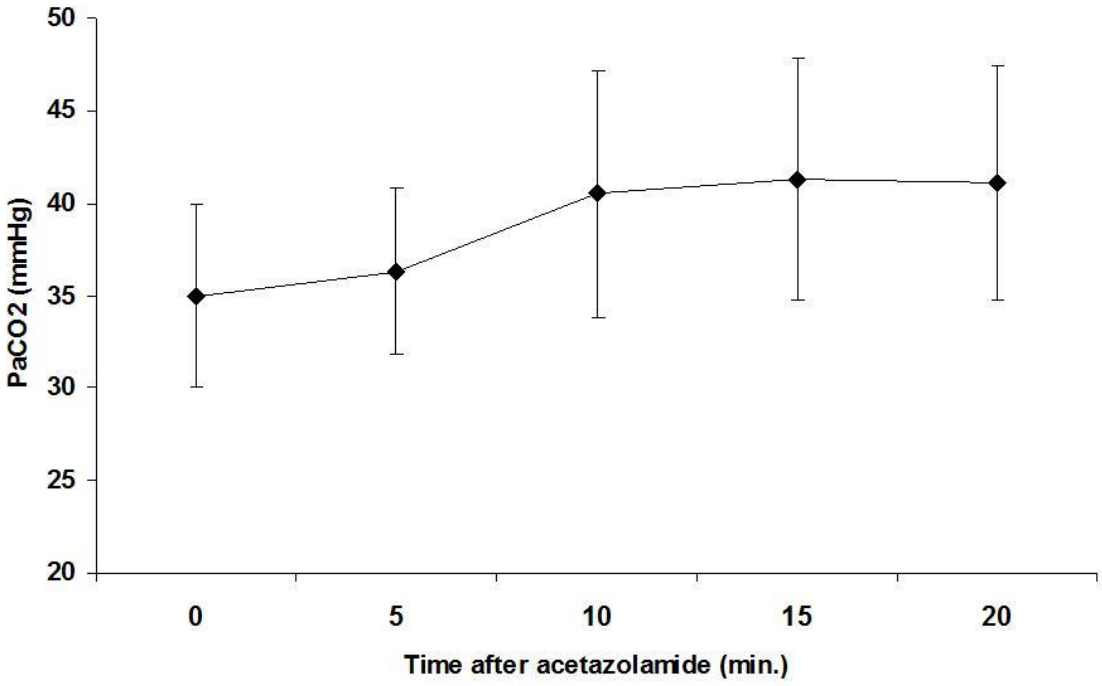

Figure 6. Change of arterial partial pressure of CO_2 before and after administration of acetazolamide (means and SD)

In contrast to this, although PaO_2 initially increased after acetazolamide administration, only a modest change was detectable in the partial pressure of oxygen during the course of the study (figure 7).

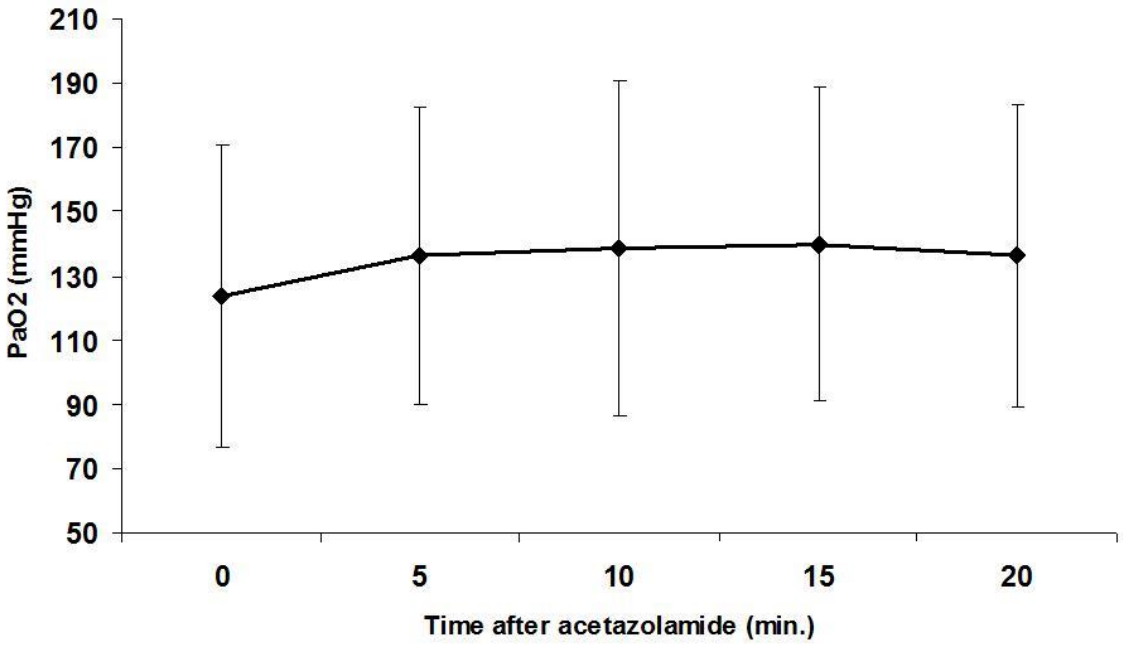

Figure 7. Change of arterial partial pressure of O_2 before and after administration of acetazolamide (means and SD)

Accordingly, a significant time main effect on the partial pressure of CO_2 was detected using repeated measures of ANOVA, suggesting that acetazolamide induced significant changes in $PaCO_2$. This was not observed in the case of PaO_2 .

