

Changes in Tissue Oxygenation of the Porcine Liver Measured by Near-Infrared Spectroscopy

Abd El-Hamid El-Desoky,* Alexander Seifalian,* Mark Cope,† David Delpy,† and Brian Davidson*

Near-infrared spectroscopy (NIRS) is a novel method for the measurement of tissue oxygenation and may have a role in monitoring liver oxygenation and viability. The aim of this study is to validate the application of NIRS for monitoring hepatic tissue oxygenation. Large Landrace pigs (n = 12) underwent laparotomy and liver exposure. Total hepatic blood flow (THBF) was measured by the Transonic Medical Flowmeter system. NIRS probes were placed on the liver surface to continuously record changes in hepatic tissue oxyhemoglobin (HbO₂), deoxyhemoglobin (Hb), and the reduction-oxidation state of cytochrome oxidase (Cyt Ox). Reduction of hepatic tissue

oxygenation was achieved by hepatic vascular inflow occlusion (n = 6) or reduction of inspired oxygen (FiO₂; n = 6). The THBF changes correlated significantly with hepatic HbO₂ (r = 0.84; P < .001) and Cyt Ox (r = 0.88; P < .001). With reduction of FiO₂, a significant correlation was found between arterial oxygen saturation and hepatic HbO₂ and Hb (r = 0.99 and r = -0.99, respectively; P < .0001). NIRS measurement of liver parenchymal oxygenation correlates well with changes in liver blood flow and arterial oxygenation.

Copyright © 1999 by the American Association for the Study of Liver Diseases

Liver parenchymal damage caused by ischemia and reperfusion injury is a well-recognized complication of liver trauma,¹ liver resection for tumor,² and liver transplantation.³ Although the precise mechanism of ischemia-reperfusion injury has not been established, key mediators have been identified, including oxygen free radicals,⁴ cytokines,⁵ and adhesion molecules⁶ that lead to capillary perfusion failure⁷ with subsequent impairment of tissue oxygenation. Hepatic tissue oxygenation has been identified in rodents as an indicator of the severity of warm ischemia-reperfusion injury⁸ and is of prognostic value for survival in liver transplantation.⁹ Therefore, an accurate method for continuous assessment of liver oxygenation could be of great value for predicting the outcome of liver surgery and transplantation.

Near-infrared spectroscopy (NIRS) is a light-based noninvasive method that allows continuous measurement of extracellular tissue oxygenation by measuring oxyhemoglobin (HbO₂) and deoxyhemoglobin (Hb).¹⁰ It can also monitor intracellular oxygenation by measuring the reduction-oxidation changes of cytochrome oxidase (Cyt Ox), the terminal enzyme of the mitochondrial electron transport chain.^{10,11} The use of NIRS for evaluating hepatic tissue oxygenation is limited to the authors¹² and one main group in Japan.¹³ However,

there is no basic experimental work to define the significance of the NIRS signal from the liver parenchyma and its relationship with liver blood flow and oxygen supply. As a prelude to human organ transplant work, we have therefore evaluated the application of NIRS for the measurement of hepatic tissue oxygenation and perfusion in a large animal model with hepatic vascular inflow occlusion and graded hypoxia.

From the *University Department of Surgery and Liver Transplant Unit, Royal Free Hospital School of Medicine; and the †Department of Medical Physics and Bioengineering, University College London, London, UK.

Supported in part by the Royal Free Hospital Special Trustees, who purchased the dual Transonic Medical Flowmeter system. The Wellcome Trust and Hamamatsu Photonics funded the equipment for determining the liver-specific near-infrared spectroscopy algorithm.

Presented at the 87th Surgical Research Society Meeting, London, UK, January 8-9, 1998, and published as an abstract in *Br J Surg* 1998;85:701.

Address reprint requests to Brian Davidson, MBCh B, MD, FRCS, University Department of Surgery and Liver Transplant Unit, Royal Free Hospital School of Medicine, Pond Street, Hampstead, London NW3 2QG, UK.

Copyright © 1999 by the American Association for the Study of Liver Diseases

1074-3022/99/0503-0010\$3.00/0

Methods

Animals and Surgical Procedure

The study was conducted under a license granted by the Home Office in accordance with the Animals (Scientific Procedures) Act 1986. Large White Landrace pigs ($n = 12$; 26 ± 2.5 kg) were used. After an overnight fast, the animals were premedicated with Azaperone (Stresnil; Janssen Pharmaceutical, Oxford, UK), 0.1 mL/kg intramuscularly. After induction of anesthesia using ketamine hydrochloride (Ketaset; Willows Francis Veterinary, Crawley, UK), 5 mg/kg intravenously, the animals were intubated and mechanically ventilated. Anesthesia was maintained using halothane (May and Baker Ltd, Dagenham, UK), nitrous oxide, and oxygen through a standard anesthetic circuit. The animals' temperature was maintained at 36°C to 38°C using an electronic heating mat. A pulse oximeter probe (Ohmeda Biox 3740 pulse oximeter; Ohmeda, Louisville, CO) was used for continuous monitoring of arterial oxygen saturation (SaO_2) and heart rate. Catheters were inserted into the internal jugular vein and carotid artery for fluid administration and blood pressure monitoring, respectively.

