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Cerebro-splanchnic oxygenation ratio (CSOR) using near infrared spectroscopy may be able to predict splanchnic ischaemia in neonates

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Abstract *Objective*: To investigate whether near infrared spectroscopy (NIRS) can detect differences in oxyhaemoglobin signal when applied to the abdomens of neonates with surgically proven splanchnic ischaemia.
Design: Prospective, observational cohort study.
Setting: Tertiary neonatal referral centre.
Patients: Medical and surgical neonates were studied. Two groups were identified, neonates with acute abdomens referred for surgery and those with normal abdomens admitted for medical reasons.
Interventions: Tissue oxygenation indexes (TOI) of cerebral and splanchnic regions were measured using near infrared spectroscopy (NIRS) and their relative values expressed as a cerebro-splanchnic oxygenation ratio (CSOR). Measurements were made on admission or immediately prior to surgery and subsequently repeated on a daily basis, whenever possible, until discharge from our unit. The area under the receiver operating characteristic (ROC) curve was evaluated and optimum diagnostic cut-off values determined.
Results: Forty neonates were studied: 10 with acute abdomens, including four with necrotising enterocolitis (NEC), 29 controls with normal abdomens and one with cerebral hypoxic ischaemic injury. Median CSOR for the control group was 0.96 (interquartile range 0.83–1.02) whereas the acute abdomen group had a significantly lower median CSOR value of 0.66 (0.45–0.69) ($p < 0.001$). The area under the ROC was 0.91 (95 % confidence limits 0.78–1.00) for CSOR. Taking a boundary value of CSOR for the prediction of splanchnic ischaemia as less than 0.75, intestinal ischaemia was identified with a positive predictive value of 0.75 (0.43–0.95) and excluded with a negative predictive value of 0.96 (0.81–1.0). This was a better performance than using abdominal TOI alone.
Conclusions: By comparing the TOI of cerebral and splanchnic regions it may be possible to establish the presence of normal splanchnic perfusion and detect when splanchnic ischaemia develops. CSOR had a 90 % (56–100 %) sensitivity to detect splanchnic ischaemia in neonates. Further work is necessary to confirm these early findings and establish whether abdominal NIRS has a clinical role in detecting splanchnic ischaemia.

Keywords Cerebro-spinal oxygenation ratio (CSOR) · Tissue oxygenation index (TOI) · Near infrared spectroscopy (NIRS) · Splanchnic ischaemia

Introduction

New near infrared spectroscopy (NIRS) techniques offer the clinician the enticing possibility of assessing regional tissue oxygenation in a non-invasive manner. Various NIRS technologies have already been used by a number of biomedical engineers and interested physicians [1, 2, 3, 4]. The older techniques remain a research tool. They are limited clinically, as it is necessary to know other physical parameters of the tissue being examined which are not measured by existing NIRS machines [5]. In particular an average pathlength for the local tissue types through which the NIR light travels needs to be established, ideally measured in real time [6]. Previous studies with NIRS applied outside the region of the head tend to be qualitative and descriptive, as changes in signal had to be relative to the start of every study. Without the ascertainment of a pathlength, absolute concentrations of haemoglobin cannot be calculated. However, because of recent advances in signal manipulation, it is now possible to express the ratio of oxygenated to reduced haemoglobin in the tissues, in real time, at the time of measurement. Thus the need to know the pathlength and the problems of movement artefact are removed [7]. This ratio of oxygenated to reduced haemoglobin is termed the tissue oxidation index (TOI).

In sick, hypotensive infants we postulate that the TOI will be altered in the vascular beds when blood flow is decreased. The resultant acidosis in poorly perfused tissues may also further increase the dissociation of oxygen from haemoglobin and increase the proportion of reduced haemoglobin detected with NIRS. Splanchnic perfusion is compromised early under hypotensive conditions as blood supply to the gastrointestinal tract is diverted to more essential organs [8]. In the adult, cerebral perfusion is autoregulated, except in extreme circumstances. Although the same level of autoregulation has not been consistently demonstrated in the newborn, there is good evidence to suggest that this may also be the case [9]. Therefore we speculated that the ratio of a measure of splanchnic over cerebral perfusion will be constant under normal conditions, but during hypotension or ischaemia this ratio would be expected to fall below normal values.

In this study we have sought to test the above hypothesis. We have measured TOI simultaneously in the brain and abdomen of neonates with a surgically confirmed diagnosis of an acute abdomen with splanchnic ischaemia and those with normal enteral function tolerating oral feeding.

