ASSESSMENT OF SPATIALLY RESOLVED SPECTROSCOPY DURING CARDIOPULMONARY BYPASS

Pippa G. Al-Rawi,[†] Piotr Smielewski,[†] Helen Hobbiger,[‡] Sunit Ghosh,[‡] and Peter J. Kirkpatrick[†]
[†]Addenbrooke's Hospital, University Department of Neurosurgery, Cambridge CB2 2QQ, United Kingdom; [‡]Papworth Hospital, Department of Anaesthesia, Cambridge CB3 8QD, United Kingdom
(Paper JBO-183 received Oct. 31, 1997; revised manuscript received Sep. 17, 1998; accepted for publication Sep. 28, 1998.)

ABSTRACT

Controversy remains about which tissue is primarily responsible for light attenuation of near infrared spectroscopy (NIRS) in the adult, the spatial resolution provided and the preferred algorithm for quantification. Until recently, changes in NIRS have not been fully quantified and have been difficult to interpret without sophisticated computation. A new development by Hamamatsu Photonics, the spatially resolved spectrometer (SRS), may be able to give a quantitative measure of oxygen saturation. We have incorporated the SRS into a multimodality monitoring system for the purpose of direct validation against jugular bulb oxygen saturation (SjO_2) in patients undergoing routine cardiopulmonary bypass (CPB). The importance of this investigation is in the development of the SRS machine which shows potential as a useful clinical tool. The results demonstrated good correlation between SRS and SjO_2 in 12 out of the 24 patients studied. Although these results are encouraging, this study suggests that the SRS, in its present form, is not a reliable clinical monitor of cerebral oxygen saturation during CPB.
[S1083-3668(99)00202-6]

Keywords spatially resolved spectroscopy; near infrared spectroscopy; cardiopulmonary bypass; jugular venous oximetry; cerebral oxygen saturation.

1 INTRODUCTION

Since it was described by Jobsis in 1977,[1] tissue near infrared spectroscopy (NIRS) has become an established research tool with numerous applications.[2–6] In particular, NIRS has shown potential as a technique for monitoring events of cerebral desaturation noninvasively with good temporal resolution in both neonates[7–13] and in adults.[1,2,14–17] However, the tissues primarily responsible for light attenuation in adult NIRS remain unclear,[18–22] as do the spatial resolution and quantification of signal changes.[7,9,23–25] Present commercial instruments detect changes in optical attenuation of a number of wavelengths of near infrared light[26,27] and various algorithms have been applied to attempt quantification.[2,9,24] Claims as to their accuracy remain controversial,[28] and recent evidence showing the variation in the differential pathlength factor among individuals[24,29] serves to highlight the importance of developing hardware that is able to accommodate differences in patients.

Hamamatsu Photonics, in conjunction with University College London (UCL), have developed a new near infrared spectrometer called the spatially resolved spectrometer (SRS) which may be able to give a quantitative measure of oxygen saturation.[30] Unlike earlier near infrared monitors developed by Hamamatsu, the NIRO 500 and 1000, the SRS is claimed to be capable of measuring the absolute concentrations of hemoglobin and oxyhemoglobin in cerebral tissue, rather than just the relative changes in the concentration of these chromophores.

By testing this instrument on patients undergoing cardiopulmonary bypass (CPB), our aim was to determine whether the SRS provides a valid measurement of oxygen saturation in the adult brain. CPB results in a general reduction in cerebral perfusion pressure.[31–33] Patients on bypass therefore reliably show global cerebral desaturation.[34–37] Under these conditions, the oxygen saturation of the venous blood exiting the cranium is uniformly affected. Measuring the right jugular venous oxygenation (SjO_2) in this group of patients allows a direct comparison between SRS measurements and invasive jugular venous oximetry.[34,36,38–40] The purpose of the study was to determine how values generated by the SRS compared with those shown by the SjO_2 measurements, thereby assessing the SRS as a po-

Address all correspondence to Mrs. Pippa G. Al-Rawi. Tel: 44 (0) 1223 217205; Fax: 44 (0) 1223 414396.

1083-3668/99/$10.00 © 1999 SPIE

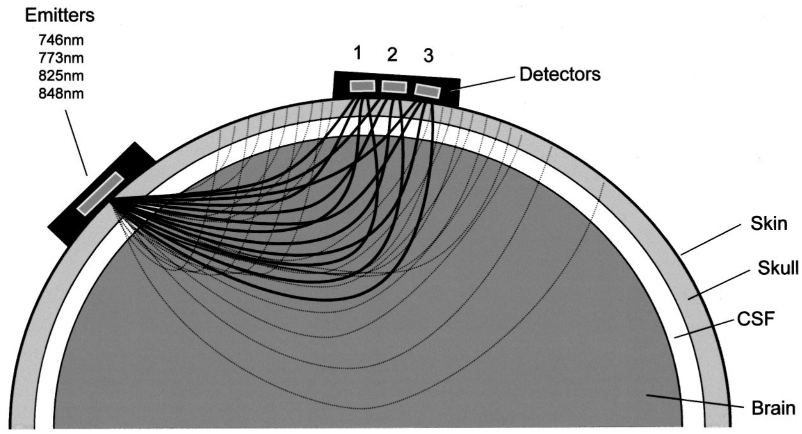

Fig. 1 Schematic representation of spatially resolved reflectance spectroscopy.

tential noninvasive tool for the monitoring of cerebral oxygenation.

2 Spatially Resolved Spectroscopy

The theory behind NIRS has been described in detail previously.[3,9,41]

The SRS differs from conventional NIRS machines by using spatially resolved reflectance spectroscopy to estimate absolute concentrations of hemoglobin (Hb) and oxyhemoglobin (HbO_2) in diffuse intracranial tissue and can theoretically provide direct, continuous on-line measurements of measured cerebral hemoglobin oxygen saturation ($SmcO_2$). The basic measurement made is the rate of increase of light attenuation with respect to source/detector spacing.

