Chapter 9
A Tale of Two Methods: Combining Near-Infrared Spectroscopy with MRI for Studies of Brain Oxygenation and Metabolism

Jeff F. Dunn, Nabeela Nathoo, and Runze Yang

Abstract Combining magnetic resonance imaging (MRI) with near-infrared spectroscopy (NIRS) leads to excellent synergies which can improve the interpretation of either method and can provide novel data with respect to measuring brain oxygenation and metabolism. MRI has good spatial resolution, can detect a range of physiological parameters and is sensitive to changes in deoxyhemoglobin content. NIRS has lower spatial resolution, but can detect, and with specific technologies, quantify, deoxyhemoglobin, oxyhemoglobin, total hemoglobin and cytochrome oxidase. This paper reviews the application of both methods, as a multimodal technology, for assessing changes in brain oxygenation that may occur with changes in functional activation state or metabolic rate. Examples of hypoxia and ischemia are shown. Data support the concept of reduced metabolic rate resulting from hypoxia/ischemia and that metabolic rate in brain is not close to oxygen limitation during normoxia. We show that multimodal MRI and NIRS can provide novel information for studies of brain metabolism.

Keywords MRI • Near-infrared • Brain • Hypoxia • Multimodal imaging

J.F. Dunn (✉)
Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada

Department of Radiology, University of Calgary, 3330 Hospital Drive, N.W., Calgary, AB, Canada T2N 4 N1

Experimental Imaging Centre, University of Calgary, Calgary, AB, Canada
e-mail: dunnj@ucalgary.ca

N. Nathoo • R. Yang
Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada

Department of Radiology, University of Calgary, 3330 Hospital Drive, N.W., Calgary, AB, Canada T2N 4 N1

H.M. Swartz et al. (eds.), *Oxygen Transport to Tissue XXXVI*, Advances in Experimental Medicine and Biology 812, DOI 10.1007/978-1-4939-0620-8_9,

1 Introduction

Hypoxia (low oxygen conditions) in brain can be both a cause and an effect of brain disorders. An obvious case of this is ischemia, or stroke, which reduces perfusion and brain oxygenation, eventually leading to neuronal death. Many disorders including Alzheimer's disease [1], multiple sclerosis [2], stroke [3], birth asphyxia, and sudden infant death syndrome [4], to name a few, are also associated with altered brain metabolic rate, reduced functional activation or with hypoxia.

Changes in metabolic rate also impact brain oxygenation. An increase in metabolic rate associated with increased functional activity leads to an increase in both perfusion and oxygenation [5, 6]. Conversely, a decrease in metabolic rate results in increased deoxyhemoglobin (HHb) and decreased oxygenation. The basis of blood-oxygen level dependent (BOLD) magnetic resonance imaging (MRI) is that the activation decreases HHb, a paramagnetic contrast agent, leading to an increase in signal on MRI [6].

Alterations in oxygenation may be the cause of a brain disorder, such as in acute hypoxia, or may reflect changes in functional activation or metabolic rate. Measurements of brain oxygenation and metabolism can provide novel information in terms of identifying the cause of a disorder, or for monitoring disease progression or treatment.

As the brain is encased within the skull, non-invasive imaging methods which can assess metabolism and oxygenation over repeated measurements are required. Both MRI and NIRS have been used extensively for this purpose. The combination of NIRS and MRI can provide a new multimodal tool that allows for improved calibration of MRI (Fig. 9.1), improved spatial resolution of NIRS and novel datasets linking metabolism with oxygenation.