Comparison of cerebral oxygen saturation between septic and control persons during acetazolamide provocation:

Administration of acetazolamide induced similar changes of absolute levels of cerebral oxygen saturation in both groups (8.9+-6.5% in septic patients and 9.2+-4.6% in controls). As demonstrated in Fig. 8, the slope and the shape of the acetazolamide curves in the two groups run in parallel, suggesting no difference in vasoreactivity.

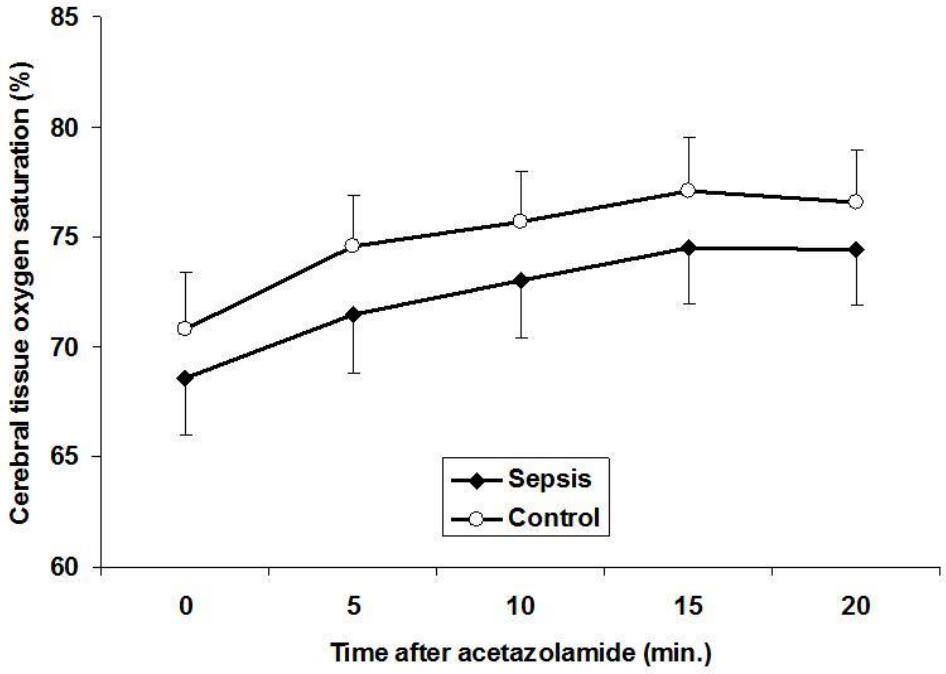

Figure 8. Changes of cerebral oxygen saturation in septic and control subjects.

Assessment of systemic and cerebral oxygen saturation during diagnostic bronchoscopy

Demographic parameters are summarized in Table 2. In the total cohort, the mean age was 61.9±12.7 years, with a female-male ratio of 40:60%. There were no differences between smokers and nonsmokers between females and males. However, females showed significantly higher preprocedural FVC% and FEV1% values.

Table 2. Demographic parameters and confounding factors (means and standard deviations, NS: nonsignificant)

	All group	**Men**	**Women**	**p-value**
Age (year)	61.9 (12.7)	62.8 (11.3)	60.5 (14.5)	NS
Smoking yes/no (%)	48.9/51.1	48.1/51.9	50/50	NS
FVC%	85.52 (23.13)	79.70 (21.26)	93.79 (23.44)	0.003
FEV1%	76.34 (25.21)	71.00 (23.97)	83.92 (25.29)	0.015

Primary end points

Average systemic and cerebral oxygen saturations before and during bronchoscopy are shown in Figure 9. The color codes for each column show the amount of O_2 used (white: no O_2 supplemetation, gray: 2 litre/min O_2, black: 4 litre/min O_2 through a nasal cannula).

