NON-INVASIVE MONITORING OF BRAIN OXYGEN METABOLISM
DURING CARDIOPULMONARY BYPASS BY NEAR-INFRARED
SPECTROPHOTOMETRY

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A new portable high performance apparatus for near-infrared (NIR) laser spectrophotometry was developed to monitor the oxygenation state of the human brain. Three different wavelengths of the NIR laser beam were used, 780, 805 and 830 nm, to illuminate the head through a fiber optic bundle. The amount of light reflected by or transmitted from the tissue was detected by a photomultiplier or photodiode. Equations as explained here, were used to calculate the oxy and deoxy Hb content and blood volume changes non-invasively. The equations were verified in vivo with the rat head in order to confirm the reliability and acceptability of our methodology. NIR monitoring was applied to 15 cases of cardiopulmonary bypass (CPB) in reflectance mode. The results demonstrated that using current CPB technique, cerebral oxygenation levels during bypass were maintained within the physiological range and changes in brain blood volume corresponded well to the pump flow balance. That is, the brain oxygenation level was maintained roughly constant at a mean perfusion pressure of over 60 mmHg during CPB, whereas below 50 mmHg, apparent decremental changes in oxy Hb content were observed. These findings led us to conclude that non-invasive monitoring of cerebral oxygenation using NIR light can provide valuable bedside data about tissue metabolism and allow for the proper management of critical patients.

Brain hypoxia and ischemia cause many severe disturbances in patients undergoing major cardiovascular surgery. Non-invasive methods are therefore required to monitor cerebral oxygenation and hemodynamics, thereby ensuring that the optimum amount of oxygen can be delivered to the brain and injury prevented. Biological tissue is relatively transparent to light in the near-infrared (NIR) region, from 700 to 1200 nm.

Key words:
NIR Spectrophotometry
Laser diodes
Brain Hb oxygenation
Brain blood volume
Cardiopulmonary bypass

We studied NIR transmission spectrophotometry using the two wavelength method, and confirmed that changes in oxy-hemoglobin (Hb), deoxy-Hb content, relative blood volume and oxidized cytochrome aa3 could be monitored quantitatively in the rat head using this technique.2 Recently we built a new, high performance apparatus for spectrophotometry using NIR light and applied this method to the monitoring of oxygenation in surgical patients.

METHOD

(1) The measuring system
A portable computer-controlled spectro-
A spectrophotometric measuring system was built whereby NIR light from three laser diodes (780, 805, and 830 nm) could illuminate the head through a fiber-optic bundle (ILG). The laser beams, which were emitted in turn using a time sharing mode, were coupled to one beam through the three-branched optical fiber in order to illuminate the tissue. Transmitted or reflected light was guided into a photomultiplier tube (R712, Hamamatsu) through a receiving fiber bundle (DLG). Recently, the photomultiplier was replaced with a silicone photodiode (S1723, Hamamatsu), which is directly placed on the skin surface. A block diagram of our system is shown in Fig. 1. Each output signal was amplified for 0.5 sec, processed by an 8-bit microcomputer, and the time course changes of calculated oxy, deoxy and total Hb values were recorded in real time using the equations outlined below. To compensate for drifting from the baseline, the amount of background light was measured at 6 second intervals and was subtracted from each output signal. The ends of the fibers were fixed to the scalp on the forehead at a mean distance of 3 to 5 cm with a black adhesive band to shield against background light.

