Online Detection of Myocardial Ischemia by Near Infrared Spectroscopy with a Fiberoptic Catheter

D. Baykut[1], M. M. Gebhard[2], H. Bölükoglu[3], K. Kadipasaoglu[3], S. Hennes[1], O. H. Frazier[3], and A. Krian[1]

[1] Cinic of Thoracic and Cardiovascular Surgery, Heart Center Duisburg, Duisburg, Germany
[2] Department of Experimental Surgery, University Clinics Heidelberg, Heidelberg, Germany
[3] Cullen Cardiovascular Research Laboratories, Texas Heart Institute, Houston, Texas, U.S.A.

Background: The interruption of myocardial O_2-supply in acute myocardial ischemia causes differences in coronary venous O_2-content. In this study, the oxygenation status of coronary sinus blood is detected in myocardial ischemia by near infrared (NIR) spectroscopy. **Method:** For the intravascular application, a new fiberoptic catheter is developed. After calibration of the catheter by perfusion of blood with standardized gas mixtures in an *in vitro* experiment, the *in vivo* application was performed in 12 domestic pigs. The catheter was placed into coronary sinus and an anterior ischemia was induced by temporary occlusion of LAD. NIR graphs and hemodynamic data were obtained for 90 min ischemia and 90 min reperfusion time. **Results:** Main NIR-spectroscopic differences between oxygenated and de-oxygenated hemoglobin took place in O_2-concentrations less than 30%. Coronary sinus NIR spectra of hemoglobin-oxygen binding showed significant, reproducible differences between pre-ischemia, LAD-occlusion and reperfusion. NIR graphs also show variations related to CO_2-concentration, pH and temperature. **Conclusion:** The intravascular application of NIR spectroscopy could be a reliable tool in detection and follow-up of acute myocardial ischemia and infarction.

Key words: Near infrared – Detection – Myocardial ischemia

Introduction

Different oxygenation states of blood or tissue-bound chromophores such as hemoglobin or myoglobin can be differentiated by nearinfrared (NIR) spectral analysis. The tissue penetration of the NIR light (wavelength interval 700 – 2000 nm) is roughly 60 – 80 mm. This makes an ***in vivo*** application of NIR spectroscopy for oxygenation monitoring possible. Initial attempts in this field were made by *Jöbsis* et al. in 1977 [4], in order to evaluate the cerebral oxygenation status. Further development showed the monitoring possibility of virtually any tissue by using specific NIR absorption spectra of oxygenated (HbO) and deoxygenated (HbR) hemoglobin [2,3,8,10].

Spectroscopic tissue analysis under in vivo conditions needs specific light diodes (optodes) which usually work in a dual configuration with one emitting and the other collecting light transmitted through the tissue sample [1,3,4]. Collected NIR light is transferred by a fiberoptic cable to a photomultiplier and converted to an electric signal. Both signal analysis and data processing are performed by a computer [10]. The distance between emitting and collecting optodes is defined as the "path-length" of the NIR light used. The path-length is a factor which sets geometric limits for the in vivo application due to the required face-to-face positioning of optodes. Therefore, a dual optode configuration becomes bulky and is not overly suited fory *in situ* monitoring. In our study, we developed a special low-diameter catheter with a concentric layout of optic fibers. The fibers are pointed at the catheter's head, which makes the transport of NIR light possible to virtually any intravascular location, and can allow online monitoring of various internal organs upon their oxygen consumption, particularly during ischemia.

The acute ischemia of the myocardium, as a result of the coronary insufficiency, is determined by a substantial impairment of the oxygenation in affected myocardial areas. Considering the fact that the myocardium does not contain sufficient O_2-reserves, any interruption of the oxygen supply will inevitably lead to changes in the HbO/HbR-ratio of the coronary venous blood. The rationale behind our study is to evaluate the possibility of an *online* ischemia detection by a continuous intravascular spectral analysis of myocardial oxygen-bound chromophores with a fiberoptics catheter in the coronary sinus.

The *in vivo* evaluation of the method was based on an animal experiment with 12 domestic pigs undergoing a temporary occlusion of the left anterior descendent branch (LAD) and continuous NIR spectral analysis of ischemic changes in coronary sinus blood.