Laparotomy was performed through a transverse subcostal incision. The ligamentous attachments from the liver to the diaphragm and the abdominal wall were divided and the liver exposed. The porta hepatis was exposed and the portal vein (PV) and hepatic artery (HA) identified and carefully dissected. For continuous measurement of total hepatic blood flow (THBF), a dual Transonic Medical Flowmeter system (HT207; Transonic Medical System, Ithaca, NY) was used with perivascular flow probes of 2 and 6 mm in diameter for HA and PV, respectively. A pair of NIRS probes (optical fiber bundles) was placed, with a 25-mm separation, on the surface of the right lobe of the liver for continuous monitoring of the hepatic tissue oxygenation and blood volume. A flexible probeholder was used to ensure a satisfactory contact with the liver surface and a fixed interprobe spacing.

Experimental Groups

In group 1 ($n = 6$), hepatic tissue oxygenation and hepatic blood volume were continuously measured by NIRS during reduction in THBF. Temporary reduction in THBF was achieved by HA occlusion for 3 minutes, PV occlusion for the same period of time, and finally total occlusion by clamping both vessels for 3 minutes. Sufficient intervals were allowed between the different occlusion periods for hepatic blood flow to return to baseline values.

In group 2 ($n = 6$), a stepwise reduction of the fraction of inspired oxygen (FIO_2) was used to decrease SaO_2 from 100% to 40% while continuously recording the hepatic blood flow, hepatic tissue oxygenation, and blood volume.

After the completion of each study, the animals were

killed by a lethal dose (20 mL of 200 mg/mL) of sodium pentobarbitone (Expiral; Sanofi Animal Health, Harlow, UK).

NIRS

NIRS depends on the relative transparency of biological tissue to light in the near-infrared region of the spectrum. Light at a visible wavelength (450 to 700 nm) is strongly attenuated in tissue and, as a result, can only penetrate a maximum distance of a few millimeters.¹⁰ However, the absorption of light by the tissue chromophores is significantly less at near-infrared wavelengths (700 to 1000 nm), and, with sensitive detectors, it is possible to detect light that has traversed up to 80 mm of tissue.¹⁴ In the liver tissue, there are three main chromophores in which the absorption of near-infrared light varies with their oxygenation status. These chromophores are HbO_2 , Hb, and Cyt Ox. The change in chromophore concentration can be quantified using a modified Beer Lambert Law.¹⁵ The NIRS instrument (NIRO-500; Hamamatsu Photonics KK, Hamamatsu, Japan) used in this study produces light at four wavelengths that are transmitted in sequential pulses through a bundle of optical fibers to the liver. Photons emerging from the liver are collected by the second bundle of optical fibers and detected by a photomultiplier tube. The difference between transmitted and received light intensity at each wavelength was used to determine the optical density changes at each wavelength. A modified computer program was used to continuously compute changes in HbO_2 , Hb, and Cyt Ox concentration in the liver based on chromophore absorption coefficient in micromoles per liter of tissue. Total hemoglobin (HbT), the sum of the HbO_2 and Hb, which reflects the liver blood volume, is computed continuously by the NIRO-500, as is the difference in hemoglobin oxygenation, HbD ($\text{HbO}_2 - \text{Hb}$), which reflects the net change in hemoglobin oxygenation independent of the blood volume.¹⁶ For accurate measurements to be made, the optical path length in the tissue must be known as a function of wavelength. The differential path length factor therefore was calculated specifically for the liver by measuring the absorption coefficient as a function of wavelength (data not shown). The differential path length factor was 2.7, and this value was used to adjust the NIRO-500 algorithm for calculating the changes in the chromophores concentrations.

Data Collection and Statistical Analysis

Values are expressed as mean \pm standard deviation. For statistical analysis, a Student's *t*-test was used with Bonferroni adjustment for multiple comparisons. *P* less than .05 was considered statistically significant. The relationships between THBF, SaO_2 , and NIRS parameters were tested using linear regression.