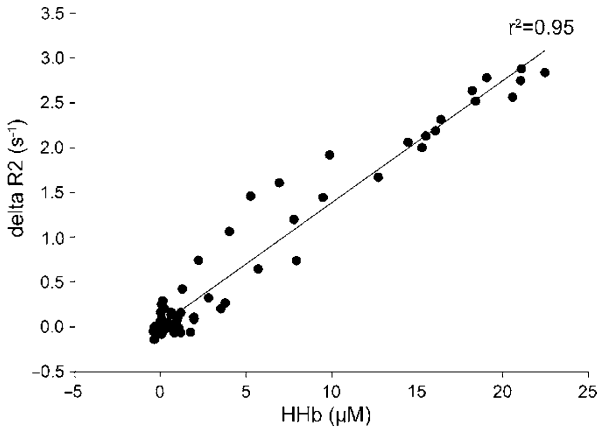

Fig. 9.1 Calibration of ΔR_2 using Δdeoxyhemoglobin (HHb). The slope of the best fit line is 0.14. Data are obtained from rat cortex during a pulse of low oxygen at 9.4 T using a T2 weighted sequence to measure ΔR_2, and a broadband NIRS system to quantify HHb. Although many factors contribute to the slope [21], R_2 can be used to estimate the changes in microvascular hemoglobin saturation and tissue oxygenation [22]

Possibly the first to actually use MRI and NIRS in combination as a multimodal tool performed functional MRI and NIRS simultaneously while subjects performed a unilateral sequential finger opposition task, with the key finding being that a task-related decrease in HHb was seen using both MRI and NIRS [7].

2 Fiber Optics and MRI, the Issues and Solutions to Multimodality Imaging

The main problem with undertaking multimodal imaging relates to the quality and location of the fiber optics. The components that are placed within the MRI need to be magnet-compatible. This means that the technology must be safe to put inside the MRI. One must also consider whether the presence of the technology will adversely impact the image quality. Most non-magnetic materials are safe, but different plastics and glass may still cause susceptibility artifacts. Probes with plastic caps may or may not be MRI-compatible.

The location of the probes can also be an issue. Since subjects are laying down in the MRI, it can be difficult to place fibers onto the back of the head. Also, many studies use an RF coil that fits closely to the head. In order for the tip of the probe to fit tightly onto the scalp and still fit inside the RF coil, the bend radius has to be very small or the fiber requires a prism to turn the light path, allowing the fibers to be positioned parallel to the skin. The requirement for a small turn radius makes fiber bundles more versatile than solid fibers.

3 Advantages of Combining NIRS and MRI

One clear advantage of the multimodal technique is the use of MRI to provide structural information that can then be applied in the reconstruction and localization of NIRS data [8, 9]. NIRS mapping data can be projected onto the surface of the cortex [10]. This provides depth information and allows 3D reconstruction of NIRS images. A second major advantage is the ability to obtain data on tissue oxygenation with NIRS at the same time as obtaining anatomical, physiological, biochemical and metabolic data from MRI. The following are examples of how multimodal MRI/NIRS provides novel data in brain.

4 Studying Cellular Redox Potential

The cellular redox potential describes the equilibrium that involves the ratio of nicotinamide adenine dinucleotide (NAD)/NADH. This, in turn, relates to the potential for mitochondria to produce adenosine triphosphate (ATP) [11].

In brain, the ratio of phosphocreatine (PCr) to inorganic phosphate (Pi) has been reported to be a non-invasive measure of intracellular redox potential and correlates with NADH [12]. In NIRS, the absorption spectrum of the copper (a) component (Cu_A) of cytochrome oxidase (cytOx) will change with oxidation state, and therefore, will also relate to redox potential [11]. However, each method has its own assumptions. For instance, the PCr/Pi ratio argument is based on a model and requires other metabolic factors to be constant, such as pH. The cytOx signal is small, making it difficult to differentiate this signal from changes associated with oxyhemoglobin (HbO_2) [13]. Combining ^{31}P NMR and NIRS allows one to study the relationship between the PCr/Pi ratio and cellular redox potential.

5 Measuring Brain Oxidative State in Hypoxia

A combined ^{31}P NMR and NIRS study was conducted to determine if the redox state of the electron transport chain is dependent on cerebral oxygenation during normoxia and normal brain function. Piglets were anesthetized with isoflurane and ventilated [11]. Broadband NIRS was undertaken with the sensitive volume in the cortex. Quantification of NIRS was carried out using second differential spectroscopy [14] in conjunction with an anoxia pulse. ^{31}P NMR was done at 7 T with non-localized spectroscopy. A repeated anoxia of 105 s was used to reduce blood oxygenation.