Thorac Cardiov Surg 2001; 49: 162 – 166
© Georg Thieme Verlag Stuttgart · New York
ISSN 0171-6425

Received for Publication: June 14, 2000

Downloaded by: Houston Academy of Medicine. Copyrighted material.

Materials and Methods

Catheter

The NIR catheter is a flexible device (Length: 1.5 m; Diameter: 2.6 mm) with coaxial configured optic fibers. The fibers are bundled in a concentric array of two groups: the one group transports the NIR light into blood, the other group collects it again. The tips of both emitting and collecting fibers are located at the catheter's head (Fig. **1**). The NIR light is transferred by emitting fibers to the catheter's head and then partly absorbed, partly reflected (or "back-scattered") from blood cells to the collecting fiber group of the NIR catheter. The continuous electronic conversion of the difference between emitted and collected NIR light gives the actual absorption spectra of HbO and HbR.

Spectrometer

For spectrometric measurements, an *Ocean Optics S 2000* miniature fiberoptic spectrometer with 2048 pixels and a wavelength range of 200 nm to 1100 nm was used. A stabilized tungsten-halogen light source was utilized. Spectral acquisition times were of the order of 2 sec per sample. In all of these embodiments, suitable software [Top Sensor Systems / SpectraWin® (version 4.0)] was provided so that appropriate data acquisition, graphing and data manipulation was possible. Prior to the animal experiment, an *in vitro* test was performed in order to simulate the changes in oxygen affinity of hemoglobin by using an oxygenator and a de-oxygenator for different grades of saturation with O_2 and CO_2 at varying temperatures. Corresponding NIR graphs were obtained continuously.

In vitro experiment

In a closed circuit with an oxygenator, de-oxygenator (perfusion with N_2 to eliminate O_2) and a pump, the tip of the NIR catheter was inserted into the bloodstream. Differences in O_2/CO_2-binding of hemoglobin in arterial and venous blood were simulated by pre-bottled constant gas mixtures at temperatures 37° C, 30° C and 27° C (Table **1**). The tests started with the "arterial" blood at the lowest O_2-level (10.0%). After an appropriate circulation time, the temperature was gradually reduced from 37° C through 30° C to 23° C. NIR graphs were registered at every concentration of O_2 in "arterial" and "venous" blood and blood gas analyses were performed.

Animal experiment

Detectable effects of an acute myocardial ischemia on HbO/HbR saturation of myocardial venous blood were evaluated in 12 domestic pigs by a temporary occlusion of the LAD on beating heart, following the insertion of the NIR catheter into the coronary sinus in an open-chest procedure. *Anesthesia:* Animal's food and water were withheld 24 and 12 hours respectively prior to the procedure. The following drugs and dosages were used as preanesthetics: *Atropine* (0.005 mglkg), *Acepromazine* (0.05 mg/kg i.m.), *Oxymorphone* (0.15 mg/kg). An angiocatheter was inserted into one of the right and left foreleg veins for fluid and drug administration. *Sodium penthotal* (10 – 15 mg/kg i.v.) was used as induction agent. Oral intubation was performed in the ventral recumbancy. *Isoflurane* (2 – 2.5%) was the anesthetic agent. ECG electrodes were placed on the foot pads on both forelegs and and the left hind leg. The animals were placed in dorsal recumbancy over a warming blanket. Temperature was monitored via rectal probe. For muscle relaxation, *Pancuronium bromide* (0.1 mg/kg i.v.) was used. Dosages were repeated as needed. *Heparin* (1 mg/kg i.v.) was administered prior to opening the pericardium. The dosages were repeated every two hours. A *lidocaine bolus* (2 – 2.5 mg/kg i.v.) and a *lidocaine drip* (0.5 mg/min) were given to prevent arrhythmic complications of subsequent ischemia and reperfusion. *Lidocaine* boluses were repeated as needed. At the end of the study, animals, still under general anesthesia, were