	Baseline	HAO	PVO	TO
HABF (mL/min)	135 ± 19	0	173 ± 16*	0
PVBF (mL/min)	686 ± 38	719 ± 42	0	0
THBF (mL/min)	821 ± 53	719 ± 42†	173 ± 16†	0
Reduction THBF (%)	0	13 ± 2.4	79 ± 2.6	100

NOTE. Values expressed as mean ± standard deviation of six pigs.
Abbreviations: HAO, hepatic artery occlusion; PVO, portal vein occlusion; TO, total occlusion; HABF, hepatic artery blood flow; PVBF, portal vein blood flow; THBF, total hepatic blood flow.
**P* < .01 v baseline.
†*P* < .001.

Results

Liver Blood Flow

The baseline THBF was 821 ± 53 mL/min. The HA supplied 16.5% ± 2.3% and the PV 83.5% ± 1.9%. HA occlusion was associated with an insignificant increase (4%) in PV blood flow and a significant reduction in THBF (13% ± 2.4%; *P* < .001 v baseline). PV occlusion resulted in a significant increase in HA blood flow (29%; *P* < .01 v baseline) and a significant reduction in THBF (79% ± 2.6%; *P* < .001 v baseline; Table 1).

**Hepatic Tissue Oxygenation
With Vascular Inflow Occlusion**

With HA occlusion (Fig. 1), there was an immediate significant decrease in HbO₂ (-21.48 ± 6.22 μmol/L; *P* < .01 v baseline) and a simultaneous

increase in Hb (11.61 ± 3.92 μmol/L; *P* < .01 v baseline). A decrease (-0.29 ± 0.18) in Cyt Ox was noticed, but this reduction was not significant. These changes were associated with a decrease in HbT and HbD (-9.88 ± 2.36 and -33.09 ± 10.13 μmol/L, respectively; *P* < .01 v baseline).

With PV occlusion (Fig. 1), a decrease in HbO₂ was observed (-33.25 ± 8.74 μmol/L; *P* < .001 v baseline) and a simultaneous increase in Hb (17.53 ± 3.89 μmol/L; *P* < .001 v baseline). A significant decrease (-2.92 ± 1.52 μmol/L; *P* < .01 v baseline) in Cyt Ox was noticed. These changes were associated with a decrease in HbT and HbD (-15.71 ± 5.02 and -50.78 ± 12.56 μmol/L, respectively; *P* < .001 v baseline).

With total inflow occlusion, there was a decrease in HbO₂ (-67.23 ± 15.76 μmol/L; *P* < .001 v baseline) and a simultaneous increase in Hb (24.80 ± 5.99 μmol/L; *P* < .001 v baseline). Also, there was a significant decrease in Cyt Ox (-6.79 ± 2.78 μmol/L; *P* < .01 v baseline). These changes were associated with a decrease in HbT and HbD (-42.43 ± 9.86 and -92.02 ± 21.70 μmol/L, respectively; *P* < .001 v baseline). NIRS measurements with hepatic vascular inflow occlusion are shown in Table 2 and Figure 2A and B.

There was a significant positive correlation between THBF and hepatic HbO₂ (*r* = 0.84; *P* < .001), hepatic Cyt Ox (*r* = 0.88; *P* < .001), and hepatic HbT (*r* = 0.80; *P* < .001).

**Hepatic Tissue Oxygenation
With Graded Hypoxia**

Reduction of F_{IO}₂ decreased the SaO₂ from 100% to 40%. This was associated with a significant de-

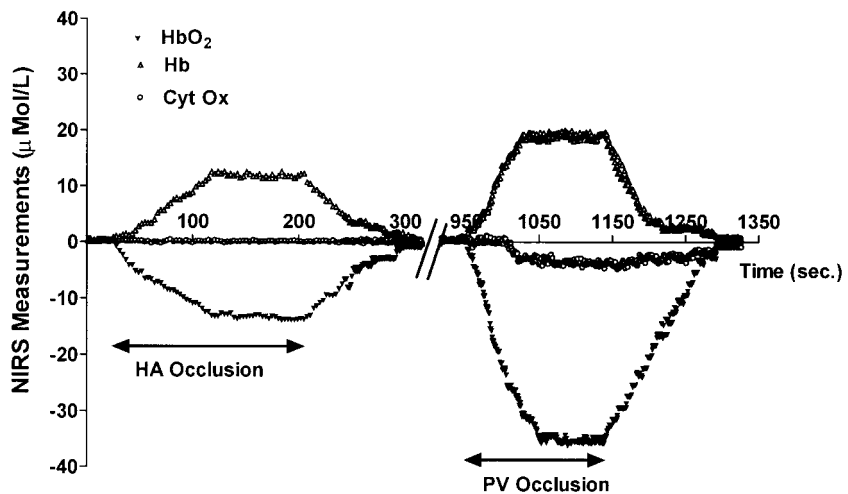


Figure 1. A typical example of NIRS measurement in one animal during hepatic artery and portal vein occlusion.