The SRS delivers four wavelengths of near infrared light through a flexible fiber optic bundle housing four laser diodes (Figure 1). Back scattered light is detected by a new design of detector which consists of three closely placed photodiodes arranged in three parallel strips. The light detected by each photodiode is used to generate a plot of log of attenuation against distance from source. The rate of increase of attenuation with respect to source/detector spacing, i.e., the slope, can then be calculated. These measurements are converted into estimates of the product of absorption and scattering coefficients of the tissue according to the equation

$$\mu_a \times \mu_s \approx \left(\frac{\delta A}{\delta d} - \frac{2}{d} \right)^2$$

where μ_a = absorption coefficient, μ_s = scattering coefficient, A = attenuation, and d = distance.

In vivo measurements have produced an algorithm which gives the scattering coefficient for the tissue and thereby estimates the total tissue absorption coefficient.[29,30] These calculations are performed at each of the four wavelengths of light. Using a regression model obtained from multiple regression analysis of known Hb and HbO_2 concentrations and absorptions, total absolute concentrations of Hb and HbO_2 for each absorption coefficient can be calculated, and hence $SmcO_2$ (Figure 2).

The SRS displays a table of readings for the light detected at each receiving photodiode for each wavelength of light. The normal measurement con-

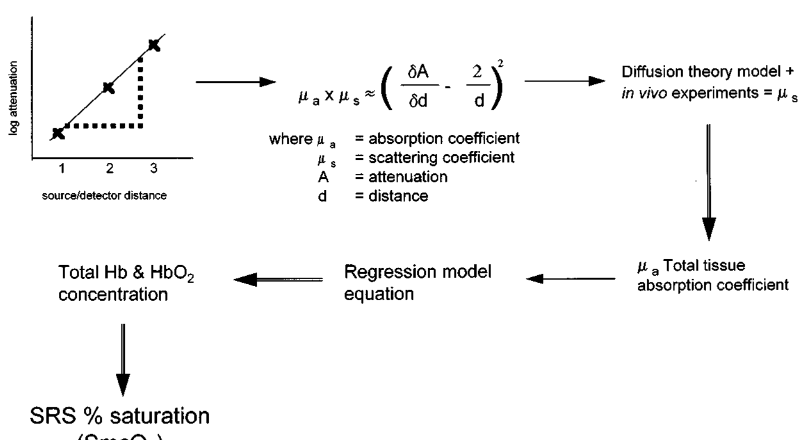

Fig. 2 Theory behind SRS quantification.

dition shows the values of the detected light flux increasing exponentially from the most distant detector channel all the way through to the closest. Spacing of the probes is adjustable to ensure that each channel of the SRS detector receives adequate light attenuation and no channel becomes saturated. The regressions of log of attenuation versus source/detector spacing are therefore kept as linear as possible. In practice this means that values should be between 20 and 980, and the offset should be less than 10% of the slope. Inadequate, or too much, flux will result in significant inaccuracies of the SRS calculation and thus invalidate the Hb, HbO_2 and $SmcO_2$ signals generated. Unlike the NIRO 500 detecting sensor, it is necessary that the SRS detector be placed in the correct orientation relative to the laser diode bundle. The correct orientation ensures that the three photodiodes in the detector head are sited at uniformly increasing distances from the source.

Other models of near infrared spectrometers use photomultiplier tubes, which essentially count individual photons. They are therefore very sensitive to ambient light and problems of oversaturation occur. Since the SRS uses photodiode detectors, which are semiconductor devices, it cannot be damaged by overexposure to room light and is unaffected by ambient light, therefore not requiring shielding. The detector connection to the patient, however, being a low voltage, shielded electrical connection, is more prone to electrical interference from other monitoring equipment and electrical apparatus such as diathermy.

The optodes themselves are held in a black custommade holder which allows them to be set at distances from 3 to 6 cm. The distance can be altered for optimal recording, but it is advisable that it should not be less than 3.5 cm since a distance of less than this would theoretically result in a large contribution to the reading coming from extracerebral tissue.[18,42]

3 METHOD

3.1 PATIENT POPULATION AND PROCEDURE

After Local Research Ethics Committee approval and with informed consent, 24 patients (22 male and 2 female) undergoing elective coronary artery bypass grafts (CABGs) were investigated. Of these, 20 cases employed hypothermic bypass and the remaining 4 were carried out at normothermia. The mean age was 62 (range 21–75). Patients with a history of pre-existing cerebrovascular or carotid artery disease were excluded. The anaesthetic technique was standardized and involved premedication with morphine (0.2 mg/kg) and hyoscine (4 mcg/kg), induction with midazolam (0.15 mg/kg) and fentanyl (15 mcg/kg) followed by muscle relaxation with pancuronium (0.15 mg/kg). Maintenance of anesthesia during surgery was achieved with either a propofol infusion (3–4 mg/kg) or isoflurane (Fi iso=0.5%–1%). The lungs were ventilated to achieve normocapnia uncorrected for temperature. Arterial oxygen saturation (SaO_2) was kept at approximately 97% (see Table 1). During hypothermic bypass nasopharyngeal temperature was maintained in the region of 29°C (moderate hypothermia). The average CPB time was 63 min.

Table 1 Pooled data (means±se) for different stages of hypothermic CABG operation.