Methods

Local ethical committee approval was obtained and parental consent was sought and acquired on all subjects. All patients admitted to our neonatal unit during the period of the study were considered eligible for inclusion. Patients with severe sepsis requiring more than one inotrope, those with congenital diaphragmatic hernias (CDH) and those with gastroschisis were excluded because of concerns over the integrity of their splanchnic perfusion and consistency of measurement of CSOR [10]. NIRS measurements were made within 24 h of admission and were planned to be repeated on a daily basis. Routine care of the infant was not interrupted. The clinical staff caring for the child were blinded to the results of our measurements and clinical management was not altered by the study.

We used a near infrared spectrophotometer (NIRO-300, Hamamatsu Photonics, London, UK) equipped with two sets of probes to measure the TOI simultaneously in both brain and abdomen. Near infrared light was transmitted through the region of interest. The emitter and receiver optodes were designed to sit flush against the skin of the head and abdomen. The NIRO-300 is able simultaneously to measure the changes in the signals received from four infrared frequencies and calculates the proportion of the haemoglobin which is in the oxygenated and reduced states. This is termed tissue oxygenation index (TOI) [11].

In our study two sets of optodes were placed in their carriers on the forehead and on the abdomen, the latter positioned just below the umbilicus (Fig. 1). The carriers were applied to the skin in the midline with the optodes horizontally aligned. Simultaneous measurements were made from both sets of optodes. On each occasion TOI measurements were recorded only after a steady state had been reached. Measurements were made for 5 min, during which a constant reading was obtained from both the head and abdomen. These measurements were then combined as a ratio of abdominal TOI over cerebral TOI (TOI_{abdo}/TOI_{brain}) to produce a cerebrosplanchnic oxygenation ratio (CSOR). Patients were allocated to two groups depending on whether they had an acute abdomen or not. The control group included neonates with bronchiolitis or other respiratory disorders. One baby who presented with severe birth asphyxia and hypoxic ischaemic encephalopathy (HIE) was also studied. The baby had a completely flat electroencephalogram on two separate occasions, which paralleled the neurological examination.

The data for CSOR are presented as medians (interquartile range). Statistical significance was determined using the Kruskall-Wallis non-parametric test for significance. Sensitivity and specificity were assessed using the receiver operating curve (ROC) and the 95% confidence intervals for these parameters are quoted in parenthesis.

Results

Forty eligible neonates were admitted to the neonatal unit during the study. There were no refusals of parental consent. A total of 77 measurements were made. There were no significant differences in weight, sex or gestational age between the study and control groups. There were ten neonates with acute abdomens, all of whom were taken to theatre. The cause of their acute abdomens included necrotising enterocolitis (NEC; 5), small bowel atresia (2), bladder extrophy (2) and peritonitis (1). The neonates with NEC were both smaller and of a

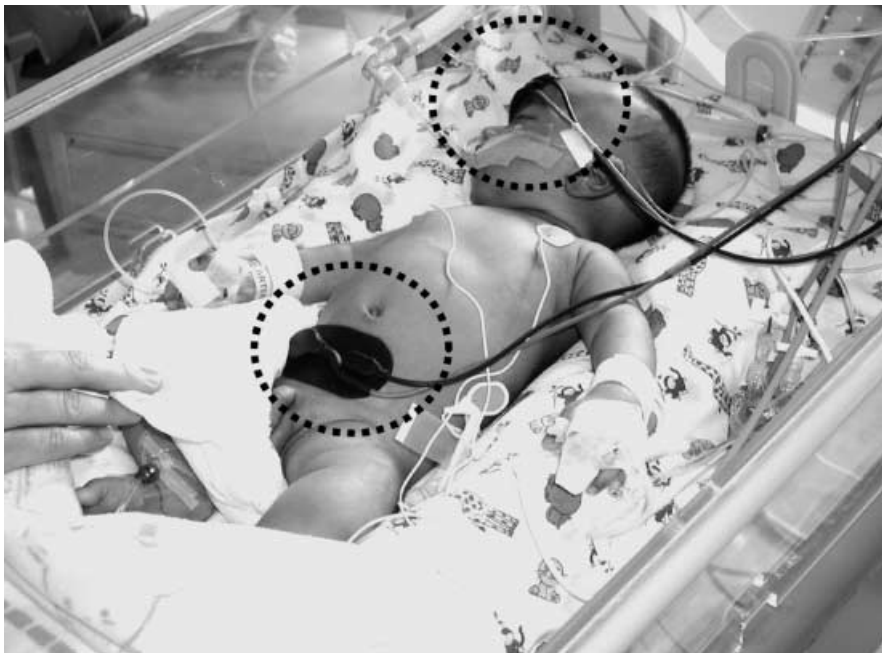

Fig. 1 Position of optodes on head and abdomen. Two sets of optodes were placed in their carriers on the forehead and on the abdomen, the latter positioned just below the umbilicus. Optodes highlighted in *dashed circles*