Table 2. Hepatic Tissue NIRS Measurements With Hepatic Vascular Inflow Occlusion			
	HAO	PVO	TO
HbO ₂ (μmol/L)	-21.48 ± 6.22*	-33.25 ± 8.74†	-67.23 ± 15.76†
Hb (μmol/L)	11.61 ± 3.92*	17.53 ± 3.89†	24.80 ± 5.99†
Cyt Ox (μmol/L)	-0.29 ± 0.18	-2.92 ± 1.52*	-6.79 ± 2.78*
HbT (μmol/L)	-9.88 ± 2.36*	-15.71 ± 5.02†	-42.43 ± 9.86†
HbD (μmol/L)	-33.09 ± 10.13*	-50.78 ± 12.56†	-92.02 ± 21.70†

NOTE. Values expressed as means ± standard deviation of six pigs.
 Abbreviations: HAO, hepatic artery occlusion; PVO, portal vein occlusion; TO, total occlusion; HbO₂, oxyhemoglobin; Hb, deoxyhemoglobin; Cyt Ox, cytochrome oxidase; HbT, total hemoglobin; HbD, difference in hemoglobin oxygenation.
 *P < .01.
 †P < .001 v baseline.

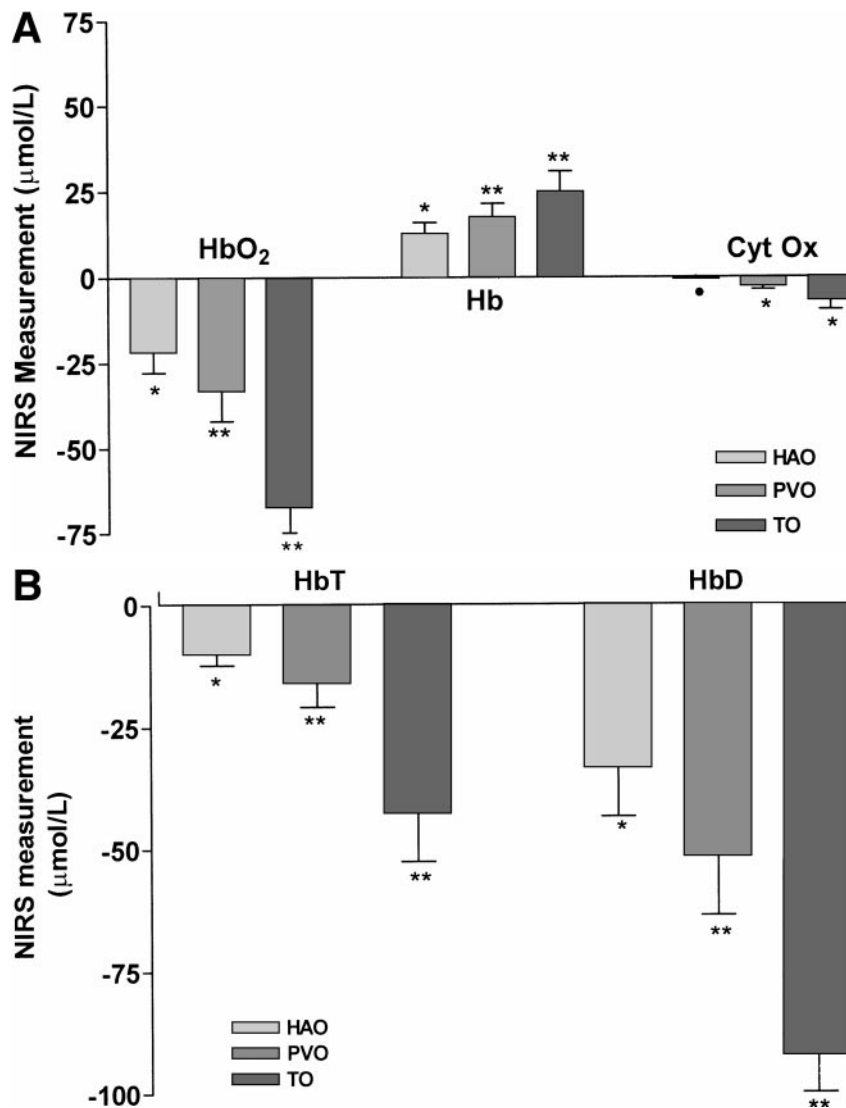


Figure 2. Changes in hepatic tissue oxygenation and blood volume after hepatic artery (HAO), portal vein (PVO), or total occlusion (TO). (A) Changes in HbO₂, Hb, and Cyt Ox. (B) Changes in HbT and HbD. Values are mean ± standard deviation of six animals. *P < .01. **P < .001. †P = not significant v baseline.