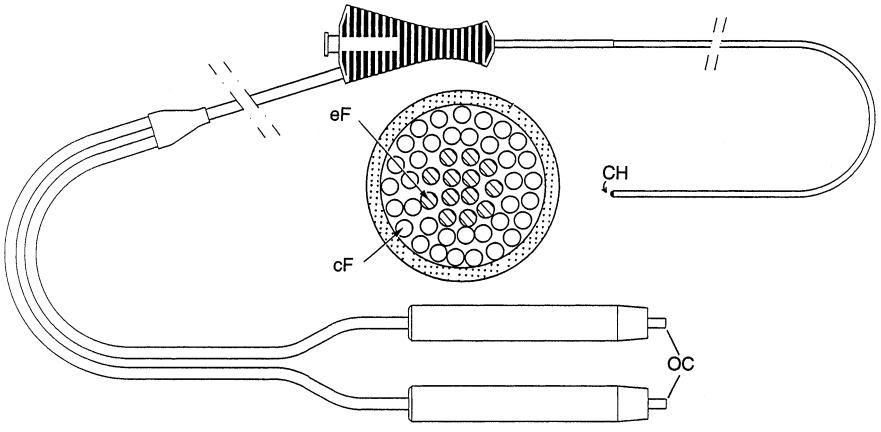


Fig. 1 The intravascular NIR spectroscopic detection catheter: CH: catheter's head; OC: optical couplings; cross section: cF: collecting fiber group; eF: emitting fiber group.

"arterial" gas mixtures	"venous" gas mixtures
Bottle 1: 10.0%O_2+ 5.6%CO_2 (+N_2)	Bottle 6: 90.0%O_2+ 9.0%CO_2 (+N_2)
Bottle 2: 30.0%O_2+ 5.6%CO_2 (+N_2)	Bottle 7: 70.0%O_2+ 9.0%CO_2 (+N_2)
Bottle 3: 50.0%O_2+ 5.6%CO_2 (+N_2)	Bottle 8: 50.0%O_2+ 9.0%CO_2 (+N_2)
Bottle 4: 70.0%O_2+ 5.6%CO_2 (+N_2)	Bottle 9: 30.0%O_2+ 9.0%CO_2 (+N_2)
Bottle 5: 90.0%O_2+ 5.6%CO_2 (+N_2)	Bottle 10: 10.0%O_2+ 9.0%CO_2 (+N_2)

Table 1 Standardized gas mixtures used in separate bottles for the in vitro-experiment

Downloaded by: Houston Academy of Medicine. Copyrighted material.

euthanised with *Beuthanasia* (0.22 mL/kg i.v.). *Surgery:* The pigs were positioned on dorsal recumbancy and the chest was opened via median sternotomy. Rhe right jugular vein was used for *Swan-Ganz*-monitoring. The left ventricular pressure was monitored via fluid filled catheter which was placed through a stab wound of the left ventricular apex. The NIR catheter was placed by opening the right atrial appendage and manually inserted into the coronary sinus. After baseline data acquisition, a string snare was placed around the LAD distal of the first diagonal branch. The ischemia lasted for 90 min, followed by the release of the occluder and reperfusion for additional 90 min. ECG and hemodynamic parameters registered continuously during the procedure. NIR data acquisition and blood gas analyses were performed every 30 min prior to, during and after the LAD-occlusion. After the experiment, gross pathological changes of the demarcated infarctation zones were evaluated and a histologic examination of the specimens was carried out.

Results

In vitro detection

The NIR spectroscopic analysis of arterial and venous blood showed identical absorbance patterns at any temperature with a minimum of the graphs at 660 nm in gas mixtures with 30–90% O_2-concentration, independent of the amount of the CO_2. At O_2-concentrations lower than 25–30%, the absorbance minimum drifted to 690 nm. The interruption of O_2-flow and the subsequent suppression of O_2 by N_2 in the de-oxygenator led to remarkable changes of the NIR graph pattern (Fig. **2**):

1. Increase of the absorbance at 660–665 nm;
2. Shift of the minimum from 690 nm to ca. 735 nm;
3. Formation of a new peak at 770 nm;
4. Isosbestic point between the graphs of oxygenated and de-oxygenated blood at 790 nm;
5. Reduction of the NIR-absorbance in higher wavelengths.

The time-related spectral changes of NIR graphs during de-oxygenation began within the first minute of the O_2-elimination with N_2, that the "arterial" NIR curve tended to be more "venous". Following 5 min of O_2-elimination, the graph demonstrated an entirely different pattern (Fig. **3**) with the typical features (1–5) mentioned above.