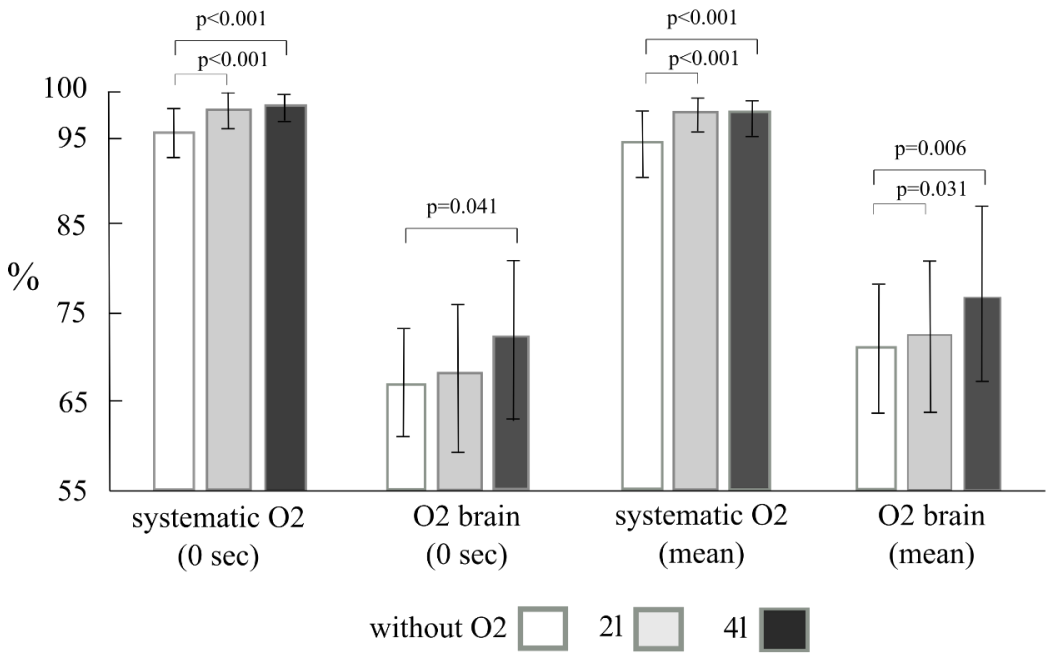

Figure 9. Absolute values of systemic and cerebral oxygen saturation at baseline (0sec) and average values during bronchoscopy (mean).

It is obvious from the figure that administration of any supplemental oxygen (2 litre/min or 4 litre/min) results in a significant improvement of both systemic and cerebral oxygen saturation. However, there were no differences in oxygen saturation values between the 2l/min and the 4l/min supplemental oxygen group.

In the entire cohort, systemic desaturation occurred in 18.5% of the patients (n=17). This corresponds to 5 patients (16%) in the O_2 (−) group, 6 patients (19%) in the 2 litre/min supplemental O_2 group, and 6 patients (20%) in the 4 litre/min supplemental oxygen group, respectively. The number of desaturations in the different groups did not reach the level of statistical significance (chi-square: 0.17; p=0.91). It has to be mentioned that detailed statistical analysis indicated that, in the O_2-negative group, the probability of desaturation is 41.7 times higher than that in the 2 litre/min supplemental oxygen group (p=0.014), while there was no difference in the probabilities of desaturation between the 2 litre/min and 4 litre/min supplemental oxygen groups (p=0.22).

Cerebral desaturation (more than 20% decrease in rSO2 compared to the baseline) did not occur in any patient in the three groups during the bronchoscopy procedure. There was no significant relationship between systemic desaturation and cerebral oxygen saturation as measured by near-infrared spectroscopy (Pearson correlation coefficient: −0.07).

Secondary end points

The effect of gender

Desaturation occurred in 22.2% of males, while it was observed in 13.2% of females. Men had a 9.3 times greater chance to develop systemic desaturation during the procedure than women, irrespective of supplemental oxygen administration (figure 10).

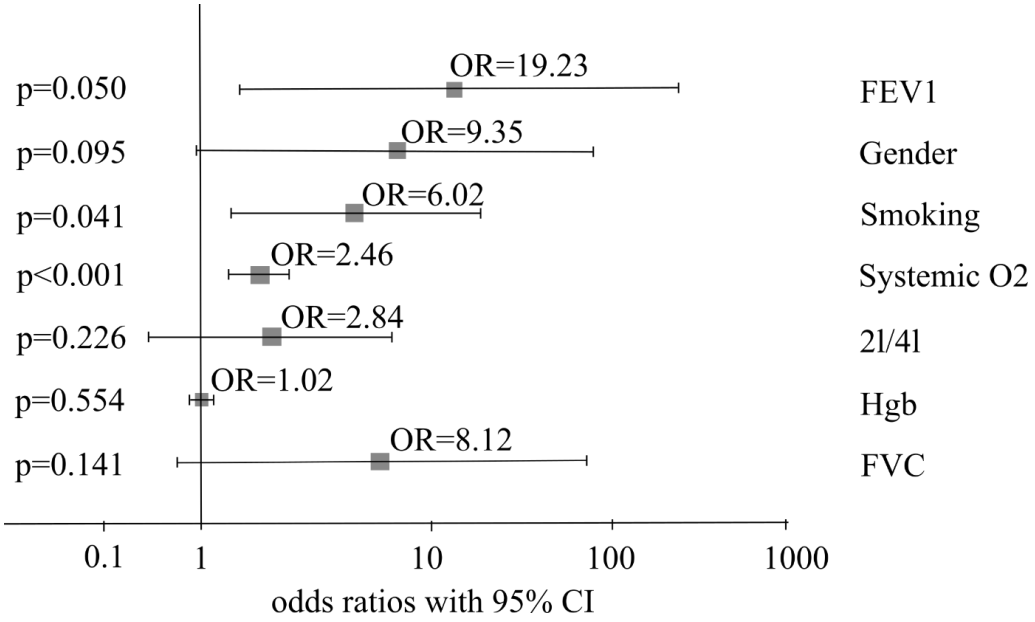

Figure 10. The effect of confounding factors on systemic desaturation.