Table 3. Hepatic Tissue NIRS Measurements With Graded Hypoxia

SaO ₂ (%)	HbO ₂ (μmol/L)	Hb (μmol/L)	Cyt Ox (μmol/L)
95	-3.39 ± 2.95	2.83 ± 3.25	-0.27 ± 0.10
90	-6.95 ± 3.32*	7.65 ± 3.65*	-0.61 ± 0.18
85	-9.66 ± 3.94*	10.62 ± 4.33*	-0.73 ± 0.22
80	-16.36 ± 3.93*	17.99 ± 4.32*	-0.59 ± 0.19
75	-21.66 ± 4.04*	23.83 ± 4.44*	-0.02 ± 0.53
70	-28.13 ± 4.29*	31.94 ± 4.72*	-0.03 ± 0.54
65	-35.58 ± 4.70*	37.13 ± 5.17*	-8.24 ± 2.69*
60	-41.59 ± 5.12*	44.75 ± 5.63*	-9.24 ± 3.04*
55	-49.43 ± 5.72*	51.37 ± 6.32*	-9.98 ± 3.44*
50	-57.48 ± 6.46†	59.23 ± 7.11†	-11.48 ± 3.35*
45	-62.89 ± 6.97†	64.18 ± 7.66†	-15.21 ± 4.80†
40	-71.72 ± 7.83†	73.90 ± 8.62†	-16.60 ± 5.28†

NOTE. Values expressed as means ± standard deviation of six pigs.
Abbreviations: SaO₂, arterial oxygen saturation; HbO₂, oxyhemoglobin; Hb, deoxyhemoglobin; Cyt Ox, cytochrome oxidase.
**P* < .01.
†*P* < .001 v baseline.

crease in hepatic tissue HbO₂ and increase in Hb (Table 3). HbO₂ changes showed a positive correlation with SaO₂ changes ($r = 0.99$; $P < .0001$; Fig. 3A). Hb changes showed a negative correlation with SaO₂ changes ($r = -0.99$; $P < .0001$; Fig. 3B). With hypoxia, the reduction in Cyt Ox started at the SaO₂ level of 65% and was significantly reduced at the SaO₂ level of 40% (-16.60 ± 5.28 μmol/L; $P < .001$ v baseline; Table 3).

Discussion

This study has shown that NIRS can monitor changes in hepatic tissue oxygenation and blood volume produced by reducing the blood and oxygen supply to the liver. This is the first study to correlate liver blood flow with hepatic tissue oxygenation and blood volume parameters, measured by NIRS, using an animal model with a liver anatomy and physiology similar to man.¹⁷ Although similar results were obtained on NIRS of the rabbit liver by Tokuka et al,¹⁸ their studies did not involve measurement of the liver blood flow. There are major differences between the liver blood supply in small animals and man. Liver transplantation, for example, can be successfully performed in rodents without restoring the HA inflow,¹⁹

whereas HA occlusion in human liver transplantation causes a significant postoperative morbidity and mortality.²⁰

This study has provided further insight into the interrelationship between the HA and PV blood flow. The portal blood flow did not increase significantly with HA occlusion, in agreement with other studies.²¹⁻²³ Conversely, the HA blood flow increased significantly in response to PV occlusion, supporting the presence of a hepatic arterial buffer response.^{24,25} More importantly, this technique has provided a means of analyzing the relationship between liver parenchymal perfusion, oxygenation, and blood supply. With HA occlusion, there was a reduction in the HbO₂ with a simultaneous increase in Hb that reflects a decrease in the hepatic oxygen supply with a concomitant increase in the fraction of oxygen extracted from blood by the tissue.²⁶ The decrease in HbT and HbD is likely to reflect the acute reduction in hepatic blood volume and oxygenation, respectively. These changes in the parenchymal oxygenation and blood volume with HA occlusion were not compensated by an increase in the PV inflow, which may explain the importance of the HA blood supply to the liver.²¹ With PV occlusion, the direction of changes in all NIRS parameters were the same as with HA occlusion, whereas the magnitude of changes was approximately twice that with the HA occlusion. This may be because the blood and oxygen supply to the liver through the PV is greater than that of the HA. Despite the HA blood flow increasing with PV occlusion, mediated by the hepatic arterial buffer response, no buffer effect was found at the level of liver parenchymal oxygenation or perfusion. This contradicts the view that the hepatic arterial buffer achieves quantitative compensation at the level of oxygen supply, rather than at the level of blood supply.²⁵ The changes in liver tissue HbO₂, Hb, and Cyt Ox after total inflow occlusion were greater than the sum of the changes after HA and PV occlusion. This would suggest the presence of a regulatory mechanism for maintaining the hepatic microcirculation that is lost after total occlusion.