	Pre-bypass	Early bypass	Rewarming	Post-bypass
SRS (%sat)	54±3.3	57±3.8	49±3.4	54±3.9
SjO_2 (%sat)	62±5.6	73±4.6	55±5.3	63±5.6
SaO_2 (%)	97±1.0	97±1.1	96±1.0	96±1.0
ABP (mm Hg)	73±5.4	56±6.4	57±5.4	68±3.8

3.2 INTRAOPERATIVE MONITORING

An Opticath jugular venous catheter (Abbott Laboratories, Maidenhead, UK) was inserted retrogradely into the right internal jugular bulb using standard techniques[43] and connected to a heparinized saline flush at a rate of 3 ml/h. Correct positioning of the jugular bulb catheter was verified by lateral cervical spine x ray.[43] The mean arterial blood pressure (ABP) was measured directly via a 20 g catheter placed in the left radial artery. Blood samples were taken from the jugular bulb catheter and arterial line every 15 min throughout the operation. The measured oxygen saturation and hemoglobin concentrations were assessed using an IL 482 co-oximeter (Instrumentation Laboratories, Warrington, UK). Anticoagulated whole blood was aspirated into the instrument, mixed with diluent, hemolyzed and brought to a constant temperature (37±0.3°C) in the cuvette. Patient temperature was continually recorded via a nasopharyngeal temperature probe.

The SRS optodes were positioned high on the ipsilateral forehead to avoid the prominent temporalis muscle and sufficiently lateral from the midline to avoid the superior saggital sinus. Care was taken to ensure no hair was between optodes and skin. Probe placement was optimized to keep the value of the offset below 10% of the slope value. In practice this meant that the optode spacing was kept at either 5 or 6 cm.

3.3 DATA PROCESSING AND ANALYSIS

Data signals from all the monitored parameters were digitized and collected on computer using specialized multimodality software.[44,45] Data were tested for autocorrelation to examine the strength of the relationship between the values. Using the Durbin-Watson test we found no significant evidence of autocorrelation for pooled data. Therefore, for purposes of comparison, multivariable linear regression was used to calculate the correlation coefficient between SjO_2 and SRS saturation obtained over the entire duration of monitoring. Multivariate ANOVA was used to compare SjO_2 and SRS during different periods.

4 RESULTS

The correlation between SjO_2 measurements and SRS varied greatly from patient to patient. For individual cases, r values were in the range of 0.08–0.97 (Table 2). However, correlation was seen in 12 out of 24 patients (denoted by † in Table 2) and of these, 9 gave consistently good results throughout.

There were no apparent clinical differences among the patients that would account for these variations.

Figure 3 demonstrates the typical data obtained for a case showing good correlation (No. 20) and one showing poor correlation (No. 13). For the latter case, it can be seen that the SRS readings did not show a great deal of change throughout, while the SjO_2 readings followed the expected pattern.[34–37]

Where SRS changes closely followed SjO_2 readings, the SRS responded to periods of desaturation more rapidly than the jugular bulb catheter (Figure 4).

Analysis of pooled data showed a significant correlation between SRS and SjO_2 changes with a partial correlation coefficient of 0.56 ($p<0.000\,01$).

4.1 HYPOTHERMIC BYPASS

Dividing the hypothermic bypass operations into four periods demonstrates a significant difference between the SjO_2 values obtained pre-bypass, during early bypass and in the rewarming phase (Figure 5). The SjO_2 values were highest during bypass and fell during the rewarming period to values lower than the pre-bypass figures. There was less of a difference between the rewarming and post-bypass values. Typically the values obtained during bypass were in the region of 75% saturation, and the lowest values obtained were seen during rewarming, typically around 52% (Table 1). The SRS readings followed a very similar pattern, with a significant difference seen between the early bypass period and rewarming. However, the SRS values were lower than the SjO_2 and the range of changes much smaller.

4.2 NORMOTHERMIC BYPASS

For those patients undergoing normothermic bypass, changes seen in both the SRS and SjO_2 readings were not found to be significant (Figure 6).

4.3 IN SUMMARY

Correlation between SjO_2 and SRS readings was seen in 50% of cases. Overall, the range of changes seen with the SRS was not as great as those seen with the SjO_2 measurements, and the SRS values tended to be 10%–15% lower than those seen with SjO_2, in particular during the bypass period (Table 1).

When the data for all 24 cases were regressed, the scatter of data points was high with an r value of 0.41 (Figure 7).

Table 2 Linear regression analysis data for all cases. † denotes those cases showing significant correlation. * denotes cases carried out with normothermic bypass. SD=standard deviation.

Case No.	n	R	Significant F	Intercept	Slope
2*	11	0.08	0.82	76.2	−0.02
3*	6	0.72	0.11	50.1	0.18
4	9	0.15	0.7	50.2	0.04
5†	9	0.77	0.02	17.3	0.47
8	9	0.52	0.15	45.1	0.24
9†	13	0.59	0.03	42.4	0.21
10	10	0.39	0.26	37.6	0.18
11*	11	0.24	0.48	43.6	0.18
12†	10	0.68	0.03	26.7	0.36
13	10	0.18	0.63	53.8	0.04
14†	6	0.97	0.001	29.3	0.31
15†	13	0.88	<0.001	32.4	0.41
16	10	0.45	0.19	44.8	0.18
17	13	0.39	0.19	46.6	0.22
18†	9	0.77	0.02	33.3	0.39
20†	19	0.76	<0.001	40.4	0.26
21†	10	0.65	0.04	41.5	0.29
22	9	0.32	0.4	47.8	0.18
23†	13	0.56	0.05	28.4	0.17
24*,†	10	0.88	<0.001	42.2	0.14
25	5	0.76	0.14	41.7	0.17
26	9	0.50	0.17	28.6	0.43
27†	16	0.86	<0.001	19.0	0.54
28†	11	0.68	0.02	13.6	0.53
Mean		0.57		38.9	0.25
SD		0.25		13.5	0.15

