

## Noninvasive Measurement of Cerebral Blood Flow in Adults Using Near-Infrared Spectroscopy and Indocyanine Green: A Pilot Study

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**Summary:** This pilot study was designed to determine the feasibility of measuring cerebral blood flow noninvasively after an intravenous bolus of indocyanine green using near-infrared spectroscopy and pulse dye–densitometry. Feasibility aside, this study did not attempt to validate the measured values of cerebral blood flow against an established method of measurement. Twelve healthy volunteers were investigated after peripheral intravenous injection of indocyanine green. Arterial and cerebral changes in indocyanine green concentration were measured using pulse dye–densitometry and near-infrared spectroscopy, respectively. Two methods of calculating cerebral blood flow were used, and a blood flow index was also estimated. Absolute cerebral blood flow was calculated using a modification of the Fick principle and a deconvolution algorithm to derive the impulse residue function. Mean (range) estimated cerebral blood flow for the Fick method was 8.2 mL/100 g/min (4.2–16.2 mL/100 g/min) and 8.3 mL/100 g/min (4.7–15.3 mL/100 g/min) for the impulse residue function method. The impulse residue function method provided a more precise intrasubject estimation of cerebral blood flow compared with the modified Fick principle, with a coefficient of variation of 10.1% versus 25.5%. The blood flow index was 8.6 mg/sec (range: 5.6–17.3 mg/sec) with an intrasubject coefficient of variation of 12.0%. Estimation of cerebral blood flow using near-infrared spectroscopy and pulse dye–densitometry can be made at the bedside after intravenous injection of indocyanine green, and the precision can be improved using a deconvolution algorithm. Notwithstanding the low values obtained for absolute cerebral blood flow, further investigation and validation of this bedside technique is warranted.

**Key Words:** Cerebral blood flow—Measurement—Near-infrared spectroscopy—Indocyanine green

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The importance of the maintenance of cerebral perfusion and oxygenation in the prevention of secondary brain injury is now well accepted. A simple method for bedside measurement of cerebral blood flow (CBF) would provide

useful information to guide the management of brain-injured patients. Positron emission tomography, single photon emission computed tomography, or magnetic resonance imaging techniques all require a potentially unstable patient to be transported to a remote scanning suite (1,2). Established bedside methods for measurement of CBF with inert tracers, such as the nitrous oxide method described by Kety and Schmidt (3) or the  $^{133}\text{Xe}$  technique (4), are invasive, technically difficult, and time-consum-

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ing. Transcranial Doppler sonography is used frequently at the bedside as an estimate of CBF, but measures blood flow velocity and therefore does not allow quantitative measurement of CBF (5). A continuous jugular thermodilution technique has been reported as another approach for measurement of CBF (6), but this is somewhat cumbersome for routine use at the bedside. Recently, a transcerebral double-indicator dilution technique for bedside use has been described, although it requires cannulation of the jugular venous bulb (7,8).

Near-infrared spectroscopy (NIRS) is a noninvasive technique that has been used to measure CBF in adults and children (9–11). This method, using the Fick principle and oxyhemoglobin as an intravascular tracer, is complicated by a low signal-to-noise ratio. Indocyanine green (ICG) is a strong near-infrared absorber that has been used recently with NIRS to measure CBF in children during cardiopulmonary bypass (12,13). Previously it has only been possible to measure arterial ICG concentration continuously with an invasive technique using an optical device placed intra-arterially, but recently a pulse dye–densitometer that measures arterial ICG concentration accurately via a finger or nasal probe has been developed (14,15). The current study describes three potential methods to estimate CBF in adults using NIRS and pulse dye–densitometry to measure changes in cerebral and plasma ICG concentrations after an intravenous injection of ICG.