The close correlation found between the total blood flow measured by the transonic flowmeter and the hepatic HbO₂ and HbT measured by NIRS reflects the precision of NIRS as a method of monitoring hepatic parenchymal blood oxygenation and blood volume. This is the first study to evaluate the relationship between HbT measured by NIRS and liver blood flow. The high level of

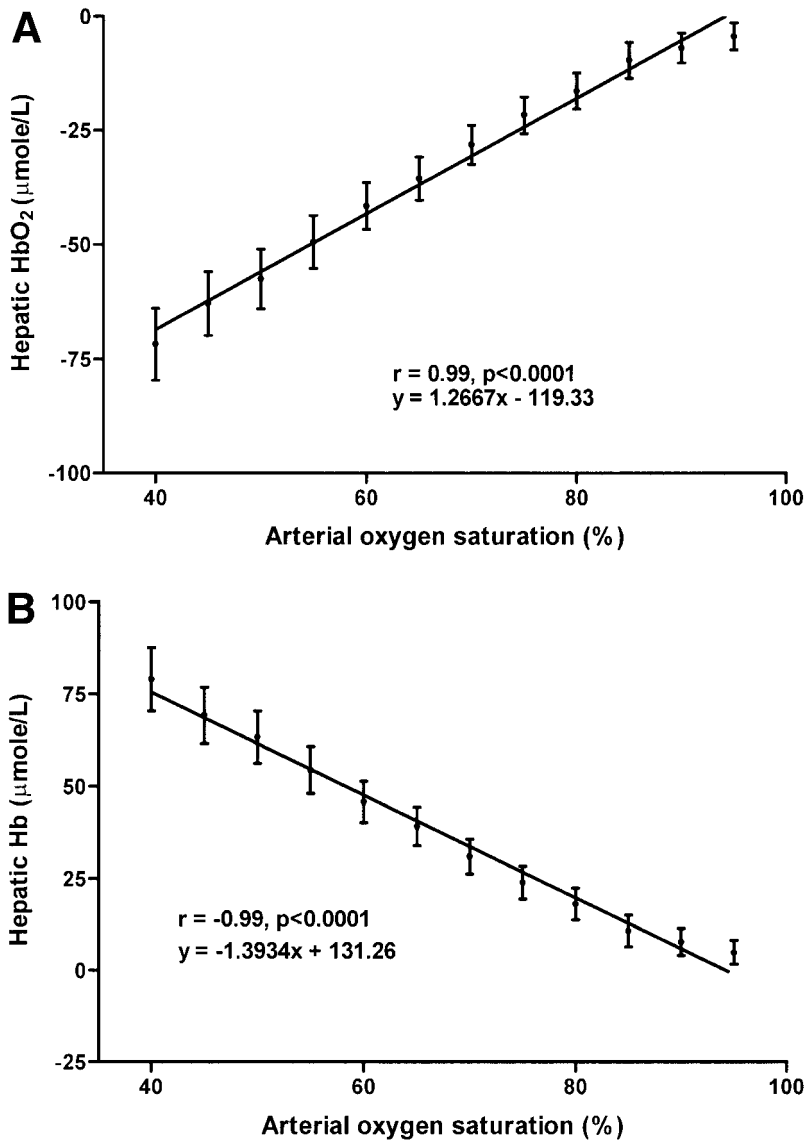


Figure 3. The relationship between the changes in hepatic tissue (A) HbO₂ and (B) Hb, measured by NIRS, and SaO₂ with graded hypoxia. Each point is mean \pm standard deviation of six animals at the end of one hypoxic period.

correlation would suggest that NIRS may have applications in which continuous monitoring of blood flow is required.

The experimental group in this study undergoing reduction of FIO₂ allowed an assessment to be made of changes in the hepatic tissue HbO₂ by NIRS without producing hepatic vascular inflow occlusion. This would therefore correlate with liver hypoxia without ischemia. There was a linear decrease in hepatic parenchymal HbO₂ and a simultaneous increase in Hb with reduction in FIO₂, again indicating the dissociation of oxygen from hemoglobin as the tissue extracts oxygen.²⁶ A highly significant correlation was found between SaO₂ changes and hepatic tissue HbO₂ and Hb over

the range of oxygen saturation studied, which would suggest that NIRS would be an accurate method of measuring changes in hepatic extracellular oxygenation.