(2) Calculation of oxy-Hb, and deoxy-Hb content

According to Lambert-Beer’s law, the following equations can be derived if we choose 3 suitable wavelengths

\[ \Delta A_{780} = K_{780} \Delta [HbO_2] + K'_{780} \Delta [Hb] \]  \hspace{1cm} (1)

\[ \Delta A_{805} = K_{805} \Delta [HbO_2] + K'_{805} \Delta [Hb] \]  \hspace{1cm} (2)

\[ \Delta A_{830} = K_{830} \Delta [HbO_2] + K'_{830} \Delta [Hb] \]  \hspace{1cm} (3)

where \( \Delta A_{780}, \Delta A_{805}, \Delta A_{830} \) are the absorption changes at wavelength 780, 805, 830 nm. \( K_{780}, K_{805}, K_{830} \) are absorption coefficients of oxy- and deoxy-Hb at each wavelength, and \([HbO_2]\), \([Hb]\) denote the change of oxy and deoxy Hb content. We could obtain these coefficients by measuring the absorbance changes of the fully oxygenated or deoxygenated red blood cell suspensions in vitro against changes of the hematocrit value. Thus the above equations (1) (2) (3) yielded

\[ \Delta [HbO_2] = -3 \Delta A_{805} + 3 \Delta A_{830} \]  \hspace{1cm} (4)

\[ \Delta [Hb] = 1.6 \Delta A_{780} - 2.8 \Delta A_{805} + 1.2 \Delta A_{830} \]  \hspace{1cm} (5)

\[ \Delta [Hb \text{ Volume}] = 1.6 \Delta A_{780} - 5.8 \Delta A_{805} + 4.2 \Delta A_{830} \]  \hspace{1cm} (6)

where \([Hb \text{ Volume}] = [HbO_2] + [Hb] \), is the change in blood volume. The details of this approach were reported by the authors elsewhere.\(^3\)\(^4\)

(3) Clinical cases

NIR spectrophotometry was carried out on 15 patients undergoing cardiovascular surgery using cardiopulmonary bypass (CPB)
in 12 cases and left heart bypass (LHB) in 3 cases. The age of patients was 5 to 76 years with the average 52±23.3 (S.D.). Selective brain perfusion was utilized in 3 cases during the repair of ascending and arch aneurysm. Mean monitoring time, 170±77.3 (S.D.) min, ranged from 70 to 300 min.

RESULTS

1) In vivo testing of the calculated Hb equations

To check the validity of the calculated Hb equations, changes in the absorbance of the three NIR wavelengths and in the calculated oxy and deoxy Hb content were measured in the anesthetized rat head when the inspired gas was changed from 95% O$_2$ to N$_2$. Fig. 2 shows that the calculated values changed by degrees in accordance with the decrease of O$_2$ concentration. At about 7% O$_2$ concentration, approximately 50% of Hb was deoxygenated, while on N$_2$ breathing, the total Hb became deoxygenated. When returned to 30% O$_2$ respiration the Hb oxygenation levels were restored to control levels. The absorbance at wavelength 805 nm, the isosbestic point, remained unchanged while O$_2$ concentration was kept over 7%. Thus, the reproducibility of this methodology was confirmed.

2) Brain oxygenation monitoring during cardiopulmonary bypass (CPB)

Figure 3 shows a case in which the aortic valve was replaced in a 65 year old patient. When the ascending aorta was declamped on the termination of ischemic arrest, the patient showed changes in oxy, deoxy Hb content and Hb volume in the brain, resulting from induced changes in the bypass flow rate. In response to the temporary fall in perfusion pressure, the oxy Hb content and Hb volume decreased to a greater degree in the former, and returned to the baseline level after the restoration of flow rate.

Figure 4 shows the case of a 71 year old patient who underwent aneurysmectomy in the proximal descending thoracic aorta under normothermic partial CPB. It shows the effect of temporary left carotid artery occlusion on brain Hb oxygenation. With a rapid fall in left temporal artery pressure, the cerebral oxy Hb content was reduced to some extent, but total Hb volume remained almost unchanged with a concomitant increase in deoxy Hb volume. This result can be explained by the active participation of cerebral autoregulation and collaterals from the opposite side.