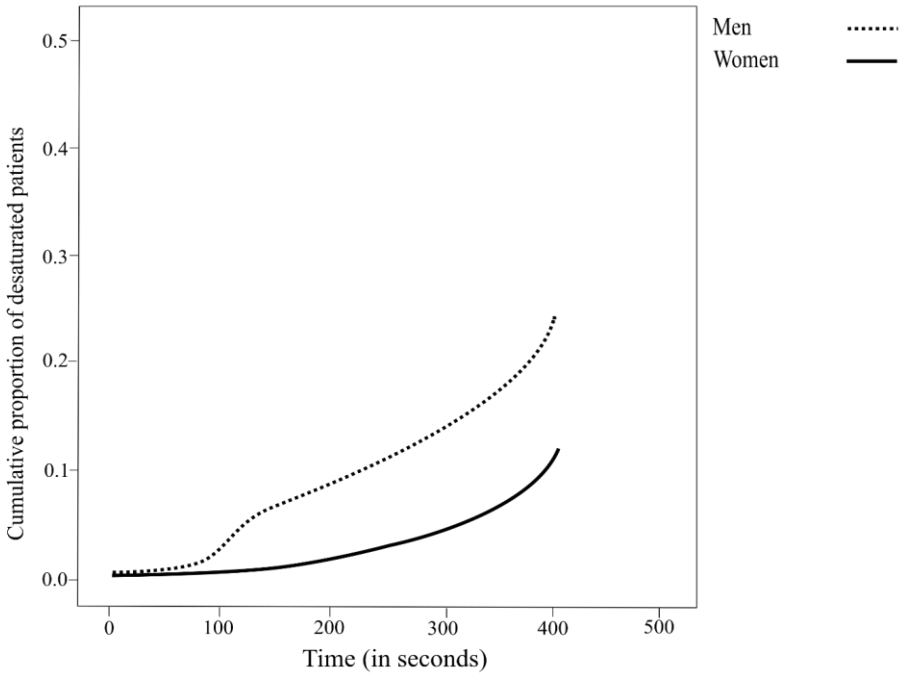

Figure 11. Cumulative proportion of systemic desaturations in female and male patients.

The time that elapsed between starting bronchoscopy and desaturation was 207±111sec for males and 226±138.3sec for females ($p<0.01$). Figure 11. demonstrates the cumulative proportion of systemic desaturations in female and male patients.

Based on a more detailed statistical analysis, in females, systemic oxygen saturation was stable throughout the procedure only if 4 litre/min supplemental oxygen was administered (Hurst exponent below 0.5), whereas in males, 2 litre/min supplemental oxygen resulted in stable systemic oxygen saturation during the entire course of the bronchoscopy procedure (Table 3.)

Table 3. Comparison of systemic O_2 saturation values in men and women at different supplemental O2 doses.

	Study group			Pairwise comparison			ANOVA F statistic
	O_2 (-)	2l/m	4l/m	O_2(-) vs. 2l/min	O_2(-) vs. 4l/min	2l/min vs. 4l/min	
	Man						
0 sec syst.O_2 %	95.20	97.79	98.25	-2.59*	-3.05**	-0.46	9.52***
Syst.O_2mean %	93.93	96.92	97.05	-2.99**	-3.12**	-0.13	5.22***
Hurst exp.syst. 0_2	0.48	0.59	0.75	-0.11	-0.27**	-0.16*	9.01***
	Woman						
0 sec syst. O_2 %	95.69	98.33	98.30	-2.65**	-2.61**	0.03	6.09**
Syst.O_2mean %	94.63	98.36	97.24	-3.73**	-2.61*	1.12	5.68*
Hurst exp. syst.O_2	0.42	0.49	0.70	-0.06	-0.27**	-0.21**	7.10**

Smoking

Desaturation occurred in roughly 20% of smokers, while it was observed in only 14% of nonsmokers. The risk of desaturation at any time point of the bronchoscopy procedure was 6-fold higher in smokers than in nonsmokers (Figure 10). In general, desaturation occurred in smokers after 194±114.6 seconds and in nonsmokers after 240±120.8 seconds. Figure 12. depicts the cumulative proportion of systemic desaturations in smokers and nonsmokers.