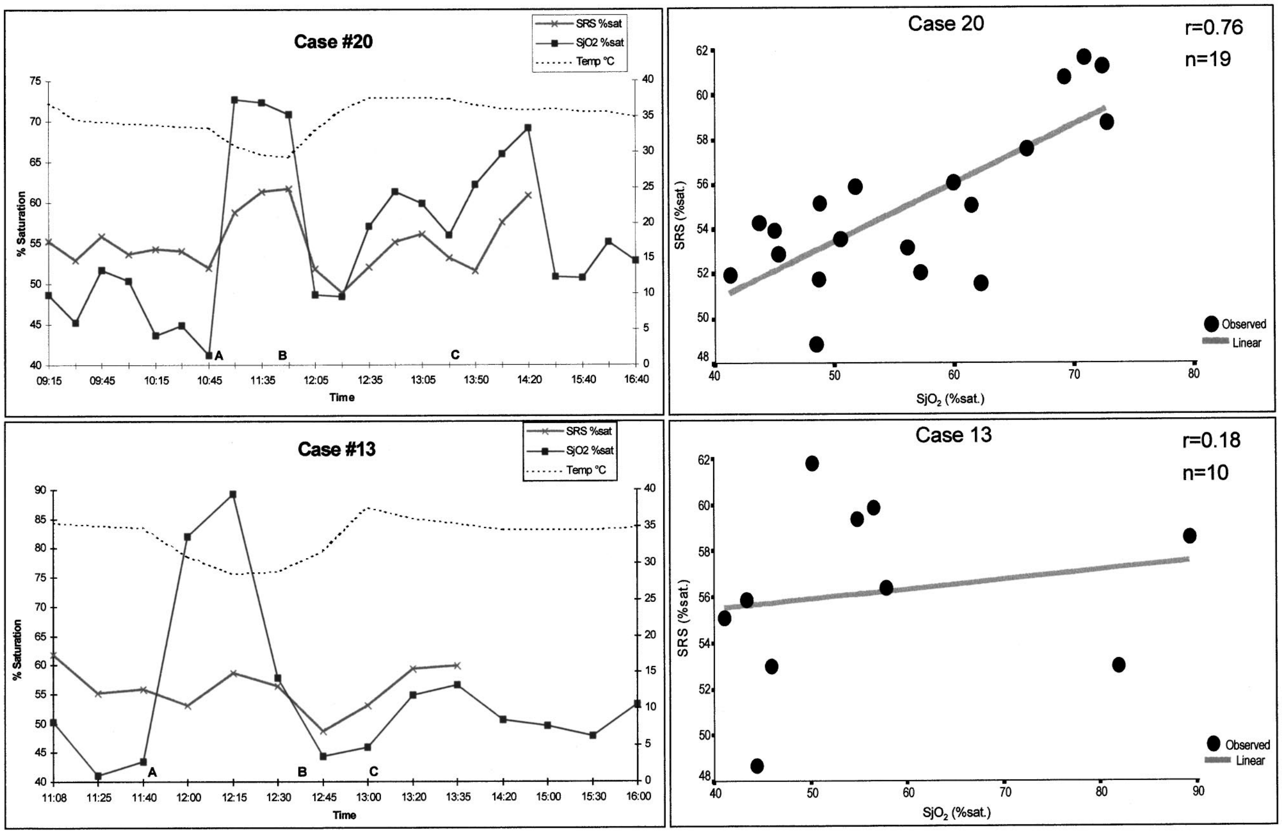

Fig. 3 Raw data graphs for two typical cardiopulmonary bypass cases and their associated regression plots (A=onto bypass, B=rewarming, C=off bypass).

5 DISCUSSION

Since the technique was used by Myerson et al.[46] placement of a retrograde jugular bulb catheter has enabled relatively safe direct access to the venous blood draining from the cerebral vasculature. Measurement of the oxygen saturation of this blood has been widely used to provide an indirect estimate of cerebral oxygenation, since it is generally regarded as a reliable indicator of the coupling of cerebral blood flow with metabolism.[47–51] In many institu-

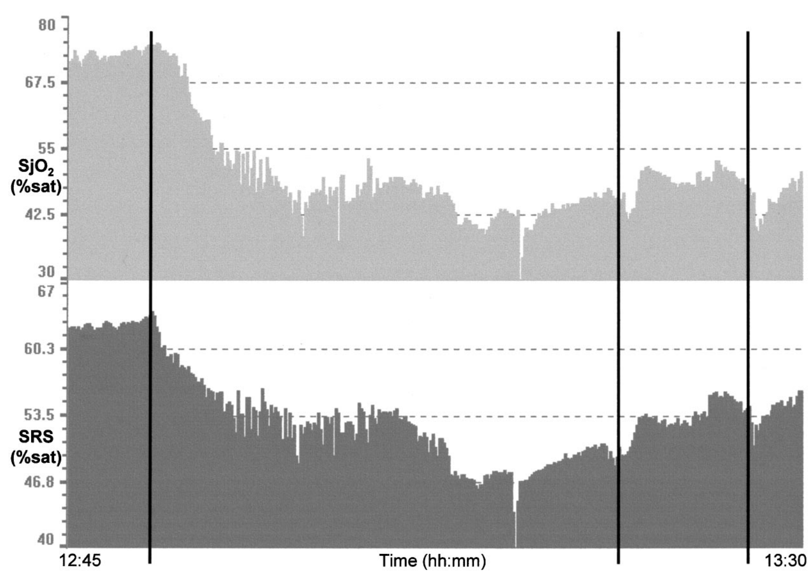

Fig. 4 Graphic display of data obtained from case No. 15, showing SjO_2 and SRS saturation during a coronary artery bypass graft operation. The vertical lines demonstrate the earlier response of SRS to episodes of desaturation.