This paradigm resulted in significant brain hypoxia. However, HbO_2 declined well before Cu_A showed a change, supporting the argument that levels of oxygen in mitochondria are normally above a limiting concentration. Also, PCr content only began to decline when Cu_A began to change, after which there was a linear relationship between the two parameters.

A similar type of study was done in piglets using a graded hypoxia paradigm. Inspired oxygen was reduced while obtaining ^{31}P NMR spectroscopy on a 4.7 T MRI and NIRS data using a NIRO-500. Changes in cytOx did not relate to changes in HbO_2 or HHb directly, providing evidence that cytOx data was independent of hemoglobin. PCr correlated best with Cu_A but neither declined immediately with reduction in oxygenation [15]. A study of cardiopulmonary bypass showed a linear relationship between cytOx redox state and relative ^{31}P concentration [16].

These multimodal studies confirm that changes in cytoplasmic PCr/Pi provide a reasonable approximation of changes in mitochondrial redox potential in brain. Additionally, the fact that the reduction in oxidation state was delayed relative to the reduction in oxygenation supports the premise that oxygen levels in the brain are not close to limiting for metabolism under normal conditions. A previous paper using electron paramagnetic resonance to quantify brain tissue PO_2 and ^{31}P NMR to quantify energetics came to a similar conclusion—oxygen levels have to drop significantly before affecting PCr or pH [17].

6 Measuring Cerebral Metabolic Rate for Oxygen ($CMRO_2$) in Hypoxia-Ischemia

In studies of hypoxia/ischemia (or stroke), NIRS/MRI can provide information on brain physiology, including cell swelling, while monitoring oxygenation and energy metabolism. A study of the metabolic effects of hypoxia-ischemia (HI) was performed on the newborn piglet brain using a broadband NIRS system in combination with 3 T MRI [18]. Metabolic energy substrates were assessed with ^{31}P NMR, ^{1}H spectroscopy was used to study lactate, and diffusion weighted MRI was used to study edema. $CMRO_2$ was calculated using the Fick principle using NIRS.

There was a significant decline in $CMRO_2$ after HI (Fig. 9.2). This decline had been observed previously [19]. The decline was progressive, with a low plateau occurring about 1.5 h post-HI. The apparent diffusion content (ADC) declined significantly

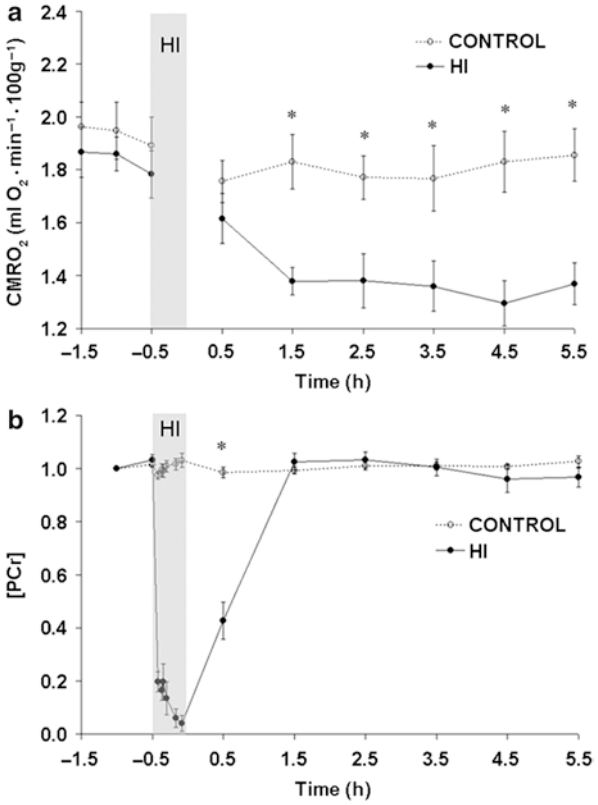

Fig. 9.2 Multimodal studies of stroke (hypoxia/ischemia, HI) in a piglet model. (**a**) metabolic rate for oxygen ($CMRO_2$) and (**b**) phosphocreatine (PCr) with time. $CMRO_2$ was calculated from NIRS data on hemoglobin saturation. Perfusion was measured with NIRS and an ICG bolus. Data show continuous reduction in $CMRO_2$ while PCr, and therefore mitochondrial redox ratios, recover; adapted from [18]