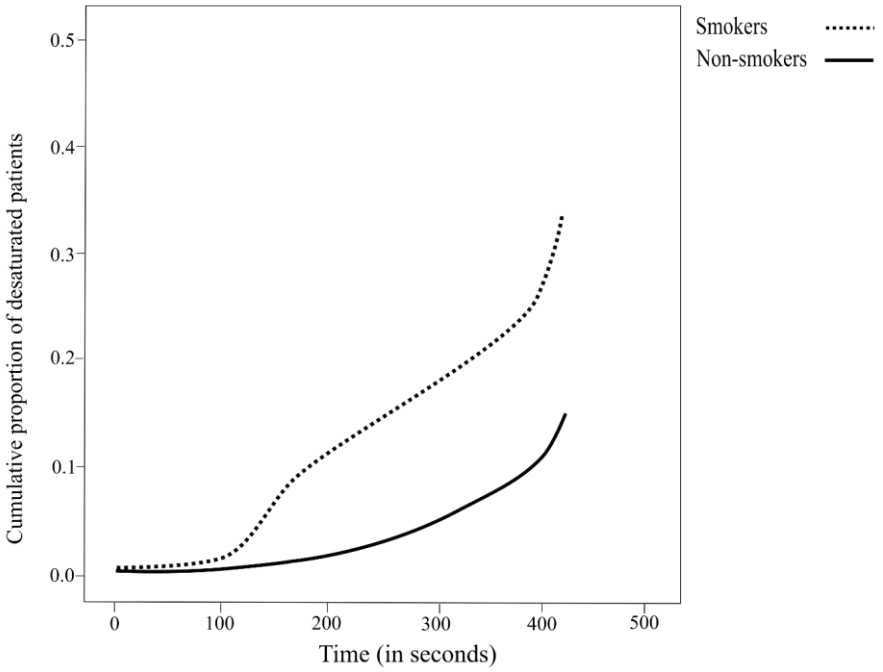

Figure 12. Cumulative proportion of systemic desaturations in female and male patients.

Other factors

Systemic desaturation was not influenced by hemoglobin concentrations. Based on the analysis, FEV1% was a significant determining factor in the development of desaturation (Figure 10). We found that every 100ml improvement in FEV1 reduced the risk of systemic desaturation by 50% during bronchoscopy. In contrast to this, FVC % did not have a significant impact on systemic desaturation. Systemic desaturation was also independent of age: the age of patients showing desaturation was 60.4±15.5 years vs. nondesaturation patients, 62.2±12.1 years; p=0.591.

Discussion

Due to the exponential technical development of recent decades non-invasive examination techniques are becoming increasingly important in anesthesiology and intensive care practice. Ultrasound diagnostics is widespread in the intensive care unit. In the past echocardiography was used almost exclusively, and now ultrasound diagnostics extends to the field of lung lesions and cerebral circulation bedside diagnosis. Hemodynamic monitors, which represent a new technology, are increasingly reliable and non-invasive in signaling changes in circulatory parameters. Information about the oxygen supply of the brain tissue in the cranial cavity can be obtained exclusively with the bedside or under surgical conditions using NIRS technology. As described in the literature review, the technology is still evolving. It needs to be clarified what threshold levels provide information indicating therapeutic intervention, and the range of clinical applications is also growing. In addition to clinical decision making, the method has also been used to study the pathophysiological changes in cerebral oxygenation during various conditions over the past 10 years. In the present dissertation, we aimed to examine two previously unexplored areas with NIRS technology, vasoreactivity in septic encephalopathy, and possible measurement of brain tissue desaturation during diagnostic bronchoscopy.

Assessment of cerebral tissue oxygen saturation in septic encephalopathy during acetazolamide provocation:

In the present study we compared changes in cerebral tissue oxygen saturation between patients suffering from severe sepsis and healthy subjects after acetazolamide stimulation. It was found that oxygen saturation was similarly influenced by the carbonic anhydrase inhibitor drug in the two groups.

For the sake of clarity, we have to recall that acetazolamide (AZ) is a drug that has been frequently used in the past decades for assessing the cerebral microvascular function in different conditions that affect the cerebral vasculature. It is a reversible inhibitor of the enzyme carbonic anhydrase which is located at the surface of the erythrocytes. The enzyme catalyzes the following reaction:

$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + CO3^-$

For obvious reasons, if the carbonic anhydrase is blocked by AZ, an accumulation of carbon dioxide occurs, resulting in slight and temporary hypercarbia and metabolic acidosis.

This increase in $PaCO_2$ has also been demonstrated in the present study. Hypercarbia is known as one of the most important vasodilatory stimuli at the level of the cerebral arterioles. Raising $PaCO_2$ leads to a dilation of the resistance arterioles of the brain resulting an increase in cerebral blood flow (CBF) and blood volume (CBV). These methods are used in various vasoreactivity tests: breath-holding, CO2 inhalation, or acetazolamide provocation test. These changes in CBF and CBV have been accurately demonstrated by different methods, such as single photon emission computed tomography, positron emission tomography and transcranial Doppler sonography. Recently it has also been suggested that acetazolamide-induced effects on CBF and CBV are reflected by changes in cerebral tissue oxygen saturation as measured by near infrared spectroscopy (NIRS).