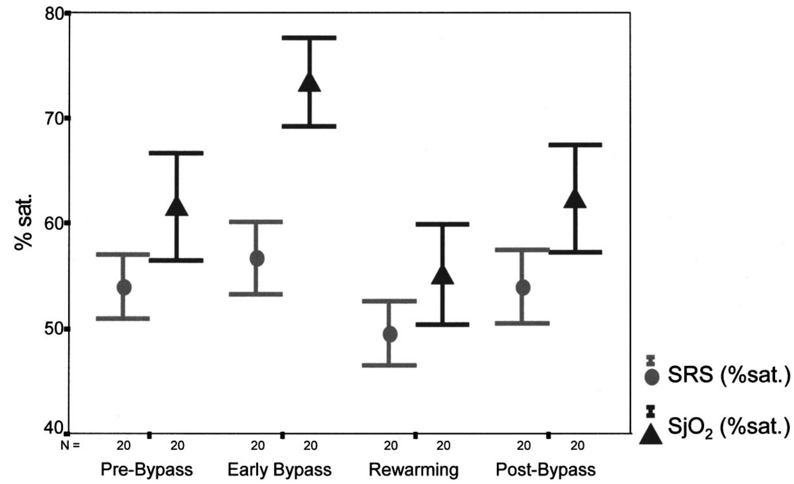

Fig. 5 Graph displaying mean values (±95% confidence limits) of SRS and SjO_2 saturation for all hypothermic cases.

tions the technique is routinely used in the management and monitoring of head injured patients, since evidence suggests an association between low SjO_2 and a poor outcome.[52,53] The SjO_2 values we obtained prior to surgery and during CPB are comparable with those obtained by other investigators.[36,54]

Despite the variations between SRS and SjO_2, 50% of the cases demonstrated good correlation, which we believe is encouraging. There are several possible reasons why the SRS and SjO_2 values may not always be similar. SjO_2 measurements give an estimation of the global cerebral oxygen saturation, whereas the SRS measures oxygen saturation in the microvasculature of cerebral tissue, thereby monitoring regional saturation. The extent to which the two sets of readings are the same will depend upon the extent to which the regional saturation monitored by the SRS reflects the average global saturation. Any inhomogeneous distribution of blood and metabolic activity will reduce the correlation between the two measurements.

The small range of SRS values may be expected since the cerebral microcirculation, from which the SRS obtains its values for Hb saturation, although largely of venous composition, has a 25% contribution from the arterial and capillary circulation. The greatest divergence between the two techniques is seen during the early bypass period. This is perhaps not surprising since it is known that the nonpulsatile flow that is associated with cardiopulmonary bypass may result in attenuation of the microcirculation and development of arteriovenous shunts. Changes in autoregulation may also be associated with CPB.

The algorithm of the SRS may be rendered inadequate under conditions of nonpulsatile CPB. Further knowledge of blood partitioning during bypass may be required to update the algorithm and to restore accuracy. Hemodilution will affect the SRS readings, since the saturation is calculated from the Hb concentration. Temperature dependent spectral changes of the near infrared absorption

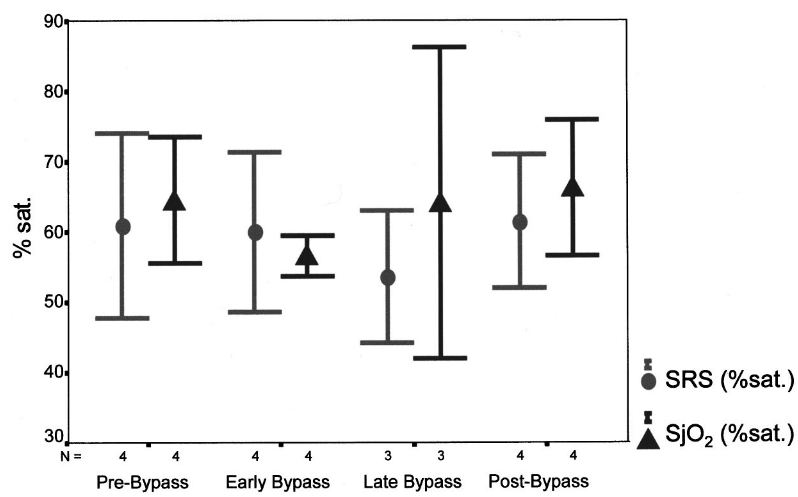

Fig. 6 Graph displaying mean values (±95% confidence limits) of SRS and SjO_2 saturation for all normothermic cases.

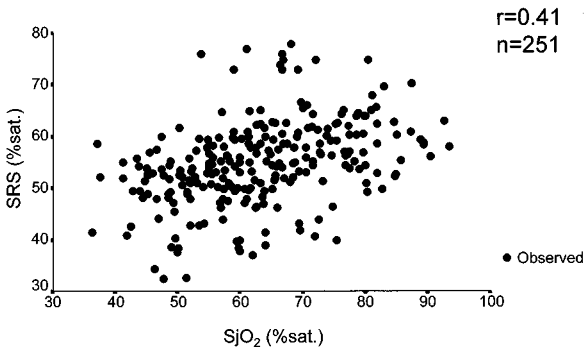

Fig. 7 Scatter plot and linear regression for pooled data.

spectra of hemoglobin have been previously reported,[55] so it is likely that the periods of hypothermia could introduce errors into the readings. Similarly, the scattering changes of near infrared spectroscopy with temperature could bias the SRS readings since the scattering coefficient for tissue (μ_s) is assumed to be constant.

When interpreting the results, an important consideration must be the theoretical problems associated with measuring small changes in Hb and HbO_2 concentrations in the adult head using NIRS. Since the changes in Hb and HbO_2 concentration may come from any compartment of the illuminated tissue,[22] the question of extracranial contamination is important.[16,18–21,56] It is known that, in the adult brain, scattering tends to be random and unpredictable.[57] Modeling based on magnetic resonance imaging (MRI) and showing photon measurement density function (PMDF) calculations carried out at UCL have demonstrated that adult head models show very little sensitivity for either NIRO 500 or SRS in gray and white matter regions (personal communication). The machines appear to probe mostly skin and skull. It is also possible that the cerebrospinal fluid (CSF) layer, by causing a uniform distribution of near infrared light, results in a reduction in the calculated SRS slope and ultimately to abnormally low values for saturation. Our own work using NIRS during carotid endarterectomy has shown a considerable extracranial component to the NIRS signal changes in adults.[16,58,59] It is likely that, as with previous NIRS techniques, the SRS will provide more reliable data when used with neonates.