Table 1 Demographics of patients studies – data are shown as medians and interquartile ranges (*M:F* ratio of males to females

	n	Gestational age (weeks)	Weight (kg)	M:F
Acute abdomens				
NEC	5	27.5 (26.8–28.3)	1.3 (1.1–1.5)	3:2
Non-NEC	5	36.5 (35.3–37.8)	2.7 (2.4–2.8)	2:3
Total	10	33.5 (28.2–36.8)	2.0 (1.5–2.7)	5:5
Control	29	38.0 (29.2–40.0)	2.4 (1.4–3.4)	15:14
Isoelectric EEG	1	40	4.0	–

reduced gestational age compared to the whole study group (Table 1), which may have contributed to the difference in CSOR, as the cerebral metabolic rate may be different for different gestational ages observed. However, the TOI values for the NEC sub-group do not differ markedly from the other five neonates with acute abdomen (Fig. 2). There were 29 controls and one neonate with an isoelectric encephalogram secondary to HIE. Clinical details of the patients are given in Table 2. The latter infant is not included in any of the statistical analysis.

Median CSOR for the control group on day 1 was 0.96 (0.83–1.02). Examining all the observations on the control group over the period of the study, the median CSOR remains unchanged but the interquartile range narrows to 0.88–1.03. Table 2 shows individual TOI values for the patients studied and Fig. 2 shows the distribution of TOI values for gut and brain in each of the groups. The study group had a significantly reduced median CSOR value of 0.66 (0.45–0.69) ($p < 0.001$, day 1 and $p < 0.03$, day 3). There were two early deaths in this group and four of the remaining eight patients were quickly discharged to the general surgical ward where measurements were not possible. The remaining four patients could not be studied every day due to wound dressings preventing clear access to their abdomens. Consequently there is a considerable drop-off in number of measurements in the study group post-operatively. However, it was possible to make some measurements of CSOR in this group prior to discharge. These suggest that their CSOR measurements were trending back towards the control value of 0.96 over a period of 10 days (Fig. 3).

To determine the suitability of this technique as a diagnostic tool we have generated a receiver operating characteristic (ROC) curve (Fig. 4). In this analysis we examined the ability of CSOR to discriminate between the infants with and without known intra-abdominal pathology using only the first CSOR measurement, recorded on admission, before surgery. The area under the CSOR ROC curve is 0.91 (0.78–1.00). The dotted line on the curve shows, for comparison, the performance of TOI_{abdo} in these infants, which might initially have been considered a more direct diagnostic test. By comparison, the area under the TOI_{abdo} curve is 0.83 (0.70–0.98). Taking a threshold value for CSOR of 0.75 to demarcate the boundary between a positive and negative study, CSOR detected the presence of intra-abdominal pathology with a sensitivity of 0.9 (0.56–1.00) and specificity of 0.96 (0.82–1.00). Measuring a CSOR of less than 0.75 gives an odds ratio of 78 (95 % CI 7–843) for the presence of intestinal ischaemia (Table 3).

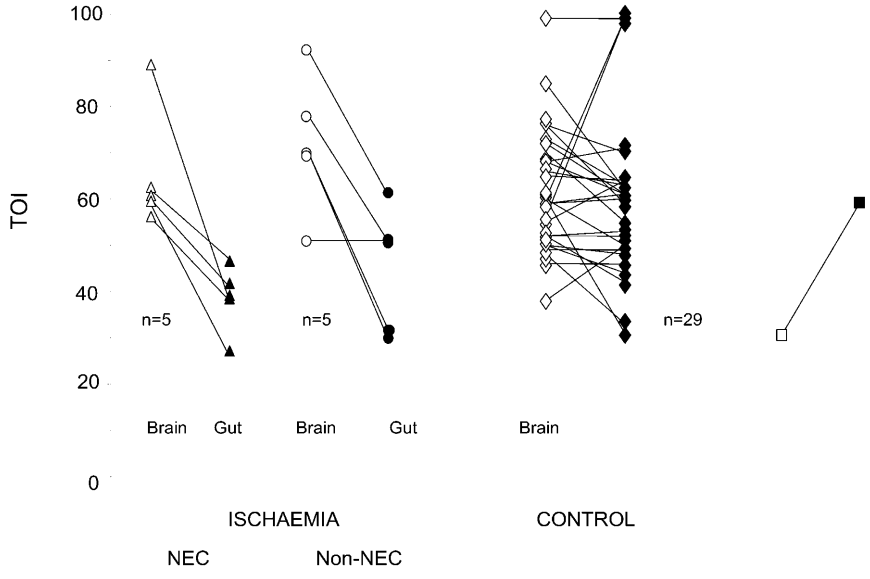

Fig. 2 Cerebral (brain) and splanchnic (gut) TOI data for the acute abdomen group, control group and the one case of hypoxic ischaemic encephalopathy. The splanchnic ischaemic group is separated into those with NEC and those with ischaemia for other reasons