## METHODS

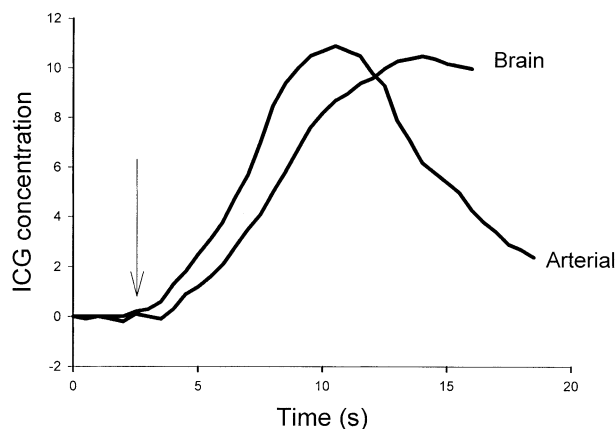
Twelve healthy volunteers were studied after the study received institutional ethics committee approval. The subjects lay supine and a rapid bolus of 0.1 mg/kg ICG was injected into an antecubital vein via an indwelling cannula. Three to five injections of ICG were made in each subject. Arterial ICG concentration was measured noninvasively using a dye–densitometer (DDG 2001 Nihon Kohden, Tokyo, Japan) and a nasal probe. Simultaneous changes in cerebral ICG concentration were measured with NIRS using an NIRO 500 spectrophotometer (Hamamatsu Photonics, Japan). The optodes were placed over the right frontal region with an interoptode spacing of 40 mm. Near-infrared spectroscopy data were collected at 0.5-second intervals, and the outputs from the pulse dye–densitometer and spectrophotometer were collected onto a personal computer using custom-written software. A differential path length factor of 6.26 was assumed for the NIRS calculations (16). Two methods of calculating CBF were applied to the data, and a blood flow index was also measured.

## Absolute Measurement of Cerebral Blood Flow

These calculations, using established algorithms and a modification of the Fick principle, have been described in detail elsewhere (9–11). Rapid intravenous injection of ICG results in an arterial ICG “bolus” that acts as the required Fick tracer. The rate of arrival of ICG in the brain a few seconds later can be observed by NIRS (Fig. 1). Cerebral blood flow may be calculated by considering the ratio of the rate of tracer accumulation in the brain to the amount of tracer delivered. The accumulation of ICG in the brain will be dependent on both arterial inflow and venous outflow. However, if measurements are made within the cerebrovascular transit time (four to six seconds), the venous outflow is negligible, and the measured increase in cerebral ICG concentration can be assumed to be entirely the result of arterial inflow of the tracer. The amount of tracer delivered to the brain can be calculated from the area under the curve of the arterial ICG concentration change measured by the dye–densitometer (see Fig. 1).

## Flow Scaled Impulse Residue Function

A method of analysis developed originally to calculate CBF using X-ray contrast media and dynamic computed tomographic imaging (17,18) was also applied to the data. This method, using linear systems techniques to model the tissue concentration of an intravascular tracer after an abrupt change in the arterial concentration, has been used recently to calculate CBF, using NIRS and ICG, in an animal model (19) and in human subjects (19,20). In our study, the same robust deconvolution algorithm was ap-



**FIG. 1.** Temporal relationship between cerebral and arterial indocyanine green concentration after an intravenous bolus of indocyanine green (administered at the point shown by the arrow). The traces have been normalized to display both curves on an arbitrary scale.

plied to the arterial and tissue concentration curves measured by NIRS to derive the flow scaled impulse residue function (IRF). This simulates the transit of the tracer through the brain as if it had been injected directly into its arterial input. The height of the IRF gives CBF in units of milliliters per gram per minute (19,20).

### Blood Flow Index

A cerebral blood flow index (BFI) was calculated according to the method of Kuebler *et al.* (21):

$$\text{BFI} = \frac{\text{maximum } \Delta \text{ ICG}}{\text{rise time}}$$

The rise time is the time interval between 10% and 90% of maximum signal during tracer inflow; in this case, the rise in brain ICG concentration measured by NIRS. A relative measure of CBF is calculated and expressed in arbitrary units of ICG concentration per second.

The precision of repeated measurements within individual subjects was assessed by calculation of the coefficient of variation (CV).

## RESULTS

High-quality NIRS and dye–densitometer recordings were obtained after every injection of ICG and all were suitable for analysis. A typical recording of simultaneous changes in arterial and cerebral ICG concentration after an intravenous injection of ICG is shown in Figure 1.