Figure 5 shows the case of a 66 year old patient who underwent total replacement of ascending and arch aorta for his type-1 dissecting aneurysm under profound hypothermia. When his body temperature was...
Fig.5 No significant changes in brain oxygenation and blood volume during right or left carotid artery occlusion while deep hypothermia was maintained. R(L)CA: right (left) carotid artery. Occl.: occlusion, CP: cardiopulmonary, OD: optical density.

lowered rapidly to 22°C, there was an apparent increase in cerebral oxy Hb content which suggested a decrease in cerebral oxygen consumption due to reduced brain temperature. In deep hypothermia, a temporary occlusion of the right or left carotid artery caused no significant changes in brain oxygenation and blood volume. This indicates that temporary cessation of cerebral perfusion under hypothermal conditions is relatively safe in that brain Hb oxygenation is preserved. In this case, the patient suffered mental disorder postoperatively for a brief period but recovered later.

The relationship between oxy Hb and total Hb volume changes in the brain and mean perfusion pressure during mild hypothermic CPB was then examined in 10 patients. In each case, the values of oxy Hb and Hb volume immediately before the bypass, were taken as a baseline and two of the corresponding variables of these parameters were plotted against each arterial perfusion pressure increment of 5 mmHg. The average perfusion pressure on measuring baseline NIR indices was 82 ± 8.4 mmHg (S.D.) and the average rectal temperature 30.5 ± 2.33°C (S.D.). These results are illustrated in Fig.6. In this figure, changes in calculated contents of oxy, deoxy and total Hb are expressed as optical density/light path-length in cm. The mean light path-length in brain tissue was estimated as equal to 4 times the distance between the optical probes. To illustrate the changes of oxy Hb and total Hb content as a percentage, the scales of calculated % change are shown in Fig. 6. In order to compare average values at each measurement with the baseline value, we calculated the 95% confidence level of the average OD value for each measurement group (the t distribution chart of $X \pm t \times 0.025 \times SD/\sqrt{n}$, $p=0.025$ was used) to obtain significant differences from the baseline value at a 5% risk of error. Although both the Hb oxygenation level (upper in Fig. 6) and total Hb volume (lower in Fig. 6) showed a slight tendency to increase from the baseline at baseline perfusion pressure, there were no significant differences. During CPB, both Hb oxygenation level and blood volume in the brain were maintained roughly constant at the mean perfusion pressure of over 60 mmHg, whereas below 50 mmHg, an apparent decrease in both Hb indices was observed. However, decreases in brain blood volume were lessened by compensa-

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tory increases in deoxy Hb content.

DISCUSSION

1) Methodology
Our previous studies demonstrated that in the rat head the absorbance changes at a given wavelength above 780 nm are caused not only by the oxygenation state of hemoglobin but by the redox state of cyt.aa₃. Therefore, for an accurate determination of Hb level in the brain, it is desirable to use laser light in shorter wavelengths than 780 nm. However, since it is extremely difficult to obtain laser diodes in these wavelengths, we used 780, 805, and 830 nm. Comparing the trace of the calculated Hb volume with that of the absorbance change at 805 nm, the isobestic wavelength of hemoglobin (Fig. 2), these traces were quite similar when the O₂ concentration of inspired gas was maintained at more than 3–5%. This result suggests that we can ignore the absorption change of cyt.aa₃ when using our system in clinical oxygenation monitoring. Moreover, both traces of the calculated oxy and deoxy Hb (Fig. 2) corresponded well to changes in the oxygen concentration of inspired gas, confirming the reliability of equations used in our system. These facts led us to conclude that our NIR system can be applied effectively to routine clinical use.

Earlier, the authors measured Hb oxygenation levels and changes in Hb volume in brain, muscle and other living tissue using two wavelengths of NIR light and the results were satisfactory! However, these results were obtained in the laboratory environment where measuring conditions are stable. In the clinical setting, however, we need to deal with optical artifacts, for instance those caused by movement of the measuring objects and disturbances by background light. Therefore, we added a wavelength of 805 nm to our system as a third reference wavelength to compensate for such adverse effects.