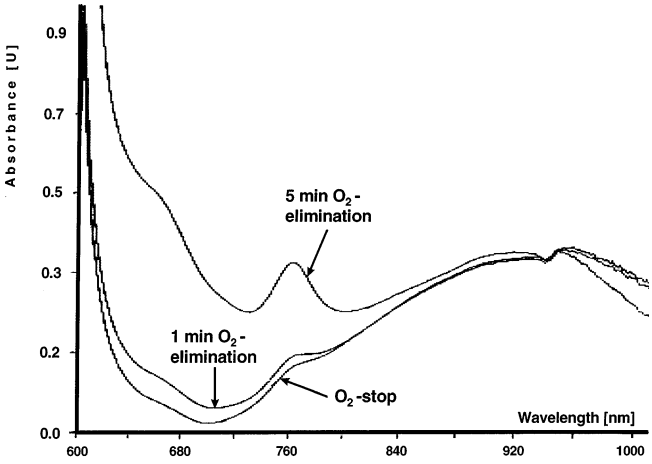


Fig. 3 In-vitro de-oxygenation with N_2: changes in NIR absorbance pattern at the time of O_2-flow interruption, 1 min and 5 min after continuous elimination with N_2. Note the significant increase of absorbance at 670–690 nm and the development of a new maximum at 770 nm.

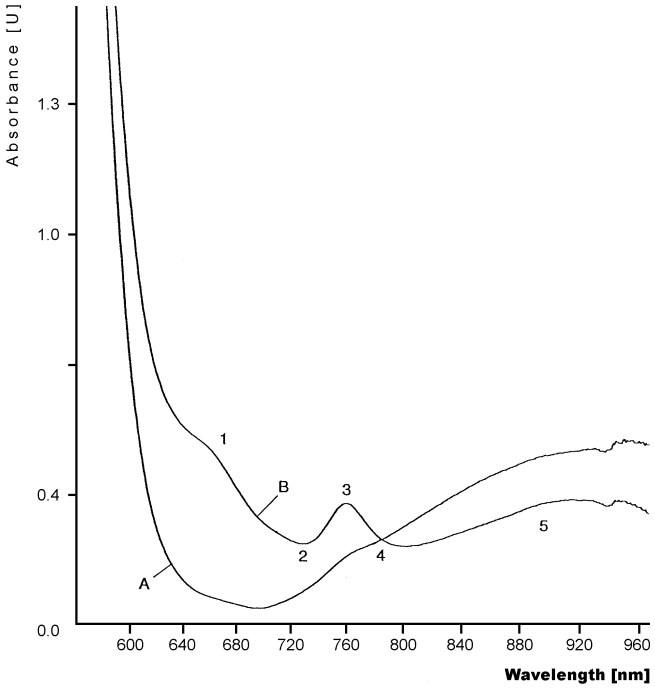


Fig. 2 Changes of the NIR absorbance pattern after perfusion with low (<30%) O_2-concentration (Graph B) compared to high O_2-concentration (>50%) (Graph A). The main spectral changes are indicated with numbers 1–5 (see text).

Animal experiment

Two animals were lost due sudden ventricular fibrillation immediately after LAD-occlusion. In the remaining 10 animals, this could be avoided by a short myocardial preconditioning by intermittent occluding and releasing the snare on the LAD. There was no remarkable difference between the arterial and venous baseline NIR graphs due to the relatively high oxygenation of the peripheral venous blood in pigs. The absorbance curve of the coronary sinus blood showed an NIR absorbance pattern which was identical to *in vitro* NIR graphs for O_2-saturation lower than 30%. The myocardial ischemia, which was set by the occlusion of LAD caused an obvious discoloration of the ischemic region with visual motion disturbances. Differences in hemodynamic parameters (heart rate, mean aortic pressure and left ventricular end-diastolic pressure) did not significantly change over time during the LAD-occlusion and reperfusion compared to baseline measurements, although typical acute ischemic ECG changes (ST-elevations, rhythm disturbances etc.) were evident. The central venous O_2 saturation did not show remarkable changes in blood gas analyses during LAD-occlusion and following reperfusion. In contrast, the NIR spectra of the coronary sinus blood showed a significant increase of the absorbance, especially at the 735 nm-minimum and 770 nm-maximum within the first 30 min of ischemia (Fig. **4**). The absorbance in wavelengths longer than 790 nm was reduced during ischemia compared to shorter wavelengths. However, after initial ischemic changes, a reduction of the elevated spectra up to the isosbestic point at 790 nm was

Downloaded by: Houston Academy of Medicine. Copyrighted material.