6 Summary and Conclusion

By estimating the absolute cerebral hemoglobin saturation, spatially resolved spectroscopy is a promising tool for the noninvasive monitoring of cerebral oxygenation. Reliable detection of cerebral desaturation from jugular vein catheterization is difficult and prone to artifacts.[60–62] There are also potential complications from the procedure. SRS is noninvasive and gives continuous on-line measurements. Since continuous cerebral perfusion is not required, it provides a means of monitoring cerebral oxygenation during surgery involving deep circulatory arrest. It also has the advantage of being less sensitive to alterations in arterial blood pressure or to acute temperature fluctuations. The probes can be applied and readings monitored without the need for expertise. Validation of such a NIRS monitor is therefore of considerable interest.

However the results of our study suggest that the SRS is not, as yet, a reliable monitor of cerebral oxygen saturation during CPB. Various factors, including hemodilution, hypothermia and extracranial changes make validation difficult. The algorithm requires correction factors be applied for these variables. In particular, we consider that future developments will need to extract the extracerebral signal components. Further validation studies to investigate SRS reliability in different clinical scenarios are required.

Acknowledgment

This project was supported by a research grant awarded by Hamamatsu Photonics K.K. Japan.

References

1. F. F. Jobsis, ''Non-invasive infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters,'' *Science* **198**, 1264–1267 (1977).
2. C. E. Elwell, M. Cope, A. D. Edwards, J. S. Wyatt, D. T. Delpy, and E. O. R. Reynolds, ''Quantification of adult cerebral haemodynamics by near-infrared spectroscopy,'' *J. Appl. Physiol.* **77**, 2753–2760 (1994).
3. M. Cope and D. T. Delpy, ''System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by near infra-red transillumination,'' *Med. Biol. Eng. Comput.* **26**, 289–294 (1988).
4. H. Kimoto, T. Ohno, S. Takashima, S. Hirano, and T. Ozaki, ''The effect of acetazolamide and carbon dioxide on cerebral haemodynamic changes on near-infrared spectroscopy in young rabbits,'' *Brain Dev.* **17**, 261–263 (1995).
5. S. Takashima, S. Hirano, S. Kamei, M. Hasegawa, and H. Kimoto, ''Cerebral haemodynamics on near-infrared spectroscopy in hypoxia and ischaemia in young animal studies,'' *Brain Dev.* **17**, 312–316 (1995).
6. P. Smielewski, M. Czosnyka, J. D. Pickard, and P. Kirkpatrick, ''Clinical evaluation of near-infrared spectroscopy for testing cerebrovascular reactivity in patients with carotid artery disease,'' *Stroke* **28**, 331–338 (1997).
7. J. S. Wyatt, M. Cope, D. T. Delpy, S. Wray, and E. O. R. Reynolds, ''Quantification of cerebral oxygenation and haemodynamics in sick newborn infants by near infrared spectrophotometry,'' *Lancet* **ii**, 1063–1066 (1986).
8. M. Ferrari, C. De Marchis, I. Giannini, A. DiNicola, R. Agostino, S. Nodari, and G. Bucci, ''Cerebral blood volume and haemoglobin oxygen saturation monitoring in the neonatal brain by near infrared spectroscopy,'' *Adv. Exp. Med. Biol.* **200**, 203–211 (1986).
9. J. S. Wyatt, M. Cope, D. T. Delpy, C. E. Richardson, A. D. Edwards, S. Wray, and E. O. R. Reynolds, ''Quantification of cerebral blood volume in newborn infants by near infrared spectroscopy,'' *J. Appl. Physiol.* **68**, 1086–1091 (1990).
10. A. J. du Plessis, J. Newburger, R. A. Jones, P. Hickey, H. Naruse, M. Tsuji, A. Walsh, G. Walter, D. Wypij, and J. J. Volpe, ''Cerebral oxygen supply and utilisation during infant cardiac surgery,'' *Ann. Neurol.* **37**, 488–497 (1995).
11. J. E. Brazy, D. V. Lewis, M. H. Mitnik, and F. F. Jobsis, ''Non invasive monitoring of cerebral oxygenation in preterm infants: preliminary observations,'' *Pediatrics* **75**, 217–225 (1985).