The principal basis of NIRS is that photons emitted from the device are transmitted in an elliptical fashion through the cerebral tissue and the absorbed spectra reflect hemoglobin saturation in venous, capillary and arterial blood comprising the sample volume. Previous studies suggested that average tissue hemoglobin in the cerebral cortex is distributed in a proportion of ~70% venous and ~30% arterial. Using acetazolamide it has been demonstrated that a positive relationship exists between cerebral blood flow and cerebral tissue oxygen saturation changes. Thus, increases in CBF and CBV after AZ result in increased cerebral tissue oxygen saturation that corresponds to an average of 5.4 ± 3.2%. It has to be noted that in the present study, the maximal percent increase of cerebral oxygen saturation was 9.2 ± 4.6% for healthy persons and 8.9 ± 6.5% for septic patients. It has to be noted that the 9% increase in cortical oxygen saturation may be due to the differential effect of acetazolamide on arterioles. If cortical blood volume is 70% on the venous side and 30% on the arterial side then an increase in blood volume by one-third after acetazolamide on the arterial side would result in a 10/115 = 8.7% relative rise in the arterial portion of the cortical blood volume. Thus, the increase in cortical oxygen saturation could simply be the consequence of a higher proportion of oxygenated arteriolar blood in the tissue sample. Faster blood flow at the capillary level (without change in total intracapillary volume) may also result in decreased oxygen tissue uptake due to the shorter transit time – again, another explanation of somewhat increased overall tissue oxygenation. Brain tissue metabolic changes therefore are not necessarily involved in the tissue oxygenation changes found in the study.

Although our results seem to differ slightly from those of Kaminogo et al., it has to be noted that we used a dose of 15 mg/kgBW acetazolemide because previous studies indicated that this dose corresponded to the supramaximal dose in cerebral hemodynamic studies.

The results of the present study suggest that vasomotor reactivity to acetazolamide in severe sepsis is comparable to that in healthy controls. These observations are in accordance with previous CO_2 reactivity and autoregulatory test results performed in sepsis, but there have also been reports suggesting impaired vasoreactivity. According to our present knowledge on sepsis it is clear that there is an initial vasogenic phase of the septic process characterized by generalized vasodilation throughout the body. In the second, later course, however, mitochondrial dysfunction and energetic failure are the dominant contributors. This concept may give an explanation why patients with severe sepsis did not show altered cerebral vasoreactivity in different studies and why early sepsis without other severe organ dysfunction was shown to alter cerebral vasomotor responses.

As NIRS reflects the amount of saturated hemoglobin in the brain tissue, the results of the present study indicate that after stimulation with acetazolamide the hypercarbia initiated a vasodilation and a consequently increased CBF and CBV of similar magnitude, resulting in a comparably increased amount of oxyhemoglobin in the two groups. Unfortunately, we do not have information on cerebral metabolic rate for oxygen ($CMRO_2$) in the two groups, which could be considered a limitation of the present study. Theoretically it might be possible that in septic patients the breakdown of the mitochondrial energetic processes results in decreased $CMRO_2$ with a consequently higher oxygen saturation at the venous side. However, if this were the case, the local production of CO_2 would also decrease, which should result in local vasoconstriction with a consequently lower CBF and CBV.

As a matter of fact, acetazolamide induced arterial hypercarbia in septic patients, which was accompanied by an increased cerebral oxygen saturation. This may indicate that, independently of the energetic stage of the brain parenchyma vasodilatory reaction of the brain arterioles are preserved in severe sepsis.

Assessment of systemic and cerebral oxygen saturation during diagnostic bronchoscopy:

In this prospective, randomized study, we found that systemic desaturation occurs in 18.5% of patients, despite supplemental oxygen therapy. It should be noted that supplemental oxygen improved both systemic and cerebral oxygen saturation during the procedure and patients who did not receive oxygen supplementation had a 41.7-fold higher risk for systemic desaturation. Another main finding of the present study is that systemic desaturation did not become manifested in the cerebral tissue.

Systemic desaturation during bronchoscopy has been described much earlier. Its incidence varies between 2.5 and 69%, depending on the definition (threshold SpO_2 and duration of desaturation), even if no sedation is used. The systemic desaturation (defined as SpO_2 <90%) occurred in 69% during and in 72% after bronchoscopy in a study. In another study, the desaturation (SpO_2 <90%) was observed in 24% of cases, but lasted for 20–30s only in 14.4%. Others administered supplemental oxygen only for patients who experienced an SpO_2 value of <90% and found that it was necessary in 5.5% of cases. In a recent study, it was shown that, during bronchoscopies performed under light midazolam-fentanyl sedation, systemic desaturation rate may be close to 90%. In our study, desaturation (SpO_2 <90% and/or a >4% decrease, lasting for more than 60 seconds) occurred in 16%, 19%, and 20% of patients in the O2 (−), 2 litre/min, and 4 litre/min groups, respectively. Thus, despite supplemental oxygen administration, desaturation did occur in all groups. It should be noted, however, that systemic desaturation developed earlier and recovery after desaturation was longer in patients who did not receive O_2 supplementation.