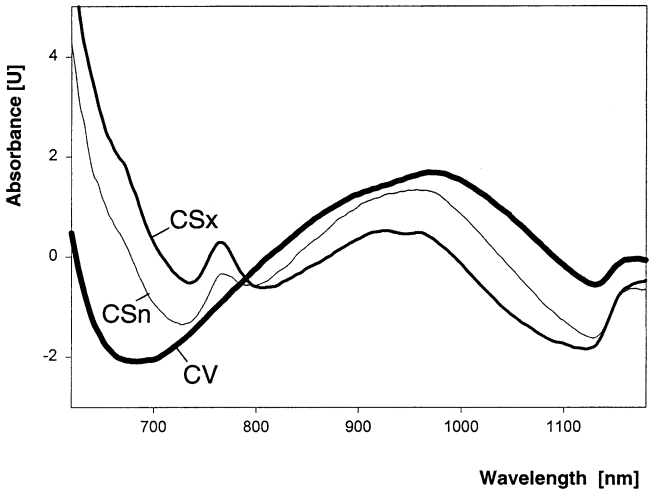


Fig. 4 Differences in the NIR spectra of the coronary sinus blood compared to baseline central venous sample (CV); in the coronary sinus before (CSn) and after ischemia (CSx).

observed between the 30. and 90. min of ischemia, together with a normalization of the hemodynamic parameters. This could be interpreted as a "recovery" of the affected myocardium. No remarkable differences were observed in the longer wavelengths of the NIR spectra. Absorbance curves 6 of 10 pigs could be evaluated and condensed in a mean absorbance graph pattern (Fig. **5**). Main spectral regions of interest for ischemic changes were pointed out at 735 nm (P1), 770 nm (P2) and 975 nm (P3) with significant absorbance differences in these areas (Table **2**). The end of the ischemic period (90th minute) was characterized by a still elevated absorbance at the maxima and minima of the graphs at wavelengths shorter than 790 nm, which, however, was not as high as compared to the initial 30 min of the LAD-occlusion.

After euthanasia of the animals, ischemic areas were sliced and underwent histologic and electron-microscopic evaluation to test for morphologic changes after ischemia. In all of the specimens, demarcated infarction zones with an extensive damage of cellular structures could be observed.

Table 2 Changes at the main points of interest (P1-3) on the intravascular NIR absorbance spectra from coronary sinus before and 30 min after setting of ischemia

Wavelength [nm]	Absorbance [U] LAD – open	Absorbance [U] LAD – 30 min occluded
735 (P1)	1.84 ± 0.37	2.52 ± 0.52 ($p < 0.05$)
770 (P2)	2.84 ± 0.10	3.60 ± 0.35 ($p < 0.01$)
975 (P3)	4.23 ± 0.34	3.53 ± 0.50 ($p < 0.05$)

Discussion

Technical feasibility

Using current technology, the NIR spectroscopic tissue analysis under *in vivo* conditions makes the use of optodes necessary, which should be configured face-to-face on the tissue to be examined to maintain a *definite* path-length [1,3,12]. Regular optodes are pads that have to be attached to the surface of the body. They are bulky devices and are not useful for in situ monitoring of internal organs due to their geometric configuration and the positioning required. Our experiments indicated that NIR spectroscopy could also be feasible for an intravascular application: By locating both emitting and collecting optodes at the tip of a fiberoptic catheter with a low diameter, very reliable results through reflectance in opaque media such as blood can be achieved. In our *single-location technique* with diodes at the catheter's tip, in contrast to the dual-optodes technique, the pathlength is *infinite,* and a "constant path-length" no longer needs to be considered in this form of spectral data acquisition. The NIR catheter can either be placed in the arterial system or inserted in the venous backflow from virtually any organ to detect its time-related specific oxygenation status.