12. J. E. Brazy and D. V. Lewis, ''Changes in cerebral blood volume and cytochrome aa3 during hypotensive peaks in preterm infants,'' *Pediatrics* **108**, 983–987 (1986).
13. J. E. Brazy, D. V. Lewis, M. H. Mitnik, and F. F. Jobsis, ''Monitoring of cerebral oxygenation in the intensive care nursery,'' *Adv. Exp. Med. Biol.* **191**, 843–848 (1986).
14. M. Tamura, ''Non invasive monitoring of brain oxygen metabolism during cardiopulmonary bypass by near infrared spectroscopy,'' *Jpn. Circ. J.* **55**, 330–335 (1991).
15. P. J. Kirkpatrick, P. Smielewski, P. C. Whitfield, M. Czosnyka, D. Menon, and J. D. Pickard, ''An observational study of near-infrared spectroscopy during carotid endarterectomy,'' *J. Neurosurg.* **82**, 756–763 (1995).
16. P. J. Kirkpatrick, P. Smielewski, J. M. K. Lam, and P. Al-Rawi, ''Use of near infrared spectroscopy for the clinical monitoring of adult brain,'' *J. Biomed. Opt.* **1**(4), 363–372 (1996).
17. P. J. Kirkpatrick, P. Smielewski, M. Czosnyka, D. K. Menon, and J. D. Pickard, ''Near-infrared spectroscopy use in patients with head injury,'' *J. Neurosurg.* **83**, 963–970 (1995).
18. T. J. Germon, P. Evans, N. Barnett, P. Wall, and R. J. Nelson, ''Optode separation determines sensitivity of near infrared spectroscopy to intra- and extracranial oxygenation changes,'' *J. Cereb. Blood Flow Metab.* **15**, 617 (1996).
19. T. J. Germon, N. M. Kane, A. R. Manara, and R. J. Nelson, ''Near-infrared spectroscopy in adults: effects of extracranial ischaemia and intracranial hypoxia on estimation of cerebral oxygenation,'' *Br. J. Anaesth.* **73**, 503–506 (1994).
20. D. N. F. Harris, F. M. Cowans, D. A. Wertheim, and S. Hamis, ''NIRS in adults: Effects of increasing optode separation,'' *Adv. Exp. Med. Biol.* **345**, 837–840 (1994).
21. D. N. Harris, F. M. Cowans, and D. A. Wertheim, ''Near infrared spectroscopy in the temporal region: Strong influence of external carotid artery,'' *Adv. Exp. Med. Biol.* **345**, 825–828 (1994).
22. E. Okada, M. Firbank, and D. T. Delpy, ''The effect of overlying tissue on the spatial sensitivity profile of near-infrared spectroscopy,'' *Phys. Med. Biol.* **40**, 2093–2108 (1995).
23. C. E. Elwell, M. Cope, A. D. Edwards, J. S. Wyatt, E. O. R. Reynolds, and D. T. Delpy, ''Measurement of cerebral blood flow in adult humans using near infrared spectroscopy—Methodology and possible errors,'' *Adv. Exp. Med. Biol.* **317**, 235–245 (1992).
24. P. van der Zee, M. Cope, S. R. Arridge, M. Essenpreis, L. A. Potter, A. D. Edwards, J. S. Wyatt, D. C. McCormick, S. C. Roth, E. O. R. Reynolds, and D. T. Delpy, ''Experimentally measured optical pathlengths for the adult head, calf and forearm and the head of the newborn infant as a function of inter optode spacing,'' *Adv. Exp. Med. Biol.* **316**, 143–153 (1992).
25. A. D. Edwards, J. S. Wyatt, C. E. Richardson, D. T. Delpy, M. Cope, and E. O. R. Reynolds, ''Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy,'' *Lancet* **ii**, 770–771 (1988).
26. K. V. Slavin, M. Dujovny, J. I. Ausman and W. Cui, ''Monitoring of cerebral saturation using near infrared spectroscopy in neurosurgical patients,'' American Association of Neurological Surgeons Annual Meeting (1994).
27. M. S. Irwin, M. S. Thorniley, C. Dore and C. J. Green, ''Near infrared spectroscopy: a non-invasive monitor of perfusion and oxygenation within the microcirculation,'' *Br. J. Plastic Surg.* **48**, 14–22 (1995).
28. D. N. Harris and S. M. Bailey, ''Near infrared spectroscopy in adults—Does the Invos 3100 really measure intracerebral oxygenation?'' *Anaesthesia* **48**, 694–696 (1993).
29. D. T. Delpy, M. Cope, P. van der Zee, S. Arridge, S. Wray, and J. Wyatt, ''Estimation of optical pathlength through tissues by direct time of flight measurement,'' *Phys. Med. Biol.* **33**, 1433–1442 (1988).
30. S. J. Matcher, P. Kirkpatrick, K. Nahid, M. Cope, and D. T. Delpy, ''Absolute quantification methods in tissue near infrared spectroscopy,'' *Proc. SPIE* **2389**, 486–495 (1995).
31. M. Nevin, A. F. C. Colchester, S. Adams, and J. R. Peppe, ''Evidence for involvement of hypocapnia and hypoperfusion in aetiology of neurological deficit after cardiopulmonary bypass,'' *Lancet* **2**, 1495 (1987).
32. J. J. Stockard, R. G. Bickford, and J. F. Schauble, ''Pressure dependent cerebral ischaemia during cardiopulmonary bypass,'' *Neurology* **23**, 521–529 (1973).
33. K. Anderson, J. Waaben, B. Husum, B. Voldby, A. Bodker, A. J. Hansen, and A. Gjedde, ''Nonpulsatile cardiopulmonary bypass disrupts the flow metabolism couple in the brain,'' *J. Thorac. Cardiovasc. Surg.* **90**, 570–579 (1985).
34. N. D. Croughwell, P. Frasco, J. A. Blumenthal, B. J. Leone, W. D. White, and J. G. Reeves, ''Warming during cardiopulmonary bypass is associated with jugular bulb desaturation,'' *Ann. Thorac. Surg.* **53**, 827–832 (1992).
35. L. Henriksen, ''Brain luxury perfusion during cardiopulmonary bypass in humans. A study of the cerebral blood flow response to changes in CO_2, O_2 and blood pressure,'' *J. Cereb. Blood Flow Metab.* **6**, 366–378 (1986).
36. T. Nakajima, M. Kuro, Y. Hayashi, K. Kitaguchi, O. Uchida, and O. Takaki, ''Clinical evaluation of cerebral oxygen balance during cardiopulmonary bypass: On-line continuous monitoring of jugular venous oxyhaemoglobin saturation,'' *Anesth. Analg.* **74**, 630–635 (1992).
37. J. M. Murkin, J. K. Farrar, W. A. Tweed, F. N. McKenzie, and G. Guiraudon, ''Cerebral autoregulation and flow metabolism coupling during cardiopulmonary bypass: The influence of $PaCO_2$,'' *Anesth. Analg.* **66**, 825–832 (1987).
38. N. Stocchetti, A. Paparella, F. Bridelli, M. Bacchi, P. Piazza, and P. Zuccoli, ''Cerebral venous oxygen saturation studied with bilateral samples in the internal jugular veins,'' *Neurosurgery* **34**(1), 38–44 (1994).
39. E. L. Gibbs, W. G. Lennox, L. F. Nims, and F. A. Gibbs, ''Arterial and cerebral venous blood, arterial-venous differences in man,'' *J. Biol. Chem.* **144**, 325–332 (1942).
40. K. H. Chan, J. D. Miller, N. M. Dearden, P. J. Andrews, and S. Midgley, ''The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe head injury,'' *J. Neurosurg.* **77**, 55–61 (1992).
41. C. A. Piantadosi, ''Near infrared spectroscopy: principles and application to non-invasive assessment of tissue oxygenation,'' *J. Crit. Care* **4**, 308–318 (1989).
42. R. Nossal, R. F. Bonner, and G. H. Weiss, ''The influence of path length on remote optical sensing properties of biological tissue,'' *Appl. Opt.* **28**, 2238–2244 (1989).
43. M. G. Goetting and G. Preston, ''Jugular bulb catheterisation: experience with 123 patients,'' *Crit. Care Med.* **18**(11), 1220–1223 (1990).
44. M. Czosnyka, H. Whitehouse, P. Smielewski, P. Kirkpatrick, E. P. Guazzo, and J. D. Pickard, ''Computer supported multimodal bed-side monitoring for neuro intensive care,'' *Int. J. Clin. Monit. Comput.* **11**, 223–232 (1994).
45. P. Smielewski, M. Czosnyka, W. Zabolotny, P. Kirkpatrick, H. Richards, and J. D. Pickard, ''*A computing system for the clinical and experimental investigation of cerebrovascular reactivity,*'' *Int. J. Clin. Monit. Comput.* **14**, 185–198 (1997).
46. A. Myerson, R. D. Halloran, and H. L. Hirsch, ''Technique for obtaining blood from the internal jugular vein and carotid artery,'' *Arch. Neurol. Psychiat.* **17**, 807 (1927).
47. M. G. Goetting, ''Validity of the jugular bulb catheter for cerebral venous monitoring,'' *Neurology Suppl.* **40**, 254 (1990).
48. R. Garlick and D. Bihari, ''The use of intermittent and continuous recordings of jugular venous bulb oxygen saturation in the unconscious patient,'' *Scand. J. Clin. Lab. Invest. Suppl.* **47**, 47–52 (1987).
49. E. Ferris, G. Engel, C. Stevens, and M. Logan, ''The validity of internal jugular venous blood in studies of cerebral metabolism and blood flow in man,'' *Am. J. Physiol.* **147**, 517–521 (1946).
50. R. Clauss, W. Hass, and J. Ronschoff, ''Simplified method for monitoring adequacy of brain oxygenation during carotid artery surgery,'' *N. Engl. J. Med.* **273**, 1127–1131 (1965).
51. M. O. Gayle, T. C. Frewen, R. F. Armstrong, J. J. Gilbert, J. B. Kronick, N. Kissoon, R. Lee, N. Tiffin, and T. Brown, ''Jugular venous bulb catheterisation in infants and children,'' *Crit. Care Med.* **17**, 385–388 (1989).
52. S. P. Gopinath, C. S. Robertson, C. F. Contant, C. Hayes, Z. Feldman, R. K. Narayan, and R. G. Grossman, ''Jugular