We found that male gender, smoking, systemic oxygen saturation at baseline, and FEV1% were the most significant factors that contributed to systemic desaturation during bronchoscopy. In contrast to our results, Fang et al. were unable to prove the determining role of male gender in desaturation. In our cohort, it could be unequivocally demonstrated that desaturation is not only more frequent in males than females but occurs earlier, despite supplemental oxygen administration. Similarly, the risk of desaturation episodes was 6 times higher in smoking patients and desaturation developed earlier. Although we could not find previous studies proving these observations, an obstructive pattern on pulmonary function tests has been shown in previous studies as a predisposing factor of desaturation and the relation between smoking and obstructive disease is widely known. Te determining role of preprocedural FEV1 in the development of systemic desaturation has been documented in several studies.

To the best of our knowledge, this was the first study to assess systemic and cerebral oxygen saturation in parallel during flexible bronchoscopy. Our main goal was to assess oxygen saturation in the organ that is most sensitive to hypoxemia, especially during desaturation episodes. In previous studies, near-infrared spectroscopy was effectively used for assessing cerebral tissue oxygen saturation during thoracic surgeries. In the present study, no significant desaturation occurred in the cerebral tissue during bronchoscopy, despite systemic desaturations. It is conceivable that short-term systemic desaturations are counteracted by the

flow-metabolism coupling regulation of the brain tissue, preserving the brain tissue during short-term decreases of systemic oxygen saturation.

In conclusion, administration of supplemental oxygen does not prevent systemic desaturation during flexible bronchoscopy, but may contribute to a shortening of desaturation episodes and faster normalization of oxygen saturation. According to our results, 2 litre/min supplemental oxygen should routinely be administered to patients throughout the procedure.

Summary

NIRS is an evolving non-invasive technology that is already being used in many clinical areas. In my thesis, I presented two studies that had no precedents, but which help in the pathophysiological understanding of disease processes in septic encephalopathy and may contribute to the improvement of patient safety during diagnostic bronchoscopy.

The results of the NIRS septic encephalopathy study are mainly of pathophysiological value. The fact that we could not demonstrate an altered cerebral vasoreactivity in patients with severe spetic encephalopathy points on the determining role of other factors than vascular in the development of septic encephalopathy, presumably metabolic factors.

Our study in patients undergoing diagnostic bronchoscopy have direct clinically useful informations: We observed that –despite a significant systemic desaturation in certain patients- cerebral desaturation does not occur during the procedure. Additonally, we were able to show that administering supplemental O_2 during diagnostic bronchoscopy is of clinical importance to avoid systemic desaturation. It seems that a supplemental O_2 dose of 2 l/minutes is sufficient to prevent systemic desaturation in the majority of the cases. Another clinically important observation is that patients with male gender, smokers and those with reduced FEV1% values are the individuals at high risk to develop systemic desaturation.

Conclusions

1. For the first time in international literature, we used the NIRS method to examine the pathophysiological background of septic encephalopathy in the study of vasoreactivity after acetazolamide provocation. We found that cerebral vasoreactivity in patients with severe sepsis did not differ from control subjects.
2. We found that systemic desaturation occurs in 16-20% of patients during diagnostic bronchoscopy.
3. For the first time in international literature, we have established that despite systemic desaturation, desaturation of brain tissue does not occur.
4. We found that during bronchoscopy, systemic desaturation can be reduced by using nasal O2 at a dose of 2 l / min, and that increasing this dose to 4 l / min has no further beneficial effect.
5. We found that the most common risk factors for systemic desaturation during bronchoscopy were male gender, a history of smoking, and decreased FEV1% in respiratory function tests.

Keywords

near infrared spectroscopy, sepsis, sepsis-associated encephalopathy, cerebral vasoreactivity, acetazolamide, bronchoscopy

Acknowledgments

I am especially grateful to Csilla Molnár and Béla Fülesdi for their help in planning, conducting and interpreting the results.

I would like to thank Sándor Kovács and Szilárd Szatmári for their work and for helping me to create the publications.

Special thanks to my director of the clinic, Nóra Bittner.

I am grateful to the staff of the Department of Anaesthesiology and Intensive Care and the Department Pulmonology of the University of Debrecen, who stood by me and made it possible for me to do my work.

And last but not least, thank you for the perseverance and support of my family.

I recommend my dissertation to my family and colleagues.

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Registry number: DEENK/163/2021.PL
Subject: PhD Publication List

Candidate: Attila Vaskó
Doctoral School: Doctoral School of Neurosciences

List of publications related to the dissertation

1. **Vaskó, A.**, Kovács, S., Fülesdi, B., Molnár, C.: Assessment of Systemic and Cerebral Oxygen Saturation during Diagnostic Bronchoscopy: a Prospective, Randomized Study.
   Emergency Medicine International. 2020, 1-6, 2020.
   DOI: http://dx.doi.org/10.1155/2020/8540350
   IF: 0.841 (2019)
2. **Vaskó, A.**, Siró, P., László, I., Szatmári, S., Molnár, L., Fülesdi, B., Molnár, C.: Assessment of cerebral tissue oxygen saturation in septic patients during acetazolamide provocation - A near infrared spectroscopy study.
   Acta Physiol. Hung. 101 (1), 32-39, 2014.
   DOI: http://dx.doi.org/10.1556/APhysiol.101.2014.1.4
   IF: 0.734