Cyt Ox is the terminal electron carrier of the mitochondrial respiratory chain that catalyzes the reduction of oxygen to H₂O in a four-electron reaction with the concomitant synthesis of adenosine triphosphate through the oxidative phosphorylation process.²⁷ In hepatocytes, approximately 90% of the oxygen taken up is consumed by Cyt Ox in the mitochondria.²⁸ Thus, assessment of the reduction-oxidation state of Cyt Ox reflects intracellular oxygen availability.^{29,30} NIRS monitors the electron-accepting site of the enzyme.³⁰ During

hepatic inflow occlusion, reduction of Cyt Ox occurred significantly with PV and total occlusion, whereas no change was found with HA occlusion. This indicates that Cyt Ox reduction occurs with a more severe degree of hypoxia than that produced with HA occlusion alone. During hypoxia, a significant reduction of Cyt Ox was encountered only with a marked reduction in the hepatic HbO₂. These results are in accordance with previous studies in rabbit livers in which Cyt Ox reduction occurred with reduction of the hepatic blood flow by hemorrhage³¹ and vascular occlusion.¹⁸ It has been shown also that cerebral Cyt Ox reduction occurs only with a severe reduction of oxygen delivery.³²

In conclusion, NIRS measurement of liver parenchymal oxygenation has been shown to correlate well with changes in liver blood flow and arterial oxygenation. These experimental data will allow a scientific basis for the development of clinical applications for liver NIRS.

Acknowledgment

The authors thank the Egyptian government for the sponsorship of Dr Abd El-Hamid El-Desoky; Duncan Moore and his staff in the Comparative Biology Unit for expertise in animal care and anesthesia; Dr Richard Morris, Senior Lecturer in Medical Statistics, Academic Department of Public Health and Primary Care at the Royal Free Hospital Medical School, for advice on statistical methods; and Dr Jem Hebden, Wellcome Senior Research Fellow, Department of Medical Physics and Bioengineering, University College London, for help performing "time of flight" measurement for the liver.

References

1. Patcher H, Spenser F, Hofstetter S, Coppa G. Experience with finger fracture technique to achieve intrahepatic hemostasis in 75 patients with severe injuries of the liver. *Ann Surg* 1983;197:771-778.
2. Delva E, Camus Y, Nordlinger B, Hannoun L, Parc R, Deriaz H, et al. Vascular occlusion for liver resections. Operative management and tolerance to hepatic ischaemia: 142 cases. *Ann Surg* 1989;209:211-218.
3. Clavien PA, Harvey PR, Strasberg SM. Preservation and reperfusion injuries in liver allografts. An overview and synthesis of current studies. *Transplantation* 1992;53:957-978.
4. Mochida S, Arai M, Ohno A, Masaki N, Ogata I, Fujiwara K. Oxidative stress in hepatocytes and stimulatory state of Kupffer cells after reperfusion differ between warm and cold ischemia in rats. *Liver* 1994;14:234-240.
5. Colletti LM, Kunkel SL, Walz A, Burdick MD, Kunkel RG, Wilke CA, et al. The role of cytokine networks in the local liver injury following hepatic ischemia/reperfusion in the rat. *Arch Pathol Lab Med* 1996;23:506-514.
6. Vollmar B, Glasz J, Menger MD, Messmer K. Leukocytes contribute to hepatic ischemia/reperfusion injury via intercellular adhesion molecule-1-mediated venular adherence. *Surgery* 1995;117:195-200.
7. Vollmar B, Glasz J, Leiderer R, Post S, Menger MD. Hepatic microcirculatory perfusion failure is a determinant of liver dysfunction in warm ischemia-reperfusion. *Am J Pathol* 1994;145:1421-1431.
8. Goto M, Kawano S, Yoshihara H, Takei Y, Hijioka T, Fukui H, et al. Hepatic tissue oxygenation as a predictive indicator of ischemia-reperfusion liver injury. *Arch Pathol Lab Med* 1992;15:432-437.
9. Sumimoto K, Inagaki K, Fukuda Y, Dohi K, Sato Y. Significance of graft tissue oxygen saturation as a prognostic assessment for orthotopic liver transplantation in the rat. *Transplant Proc* 1987;19:1098-1102.
10. Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977;198:1264-1267.
11. Edwards AD, Brown GC, Cope M, Wyatt JS, McCormick DC, Roth SC, et al. Quantification of concentration changes in neonatal human cerebral oxidized cytochrome oxidase. *J Appl Physiol* 1991;71:1907-1913.
12. Ogbeide S, Seifalian AM, Doctor N, Javed M, Davidson BR. Monitoring of liver oxygenation by near-infrared spectroscopy [abstr]. *Gut* 1996;39:A18.
13. Kitai T, Tanaka A, Tokuka A, Tanaka K, Yamaoka Y, Ozawa K, et al. Quantitative detection of hemoglobin saturation in the liver with near-infrared spectroscopy. *Hepatology* 1993;18:926-936.
14. Wyatt JS, Cope M, Delpy DT, Wray S, Reynolds EO. Quantification of cerebral oxygenation and haemodynamics in sick newborn infants by near-infrared spectrophotometry. *Lancet* 1986;2:1063-1066.
15. Cope M, Delpy DT, Reynolds EO, Wray S, Wyatt J, van der Zee P. Methods of quantitating cerebral near-infrared spectroscopy data. *Adv Exp Med Biol* 1988;222:183-189.
16. Lane NJ, Thorniley MS, Manek S, Fuller BJ, Green CJ. Hemoglobin oxygenation kinetics and secondary ischemia in renal transplantation. *Transplantation* 1996;61:689-696.
17. Copper DKC, Ye Y, Rolf JLL. The pig as a potential organ donor for man in xenotransplantation. In: Copper DKC, Kemp E, Reemtsma K, White DJG (eds). *The transplantation of organs and tissues between species* (ed 1). Berlin: Springer, 1991:481-500.
18. Tokuka A, Tanaka A, Kitai T, Yanabu N, Mori S, Sato B, et al. Interrelationship of oxygen supply by hepatic artery and portal vein: Rapid analysis of ischemia-reflow-induced changes in hepatic oxygenation in experimental and clinical subjects by tissue near-infrared spectroscopy. *Eur Surg Res* 1994;26:342-352.
19. Kamada N, Calne RY. Orthotopic liver transplantation in the rat: Technique using cuff for portal vein anastomosis and biliary drainage. *Transplantation* 1979;28:47-50.
20. Tzakis AG, Gordon RD, Shaw BW, Iwatsuki S, Starzl TE. Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporine era. *Transplantation* 1985;40:667-671.