venous desaturation and outcome after head injury,'' *J. Neurol., Neurosurg. Psychiatry* **57**, 717–723 (1994).
53. C. S. Robertson, C. F. Contant, Z. L. Gokaslan, R. K. Narayan, and R. G. Grossman, ''Cerebral blood flow, arteriovenous oxygen difference, and outcome in head injured patients,'' *J. Neurol., Neurosurg. Psychiatry* **55**, 594–603 (1992).
54. D. J. Cook, W. C. Oliver, T. A. Orszulak, and R. C. Daly, ''A prospective randomised comparison of cerebral venous oxygen saturation during normothermic and hypothermic cardiopulmonary bypass,'' *J. Thorac. Cardiovasc. Surg.* **107**, 1020–1029 (1994).
55. R. Sfareni, A. Boffi, V. Quaresima, and M. Ferrari, ''Near infrared absorption spectra of human deoxy- and oxyhaemoglobin in the temperature range 20–40 C,'' *Biochim. Biophys. Acta* **1340**, 165–169 (1997).
56. T. J. Germon, A. E. Young, A. R. Manara, and R. J. Nelson, ''Extracerebral absorption of near infrared light influences the detection of increased cerebral oxygenation monitored by near infrared spectroscopy,'' *J. Neurol. Neurosurg. Psychiatry* **58**, 477–479 (1995).
57. S. Wray, M. Cope, D. T. Delpy, J. S. Wyatt, and E. O. R. Reynolds, ''Characterisation of the near infrared absorption spectra of cytochrome aa3 and haemoglobin for the non-invasive monitoring of cerebral oxygenation,'' *Biochim. Biophys. Acta* **933**, 184–192 (1988).
58. J. M. K. Lam, P. Smielewski, P. Al-Rawi, P. Kirkpatrick, and J. D. Pickard, ''Internal and external carotid contribution to near infrared spectroscopy during carotid endarterectomy,'' *Stroke* **28**(5), 1–6 (1997).
59. J. M. K. Lam, P. Smielewski, P. Griffiths, P. Al-Rawi, J. D. Pickard, and P. J. Kirkpatrick, ''Collateral circulation and NIRS changes in patients for carotid endarterectomy,'' *New Trends in Cerebral Haemodynamics* (in press).
60. P. J. D. Andrews, N. M. Dearden, and J. D. Miller, ''Jugular bulb cannulation: Description of a cannulation technique and validation of a new continuous monitor,'' *Br. J. Anaesth.* **67**, 553–558 (1991).
61. J. Cruz, ''Contamination of jugular venous oxygen measurements,'' *J. Neurosurg.* **77**, 975–976 (1992).
62. N. M. Dearden and S. Midgely, ''Technical considerations in continuous jugular venous oxygen saturation measurement,'' *Acta Neurochir. Suppl.* **59**, 91–97 (1993).