The mean (range) value for CBF using the modified Fick principle was 8.2 mL/100 g/min (4.2–16.2 mL/100 g/min) and 8.3 mL/100 g/min (4.7–15.3 mL/100 g/min) using the IRF methodology. The blood flow index was 8.6 mg/sec (5.6–17.3 mg/sec). The CV for intrasubject repeated measurement of CBF estimated using the Fick, IRF, and BFI methodologies was 25.5%, 10.1%, and 12.0% respectively.

## DISCUSSION

This is the first study to attempt to measure CBF in adults using NIRS and intravenous ICG. The development of a reliable and noninvasive method of measuring arterial ICG concentration using pulse dye–densitometry (14,15) has allowed repeated, noninvasive measurements to be made. This pilot study did not attempt to validate the estimations of CBF by comparison with a conventional method of measurement, but was designed to investigate

the feasibility of the method. The absence of a “gold standard” value for CBF in each individual means that the actual intersubject CBF variation for this cohort of volunteers is unknown. For this reason, we also did not attempt to assess intersubject variation of NIRS-derived estimates of CBF, but only measured the intraindividual variation of repeated CBF measurements.

We used a similar technique to that described to measure CBF in children during cardiopulmonary bypass (12,13), although in those studies ICG was injected into the cardiopulmonary bypass circuit and arterial ICG concentration was measured invasively. Kuebler *et al.* (21) compared NIRS-derived BFI with regional CBF measured using radioactive microspheres in piglets. They found that the NIRS-derived BFI correlated with cortical blood flow but not with galeal blood flow. This confirms that the signals recorded by NIRS reflect cerebral rather than extracerebral phenomena when ICG is used as the intravascular tracer. We think that the ease with which the measurements were made in our study, the noninvasive nature of the technique, and the improved precision using IRF or BFI calculations warrants further investigation. Studies to determine whether this technique is able to detect changes in CBF in volunteers and in patients on the intensive care unit are already underway, and validation studies are planned.

The absolute values for CBF measured in our study are low compared with values obtained by conventional methods (1). All NIRS methods strikingly underestimate CBF in adults (22), and this may relate to the contribution of extracerebral tissue within the field of view (23). The head is not opaque to infrared light, but scatters the light very intensely. Computer modeling has shown that in the adult head, of the typical volume of tissue examined by conventional NIRS equipment, approximately 20 to 30% is brain and 70 to 80% is extracerebral—in other words, scalp and skull (22). Extracerebral blood flow is low, (24) and therefore, at most, only 30% of the illuminated volume has a rapidly varying tracer concentration during CBF measurements. However, the differential path length factor used in the calculation applies to the entire illuminated tissue volume and thus leads to a scaled reduction in the measured brain ICG concentration (and hence blood flow) of some four to five times. The contribution of extracerebral tissue to NIRS-derived CBF measurements must be investigated further if this technique is to find a place in clinical practice.

New-generation instrumentation may improve the sensitivity of NIRS-derived measurements to intracerebral changes. In a recent study, the Hamamatsu NIRO 300

spectrophotometer (which uses spatially resolved spectroscopy) was used to measure changes in brain tissue oxygen index during carotid surgery (25). Tissue oxygen index was 87.5% sensitive to and 100% specific for intracranial changes, whereas the sensitivity and specificity to extracranial changes were 0%. This suggests that tissue oxygen index, as measured by the NIRO 300, reflects changes in *cerebral* tissue oxygenation with little contribution from extracranial sources.

The low values obtained for CBF in the current study may also result from the slow rise of the arterial ICG bolus because of the intravenous injection route. Under these circumstances, the alternative BFI calculation described by Kuebler *et al.* (21) may be more appropriate. The use of the rise time function in this calculation eliminates the need for exact temporal definition of the start and end of tracer inflow. BFI is therefore only a *relative* measure of blood flow but should nonetheless be capable of detecting CBF *changes* within an individual. Because we did not attempt to change CBF in this study, it is impossible to test this hypothesis. The significant linear correlation between BFI and cortical CBF in the study by Kuebler *et al.* (21) suggests that it should be possible to transform BFI into CBF data. Because there was an "offset" in this correlation, it is likely that the relationship will be species, or even individual, specific. However, BFI has the potential to monitor therapeutic manipulation of CBF during treatment of brain-injured patients in the intensive care unit, and further work in this area is merited.