Clinical value

The interruption of the myocardial oxygen supply by occluding an important coronary artery leads to a rapid de-oxygenation of the affected myocardial zone, originating from the continued consumption of oxygen. As a result, the coronary sinus blood shows differences in the NIR absorbance pattern of hemoglobin, with a rapid, significant turnover of HbO to HbR. In this initial phase of ischemia, the cellular damage occurs at a

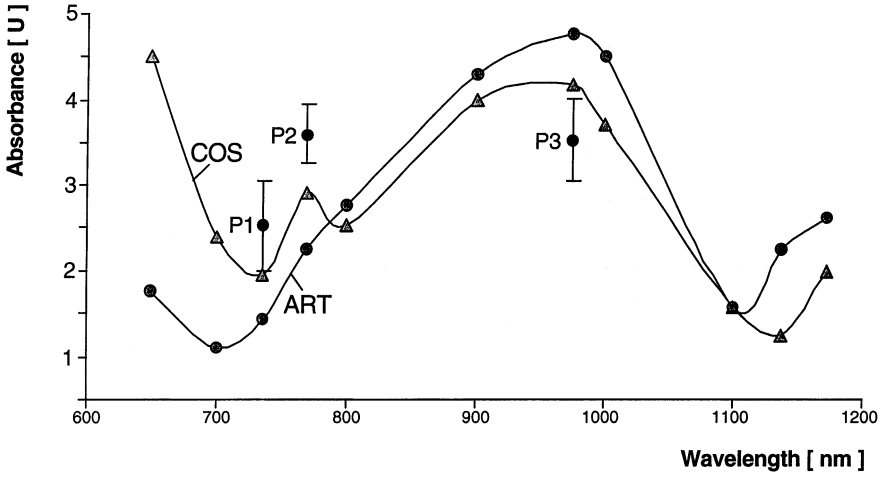


Fig. 5 Mean NIR absorbance pattern under *in vivo* conditions evaluated from 6 pigs: ART: arterial baseline graph; COS: coronary sinus baseline graph without ischemia. Bars at absorbance points of interest [735 nm (P1), 770 nm (P2) and 975 nm (P3)] show the standard deviation of ischemic changes within the first 30 min of LAD occlusion.

Downloaded by: Houston Academy of Medicine. Copyrighted material.

metabolic level and the cellular morphology is not impaired yet. Therefore, routine laboratory parameters originating from a structural injury such as Troponin-T/Troponin-I or CK/MB would not show any significant elevation. In our animal experiment, however, ischemic changes in the coronary sinus NIR pattern occured even *before* ST alterations in the ECG or impaired hemodynamic parameters observed. *Thorniley* et al. examined changes in hemoglobin and myoglobin oxygenation and volume to achieve information on tissue perfusion and flow in 9 pigs using NIR spectroscopy [11]. Although different data acquiring and processing techniques were used in their study and ours, the results show a broad similarity as we conclude on the usefulness of NIR spectroscopy to measure changes in myocardial oxygenation in response to ischemic episodes. The same conclusion was also reached by *Parsons* et al., who used NIR spectroscopic detection of myocardial ischemia in dogs in open-chest studies [7,8], declaring the application of NIR spectroscopy suitable for assessing the relation of tissue oxygenation to contractile function during ischemia. Both these studies, together with many others, demonstrate the species-independent characteristics of ischemic differences in myocardial tissue. In our study, we made the first attempt to access the myocardial venous backflow by NIR spectroscopy using an intravascular detection method by a fiberoptic catheter. The animal experiment with 12 pigs demonstrated that NIR spectroscopic measurements can show ischemia-related changes of chromophore oxygenation in coronary sinus blood, often earlier than ECG or hemodynamic parameters. This study is presently based on a semi-quantitative evaluation of observations. However, the *in situ* online/real time detection possibility of acute ischemic events could be more decisive for diagnostics and clinical outcome compared to current methods in ischemia monitoring. Our results definitely encourage the use of intravascular NIR spectroscopy as a reliable tool in detection, follow-up and prevention of the myocardial ischemia and/or infarction in cardiac surgery and cardiology.