21. Kim DK, Kinne DW, Fortner JG. Occlusion of the hepatic artery in man. *Surg Gynecol Obstet* 1973;136:966-1002.
22. Andreen M, Irestedt L. Decrease of oxygen consumption in the dog liver during temporary arterial occlusion. *Acta Physiol Scand* 1976;98:103-109.
23. Kock NG, Hahnloser P, Roding B, Schenk WG. Interaction between portal and hepatic arterial blood flow: An experimental study in the dog. *Surgery* 1972;72:414-419.
24. Lautt WW. Mechanism and role of intrinsic regulation of hepatic arterial blood flow: The hepatic arterial buffer response. *Am J Physiol* 1985;249:G459-G556.
25. Mathie RT, Blumgart LH. The hepatic haemodynamic response to acute portal venous blood flow reductions in the dog. *Pflugers Arch* 1983;399:223-227.
26. Lautt WW, Greenway CV. Conceptual review of the hepatic vascular bed. *Arch Pathol Lab Med* 1987;7:952-963.
27. Capaldi RA. Structure and function of cytochrome-c oxidase. *Annu Rev Biochem* 1990;59:569-596.
28. de Groot H, Noll T. Halothane-induced lipid peroxidation and glucose 6 phosphatase inactivation in microsomes under hypoxic conditions. *Anaesthesiology* 1985;62:44-48.
29. Erecinska M, Wilson DF. Regulation of cellular energy metabolism. *J Membrane Biol* 1982;70:1-14.
30. Cooper CE, Matcher SJ, Wyatt JS, Cope M, Brown GC, Nemoto EM, et al. Near-infrared spectroscopy of the brain: Relevance to cytochrome oxidase bioenergetics. *Biochem Soc Trans* 1994;22:974-980.
31. Kitai T, Tanaka A, Tokuka A, Tanaka K, Yamaoka Y, Ozawa K, et al. Changes in the hepatic oxygenation state during hemorrhage and following epinephrine or dextran infusion as assessed by near-infrared spectroscopy. *Circ Shock* 1993;41:197-205.
32. Ferrari M, Williams MA, Wilson DA, Thakor NV, Traustaman RJ, Hanley DF. Cat brain cytochrome-c oxidase redox changes induced by hypoxia after blood-fluorocarbon exchange transfusion. *Am J Physiol* 1995;269:H417-H424.