by 3.5 h post-HI. By that time, energy metabolites including PCr and Pi had totally recovered while nucleoside triphosphate remained approximately 8 % lower than pre-HI conditions. Proton spectroscopy showed that lactate increased after HI, but had largely recovered by 1.5 h post-HI. The recovery of metabolites and oxygenation occurred in conjunction with reduced $CMRO_2$. The reduced $CMRO_2$ is consistent with a controlled reduction in metabolic rate rather than a condition where metabolic rate is inhibited by deficient substrate or direct effects of hypoxia [18].

Another group also using a piglet model combined a four wavelength NIRS system outside the MRI with alternating measurements of ^{31}P NMR obtained at 4.7 T. Although the study was not strictly simultaneous, it shows that relevant multimodal data can be obtained when NIRS is undertaken before and after MRI. HI was induced by blocking both carotid arteries and reducing inspired O_2 until the PCr/Pi ratio was reduced to approximately 30 % of pre-hypoxia values for 1 h [20]. It was suggested that when energy utilization was drastically reduced, and the cells were in an energy failure condition, there could actually be an increase in cytOx oxidation state. When energy production is moderately reduced, then cytOx can decline. Low PCr/Pi ratios reflect reduced energy status in both cases. Increased neuronal death was confirmed with histology. This suggests that measurements of PCr and cytochrome oxidation state may predict post-HI damage.

7 Conclusion

In this review, we have demonstrated that multimodal NIRS/MRI provides added capability for brain studies where there are changes in oxygenation and/or functional activation and metabolic rate. Among other things, this multimodal configuration has shown that brain metabolism is not oxygen-limited and that it is possible for metabolic rate to decline with hypoxia/ischemia. The studies described illustrate how NIRS/MRI can be applied to monitor brain metabolism in various physiological settings.

Acknowledgments Work was supported by NSERC, CIHR, endMS, the MS Society of Canada and AIHS.

References

1. Ishii K, Kitagaki H, Kono M, Mori E (1996) Decreased medial temporal oxygen metabolism in Alzheimer's disease shown by PET. J Nucl Med 37(7):1159–1165
2. Brooks DJ, Leenders KL, Head G, Marshall J, Legg NJ, Jones T (1984) Studies on regional cerebral oxygen utilisation and cognitive function in multiple sclerosis. J Neurol Neurosurg Psychiatry 47(11):1182–1191
3. Heiss WD, Podreka I (1993) Role of PET and SPECT in the assessment of ischemic cerebrovascular disease. Cerebrovasc Brain Metab Rev 5(4):235–263