Content of new physical data

Currently, NIR based monitoring is mainly used for the detection of tissue oxygenation, especially for cerebral measurements. The known pattern of NIR graphs in oxygenated and deoxygenated tissue samples are strongly related to the changes in the oxygenation states of different chromophores such as hemoglobin and tissue-dependent chromophores, i.e. cytochrome aa_3 [2,5,9,11]. In our isolated blood analysis, however, we found out that equal NIR spectra can be obtained in whole blood, which normally contains no free amounts of further chromophores than hemoglobin. In our opinion, the externally applied dual optode technique can quickly mislead to a conclusion with less exact NIR data interpretation due to the overlapping of blood- and tissue-bound parameters. In the current literature, the characteristic NIR graphs of hemoglobin are still considered as either "oxygenated" or "de-oxygenated", regardless of many additional possibilities in physiological variation of the hemoglobin structure during the oxygen transport process [1,6,13]. In addition, the hemoglobin-CO_2 binding, which takes place on a different location at the hemoglobin macromolecule, generally eludes a description in the current literature regarding to the effects of either pH-value as temperature. In the *in vivo* n part of our study, however, we could register various *"irregularities"* in the detailed analysis of different points of the NIR pectrum, which probably contain more physical information from pO_2, pCO_2, pH-value and blood temperature. The continuous, reproducible changes of absorbance spectra, as we observed in this first intravascular application of the NIR spectroscopy *in vivo* by a fiberoptic catheter, could allow a more profound understanding of tissue oxygenation and de-oxygenation.

References

[1] Cope M, Delpy DT. System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by near infrared transillumination. Med Biol Eng Comput 1988; 26: 289 – 294

[2] Gagnon RE, Gagnon FA, Macnab AJ. Comparison of 13 published cytochrome c oxidase near-infrared spectroscopy algorithms. Eur J Appl Physiol 1996; 74: 487 – 495

[3] Irwin MS, Thorniley MS, Doré CJ, Green CJ. Near infra-red spectroscopy: a non-invasive monitor of perfusion and oxygenation within the microcirculation of limbs and flaps. Br J Plastic Surg 1995; 48: 14 – 22

[4] Jöbsis FF. Non-invasive, infra-red monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 1977; 198: 1264 – 1267

[5] Macnab AJ, Leblanc J, Gagnon FA, Gagnon RE. Near infrared spectroscopy oxidized cytochrome aa_3 patterns of change during cardiac surgery in children. Pediatr Res 1995; 38: 442

[6] Matcher SJ, Elwell CE, Cooper CE, Cope M, Delpy DT. Performance comparison of several published tissue near-infrared spectroscopy algorithms. Anal Biochem 1995; 227: 54 – 68

[7] Parsons WJ, Rembert JC, Bauman RP, Greenfield JC Jr, Piantadosi CA. Dynamic mechanisms of cardiac oxygenation during brief ischemia and reperfusion. Am J Physiol 1990; 259: 1477 – 1485

[8] Parsons WJ, Rembert JC, Bauman RP, Duhaylongsod FG, Greenfield JC Jr, Piantadosi CA. Myocardial oxygenation in dogs during partial and complete coronary artery occlusion. Circ Res 1993; 73: 458 – 464

[9] Rhee P, Langdale L, Mock C, Gentilello LM. Near-infrared spectroscopy: Continuous measurement of cytochrome oxidation during hemorrhagic shock. Crit Care Med 1997; 25: 166 – 170

[10] Seiyama A, Hazeki O, Tamura M. Noninvasive quantitative analysis of blood oxygenation in rat skeletal muscle. J Biochem 1988; 103: 419 – 424

[11] Thorniley MS, Lahiri A, Glenville B, Shurey C, Baker G, Ravel U, Crawley J, Green CJ. Non-invasive measurement of cardiac oxygenation and hemodynamics during transient episodes of coronary artery occlusion and reperfusion in the pig. Clinical Science 1996; 91: 51 – 58

[12] Van der Zee P, Arridge SR, Cope M, Delpy DT. The effect of optode positioning on optical pathlength in near infrared spectroscopy of brain. In: Ed. By Püper J et al. Oxygen Transport to Tissue XII Plenum Press, New York 1990: 79 – 84

[13] Wray S, Cope M, Delpy DT, Wyatt JS, Reynolds EOR. Characterization of the near infrared absorption spectra of cytochrome aa_3 and haemoglobin for the non-invasive monitoring of cerebral oxygenation. Biochim Biophys Acta 1988; 933: 184 – 192

Dr. med. D. Baykut

Department of Cardiac and Thoracic Surgery
Kantonsspital Basel – Universitätskliniken
Spitalstrasse 21
4031 Basel
Switzerland

Downloaded by: Houston Academy of Medicine. Copyrighted material.