The slow rise of the arterial ICG bolus after intravenous administration may also affect adversely the precision of the technique. Repeated measurement of CBF using the Fick principle resulted in a CV of 11% when ICG was injected arterially via a CPB circuit in children undergoing cardiac surgery (13). This is better than the precision in our study, in which intraindividual repeated CBF measurements using the Fick principle resulted in a CV of 25.5%. However, it is similar to the precision we obtained using the IRF and BFI calculations, with a CV of 10.1% and 12.0% respectively. The intravenous route for ICG administration is less invasive than arterial or central venous routes and may be preferable under many circumstances. We have demonstrated that, if IRF or BFI calculations are used, the precision of repeated CBF measurements using intravenous ICG is within a clinically acceptable range.

A stringent requirement of the established method of CBF calculation is that only data before washout of the tracer from the brain can be used in the Fick calculation, because the method assumes that there is no venous out-

flow (9–11). Because the minimum transit time through the brain is less than four to six seconds (26), there is a requirement for fast and high signal-to-noise data acquisition during the tracer inflow phase. Both of these are difficult to achieve simultaneously using conventional NIRS equipment, which collects data at 0.5-second intervals. Limited data points are therefore available for calculation of CBF using the modified Fick principle, resulting in the poor precision of this technique. More recently introduced NIRS instruments, such as the Hamamatsu NIRO 300, are able to sample more frequently and overcome this problem. The IRF methodology, on the other hand, does not require fast data acquisition and extends the use of data beyond the inflow phase to cover the whole of the first circulation period of tracer through the brain (20–30 seconds versus 4–6 seconds). This results in greater noise averaging and a more precise estimate of CBF than other techniques. In this study, the IRF methodology improved the precision of the CBF estimation to clinically acceptable levels.

A further source of variability contributing to poor precision is the intersubject variation in differential path length factor—typically around 9% (27). This variability can, in principle, be eliminated by newer NIRS instrumentation that can measure simultaneously the optical path length for each subject (28).

This preliminary investigation has demonstrated that bedside estimation of CBF is possible using NIRS and intravenous ICG. Although the absolute values for CBF are low, this noninvasive technique, combining NIRS and pulse dye–densitometry, allows repeated measurements to be made and therefore may be ideal for measuring relative changes in CBF over short periods of time. Sophisticated methods of data analysis result in more precise estimates of CBF. Furthermore, arterial or central venous injection of the ICG bolus should also improve the precision of the technique, as would precise determination of the contribution of extracranial tissue to the overall optical path length. Under these circumstances, it may be possible to develop a technique that allows more accurate estimates of absolute CBF to be made. The simpler BFI measurement allows changes in CBF to be estimated when absolute values are not required. Further investigation and validation of the use of ICG and NIRS for noninvasive measurement of CBF at the bedside is warranted.