One of the problems with this method is how to indicate changes in brain oxygenation and blood volume. We adopted a reflectance mode for monitoring in humans because of instrumental limitations of light source powers. In reflectance mode, it is extremely difficult to calculate accurately the distance of the light traversing the head (path-length). On the basis of the works by Delpy et al., the authors assumed that the mean light path-length in the brain tissue is equal to 4 times the distance between the optical probes. The relative changes in Hb absorption were expressed as OD/cm in brain tissue to standardize the measured values for each case. Since it is difficult for this system to measure the absolute amount of light absorbed in the brain, we used the Hb absorption coefficients at the wavelength of 805 nm (0.88) and calculated the Hb absorption rate in brain tissue per cm, assuming that the average blood volume is 5% and normal Hb concentration in whole blood 15 g/dl. Thus, 0.1 OD/cm was obtained in brain tissue. By measuring relative changes in Hb absorption in the tissue, we can calculate percentage changes in brain blood volume using this particular value. It is for this purpose that the % scale was added to Fig. 6.

2) Clinical application
Our spectrophotometer was analysed for laser safety before use in clinical studies. The laser light energy emitted from the light guide (5 mm in diameter) was measured as 10 mW and the lasers used in this system, which were of Class 3B, cause no direct damage to the skin. The calculated amount of energy absorbed by the tissue is several orders of magnitude below the U.S. safety standards for 90 mW/cm² for long term exposure. We think the laser light in our photometer can be illuminated safely for several hours. We have not seen any abnormalities on the skin where the probes were attached nor have we experienced any adverse effects whatsoever in the brain and nervous system due to use of our system.

Brain oxygen monitoring with our NIR system confirmed that the current CPB technique can provide adequate oxygen to the brain tissue, as shown by maintained physiological oxygenation and blood volume throughout CPB. Changes in brain oxy Hb content were found to express the Hb oxygenation levels in the cerebral venous compartment! and thus are highly indicative of cerebral oxygen balance. Therefore, monitoring of these changes can be an im-

portant indicator of the tissue perfusion and provide critical information. The curves between Hb oxygenation and mean perfusion pressure shown in Fig. 6 closely resemble the cerebral pressure-flow curve, indicating the presence of active autoregulation in the brain even during hypothermic CPB. Lowering of the oxygenation level of cerebral venous blood was seen when mean perfusion pressure was reduced to 60 mmHg or less, which suggested a decrease in cerebral blood flow on the assumption that cerebral oxygen consumption did not change much. Moreover, when deep hypothermia was induced (Fig. 5), significant increases in the brain oxygen content were noticed, indicating that oxygen consumption was reduced in the brain. In this case, we noted that, unlike the carotid artery occlusion at normal temperature (Fig. 4), there was little change in the cerebral oxygen content.

Recent studies have demonstrated that in moderate hypothermic CPB, cerebral blood flow (CBF) autoregulation was lost below 30–50 mmHg of mean arterial perfusion pressure\(^7,8\); also, with impaired autoregulation, CBF becomes more dependent on perfusion pressure. In our present study, the safe lower limits of autoregulation seemed somewhat high at 50 mmHg, which was probably due to the fact that our study group included many hypertensive patients.

The results we obtained with humans seem to be theoretically reasonable and therefore we were able to conclude that this methodology is extremely significant because this variable information can be obtained non-invasively and easily.

At present, we do not have enough quantitative data to make clinical judgements. However, with the accumulation of additional clinical data, we believe such an analysis will become possible in the future. Problems that remain to be solved when this system is used clinically include: 1) clinical introduction of a cyt.oxidase redox measuring system to obtain information concerning the brain cell functions directly; 2) use of a more powerful laser source and confirmation of its safety; 3) improvement in the optical probes and in the shielding against outside light; 4) the quantification of the changes in cerebral oxygenation and future clinical evaluation of NIR informations.

REFERENCES