List of other publications

3. **Vaskó, A.**, Bittner, N.: A D-vitamin és a COPD exacerbációja.
   Orvostovábbk. Szle. 26 (12), 47-50, 2020.
4. **Vaskó, A.**: Fix hármas kombinációs inhalációs terápia COPD-ben.
   Med. Thorac. 73 (5), 331-333, 2020.
5. **Vaskó, A.**, Mikáczó, A., Bittner, N.: Milyen mértékű középsúlyos, súlyos exacerbáció-csökkentés érhető el COPD-ben extrafinom fix hármas kombinációs kezeléssel?: gondolatok a TRINITY vizsgálat margójára.
   Med. Thorac. 73 (4), 286-292, 2020.
6. Végh, T., Juhász, M., László, I., **Vaskó, A.**, Tassonyi, E., Fülesdi, B.: Clinical observations on reversal of rocuronium-induced residual neuromuscular blockade by sugammadex after thoracic surgery.
   Romanian J Anaesth. Int. Care. 21 (1), 7-11, 2014.

7. Végh, T., Szatmári, S., Juhász, M., László, I., **Vaskó, A.**, Takács, I., Szegedi, L., Fülesdi, B.: One-lung ventilation does not result in cerebral desaturation during application of lung protective strategy if normocapnia is maintained.
Acta Physiol. Hung. 100 (2), 163-172, 2013.
DOI: http://dx.doi.org/10.1556/APhysiol.100.2013.003
IF: 0.747

8. **Vaskó, A.**, Végh, T., László, I., Takács, I., Szilasi, M., Fülesdi, B.: Reexpanziós tüdőödéma.
Orv. Hetil. 151 (41), 1708-1711, 2010.
DOI: http://dx.doi.org/10.1556/OH.2010.28949

9. Végh, T., Sira, G., Béczy, K., **Vaskó, A.**, Kiss, S. S., Fülesdi, B.: Kétlumenű endobronchialis tubus és a Coopdech endobronchialis blokkoló tubus egyidejű használata mellkassebészeti műtétek során.
Anaesthesiol. Intenziv Ther. 1, 41-47, 2009.

10. Végh, T., Sira, G., Béczy, K., **Vaskó, A.**, Kiss, S. S., Fülesdi, B.: Kétlumenű endobronchialis tubus és a Coopdech endobronchialis blokkoló tubus egyidejű használata mellkassebészeti műtétek során.
Anaesthesiol. Intenziv Ther. 39 (1), 41-45, 2009.

11. Csánky, E., Rühl, R., Scholtz, B., **Vaskó, A.**, Takács, L., Hempel, W.: Lipid metabolite levels of prostaglandin D2 and eicosapentaenoic acid recovered from bronchoalveolar lavage fluid correlate with lung function of chronic obstructive pulmonary disease patients controls.
Electrophoresis. 30 (7), 1228-1234, 2009.
DOI: http://dx.doi.org/10.1002/elps.200800722
IF: 3.077

12. Csánky, E., **Vaskó, A.**: Az idiopathiás tüdőfibrosis kivizsgálása és kezelése.
Tüdőgyógyászat 2 (7), 34-42, 2008.

13. Csánky, E., Asztalos, L., **Vaskó, A.**, Szűcs, I., Dévényi, K., Szilasi, M., Balla, J.: Sikeres vesetranszplantáció tüdőátültetés után: az első magyarországi eset ismertetése.
Orv. Hetil. 148 (45), 2147-2151, 2007.
DOI: http://dx.doi.org/10.1556/OH.2007.28129

14. Csánky, E., Asztalos, L., **Vaskó, A.**, Szűcs, I., Dévényi, K., Szilasi, M., Balla, J.: Succesful renal transplantation following lung transplantation: a survey of the first hungarian case.
Hung. Med. J. 1 (4), 509-515, 2007.
DOI: http://dx.doi.org/10.1556/HMJ.1.2007.28129

15. **Vaskó, A.**, Kiss, S. S., Dévényi, K., Ördög, C., Szilasi, M., Csánky, E.: A volumenredukciós műtét, mint kezelési lehetőség a korai stádiumú krónikus obstruktív tüdőbetegség terápiájában.
Orv. Hetil. 147 (43), 2091-2096, 2006.

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16. **Vaskó, A.**, Kovács, J., Fodor, A., Szilasi, M., Árkosy, P., Csánky, E.: A tüdőben perifériás kerekárnyék formájában jelentkező cysticus adenomatoid malformatio.
Orv. Hetil. 146 (17), 803-806, 2005.

17. Csánky, E., Szabó, P., **Vaskó, A.**, Szilasi, M., Lang, G., Klepetko, W.: Végstádiumú tüdőbetegségben szenvedő betegek kezelése: áttekintés a tüdőtranszplantációról négy eset kapcsán.
Orv. Hetil. 144 (15), 691-699, 2003.

Total IF of journals (all publications): 5,399
Total IF of journals (publications related to the dissertation): 1,575

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

07 April, 2021