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## REFERENCES

1. Leenders KL, Perani D, Lammertma AA, et al. Cerebral blood flow, blood volume and oxygen utilisation. Normal values and effect of age. *Brain* 1990;113:27–47.
2. Liu Y, Karonen JO, Vanninen RL, et al. Cerebral hemodynamics in human acute ischaemic stroke: a study with diffusion- and perfusion-weighted magnetic resonance imaging and SPECT. *J Cereb Blood Flow Metab* 2000;20:910–20.
3. Kety SS, Schmidt CF. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J Clin Invest* 1948;27:476–83.
4. Obrist WD, Thomson HK, Wang HS, et al. Regional cerebral blood flow estimated by 133-xenon inhalation. *Stroke* 1975;6:245–56.
5. Kirkham FJ, Padayachee TS, Parsons S, et al. Transcranial measurement of blood velocities in the basal cerebral arteries using pulsed Doppler ultrasound: velocity as an index of flow. *Ultrasound Med Biol* 1986;12:15–21.
6. Melot C, Berre J, Moraine JJ, et al. Estimation of cerebral blood flow at bedside by continuous jugular thermodilution. *J Cereb Blood Flow Metab* 1996;16:1263–70.
7. Wietasch JK, Mielck F, Scholz M, et al. Bedside assessment of cerebral blood flow by double-indicator dilution technique. *Anesthesiology* 2000;92:367–75.
8. Keller E, Wietasch JK, Ringleb P, et al. Bedside monitoring of cerebral blood flow in patients with acute hemispheric stroke. *Crit Care Med* 2000;28:511–6.
9. Edwards AD, Wyatt JS, Richardson C, et al. Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy. *Lancet* 1988;ii:770–1.
10. Elwell CE, Cope M, Edwards AD, et al. Quantification of adult cerebral hemodynamics by near infrared spectroscopy. *J Appl Physiol* 1994;77:2753–60.
11. Elwell CE, Cope M, Edwards AD, et al. Measurement of cerebral blood flow in adult humans using near infrared spectroscopy—methodology and possible errors. *Adv Exp Med Biol* 1992;317:235–45.
12. Roberts I, Fallon P, Kirkham FJ, et al. Estimation of cerebral blood flow with near infrared spectroscopy and indocyanine green. *Lancet* 1993;342:1425.
13. Roberts IG, Fallon P, Kirkham FJ, et al. Measurement of cerebral blood flow during cardiopulmonary bypass with near-infrared spectroscopy. *J Thorac Cardiovasc Surg* 1998;115:94–102.
14. Iijima T, Aoyagi T, Iwao Y, et al. Cardiac output and circulating blood volume analysis by pulse dye–densitometry. *J Clin Monit* 1997;13:81–9.
15. Haruna M, Kumon K, Yahagi N, et al. Blood volume measurement at the bedside using ICG pulse spectrophotometry. *Anesthesiology* 1998;89:1322–8.
16. Duncan A, Meek JH, Clemence M, et al. Measurement of cranial optical pathlength as a function of age using phase resolved optical spectroscopy. *Pediatr Res* 1996;39:1–7.
17. Cenic A, Nabavi DG, Craen RA, et al. Dynamic CT measurement of cerebral blood flow: a validation study. *AJNR Am J Neuroradiol* 1999;20:63–73.
18. Nabavi DG, Cenic A, Craen RA, et al. CT assessment of cerebral perfusion: experimental validation and initial clinical experience. *Radiology* 1999;213:141–9.
19. Brown DW, Picot PA, Springett R, et al. Comparison of near-infrared spectroscopy with CT cerebral blood flow measurements in newborn piglets. *Proc SPIE* 2001;4321:168–76.
20. Lee T-Y, Gora F, Elwell C, et al. New method for the calculation of cerebral blood flow using near-infrared spectroscopy. In: Gandjbakhche AH, ed. *Proceedings of Inter-Institute Workshop on in-vivo Optical Imaging at NIH*. Washington, DC: Optical Society of America, 2000:81–8.
21. Kuebler WM, Sckell A, Habler O, et al. Noninvasive measurement of regional cerebral blood flow by near-infrared spectroscopy and indocyanine green. *J Cereb Blood Flow Metab* 1998;18:445–56.
22. Hiraoka M, Firbank M, Essenpreis M, et al. A Monte Carlo investigation of optical pathlength in inhomogeneous tissue and its application to near infrared spectroscopy. *Phys Med Biol* 1993;38:1859–77.
23. Owen–Reece H, Smith M, Elwell CE, et al. Use of near-infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetised adult subjects. *Br J Anaesth* 1996;76:43–8.
24. Friberg L, Kastrop J, Hansen M, Bulow J. Cerebral effects of scalp cooling and extracerebral contribution to calculated blood flow values using the intravenous <sup>133</sup>Xe technique. *Scand J Clin Lab Invest* 1986;46:375–9.
25. Al-Rawi PG, Smielewski P, Kirkpatrick PJ. Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. *Stroke* 2001;32:2492–500.
26. Carlsen O, Hedegard O. Evaluation of regional cerebral circulation based on absolute mean transit times in radionuclide cerebral angiography. *Phys Med Biol* 1987;32:1457–67.
27. Delpy DT, Cope M, van der Zee P, et al. Estimation of optical pathlength through tissue from direct time of flight measurement. *Phys Med Biol* 1988;33:1433–42.
28. Delpy DT, Cope M. Quantification in tissue near infrared spectroscopy. *Phil Trans R Soc London* 1997;352:649–59.