4. Oehmichen M, Woetzel F, Meissner C (2009) Hypoxic-ischemic changes in SIDS brains as demonstrated by a reduction in MAP2-reactive neurons. Acta Neuropathol 117(3):267–274
5. Buxton RB, Frank LR (1997) A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. J Cereb Blood Flow Metab 17(1):64–72
6. Ogawa S, Lee TM, Kay AR, Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 87(24):9868–9872
7. Kleinschmidt A, Obrig H, Requardt M, Merboldt KD, Dirnagl U, Villringer A, Frahm J (1996) Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. J Cereb Blood Flow Metab 16(5):817–826. doi:10.1097/00004647-199609000-00006
8. Gagnon L, Yucel MA, Dehaes M, Cooper RJ, Perdue KL, Selb J, Huppert TJ, Hoge RD, Boas DA (2012) Quantification of the cortical contribution to the NIRS signal over the motor cortex using concurrent NIRS-fMRI measurements. Neuroimage 59(4):3933–3940. doi:S1053-8119(11)01218-3 [pii]. 10.1016/j.neuroimage.2011.10.054
9. Xu H, Deghani H, Pogue BW, Springett R, Paulsen KD, Dunn JF (2003) Feasibility of NIR tomographic reconstruction with multispectral continuous wave data by mapping into frequency domain data. Proc of SPIE 4955
10. Chuang CC, Chen CM, Hsieh YS, Liu TC, Sun CW (2012) Brain structure and spatial sensitivity profile assessing by near-infrared spectroscopy modeling based on 3D MRI data. J Biophotonics 6(3):267–274. doi:10.1002/jbio.201200025
11. Springett R, Wylezinska M, Cady EB, Cope M, Delpy DT (2000) Oxygen dependency of cerebral oxidative phosphorylation in newborn piglets. J Cereb Blood Flow Metab 20(2):280–289
12. Mayevsky A, Nioka S, Subramanian VH, Chance B (1988) Brain oxidative metabolism of the newborn dog: correlation between 31P NMR spectroscopy and pyridine nucleotide redox state. J Cereb Blood Flow Metab 8(2):201–207
13. Matcher SJ, Elwell CE, Cooper CE, Cope M, Delpy DT (1995) Performance comparison of several published tissue near-infrared spectroscopy algorithms. Anal Biochem 227(1):54–68. doi:S0003-2697(85)71252-3 [pii]. 10.1006/abio.1995.1252
14. Matcher SJ, Cooper CE (1994) Absolute quantification of deoxyhaemoglobin concentration in tissue using near infrared spectroscopy. Phys Med Biol 39:1295
15. Tsuji M, Naruse H, Volpe J, Holtzman D (1995) Reduction of cytochrome aa3 measured by near-infrared spectroscopy predicts cerebral energy loss in hypoxic piglets. Pediatr Res 37(3):253–259. doi:10.1203/00006450-199503000-00001
16. Shin'oka T, Nollert G, Shum-Tim D, du Plessis A, Jonas RA (2000) Utility of near-infrared spectroscopic measurements during deep hypothermic circulatory arrest. Ann Thorac Surg 69(2):578–583
17. Rolett EL, Azzawi A, Liu KJ, Yongbi MN, Swartz HM, Dunn JF (2000) Critical oxygen tension in rat brain: a combined (31)P-NMR and EPR oximetry study. Am J Physiol Regul Integr Comp Physiol 279(1):R9–R16
18. Winter JD, Tichauer KM, Gelman N, Thompson RT, Lee TY, St Lawrence K (2009) Changes in cerebral oxygen consumption and high-energy phosphates during early recovery in hypoxic-ischemic piglets: a combined near-infrared and magnetic resonance spectroscopy study. Pediatr Res 65(2):181–187
19. Tichauer KM, Brown DW, Hadway J, Lee TY, St Lawrence K (2006) Near-infrared spectroscopy measurements of cerebral blood flow and oxygen consumption following hypoxia-ischemia in newborn piglets. J Appl Physiol 100(3):850–857
20. Peeters-Scholte C, van den Tweel E, Groenendaal F, van Bel F (2004) Redox state of near infrared spectroscopy-measured cytochrome aa(3) correlates with delayed cerebral energy failure following perinatal hypoxia-ischaemia in the newborn pig. Exp Brain Res 156(1):20–26. doi:10.1007/s00221-003-1761-5
21. Dunn JF, Zaim-Wadghiri Y, Pogue BW, Kida I (1998) BOLD MRI vs. NIR spectrophotometry. Will the best technique come forward? Adv Exp Med Biol 454:103–113
22. Punwani S, Cooper CE, Clemence M, Penrice J, Amess P, Thornton J, Ordidge RJ (1997) Correlation between absolute deoxyhaemoglobin [dHb] measured by near infrared spectroscopy (NIRS) and absolute R2' as determined by magnetic resonance imaging (MRI). Adv Exp Med Biol 413:129–137