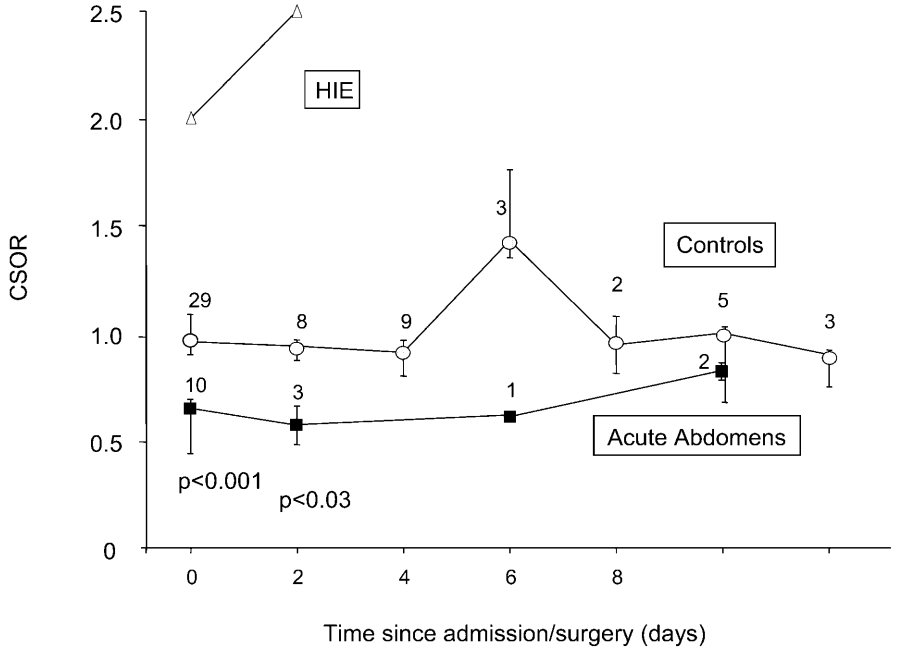

Fig. 3 Median CSOR data for the three groups studied against time from admission (control and isoelectric group), or from immediately before surgery (NEC/major abdominal surgery group). The *error bars* show the interquartile range for each sample group and the *numbers above the bars* the number of patients studied. (*HIE* hypoxic ischaemic encephalopathy)

The one case with HIE and an isoelectric EEG on the day of the study had a CSOR of 2.0. Although we draw no definite conclusions from this single subject, the result suggests that there was a significantly reduced proportion of oxygenated haemoglobin within the brain compared to abdominal tissues. However, it was felt unethical to perform a cerebral perfusion scan to support our observations and therefore no further comment can be made as to the validity of our speculation. Positive predictive value (9/12) = 0.75 (CI 0.43–0.95), negative predictive value (26/27) = 0.96 (CI 0.81–1.0)

Discussion

Near infrared spectroscopy has been extensively used to study cerebral perfusion in neonates and infants [12, 13]. It has also been used in adults to quantify cerebral haemodynamics [14] and as a non-invasive measure of forearm blood flow and oxygen consumption [15]. Early reports with NIRS described measurements of changes in chromophore concentrations relative to the start of the study. Application of NIRS to other tissues has been hindered by a number of concerns. In particular for the

Table 2 Clinical details of all the patients studied, with examples of the cerebral TOI, splanchnic TOI and CSOR ratio obtained (*CMV* cytomegalovirus, *NEC* necrotising enterocolitis)

Patient No.	Diagnosis	Brain TOI	Gut TOI	CSOR
Controls				
1	CMV pneumonia	99	99	1.00
2	Congenital myasthenia	55	64	1.16
3	Alagilles	50	48	0.96
4	Polycystic kidneys	56	99	1.77
5	Group B streptococcal sepsis	48	33	0.69
6	Tracheo-oesphageal fistula	49	49	1.00
7	Bronchomalacia	60	99	1.65
8	Respiratory distress syndrome	52	53	1.02
9	Tracheal stenosis& stridor	59	60	1.02
10	Patent ductus arteriosus	50	44	0.88
11	Inguinal hernia	52	52	1.00
12	Hirschprung's	85	62	0.73
13	Sepsis	73	63	0.86
14	Coarctation	70	55	0.78
15	Meconium aspiration	46	46	1.00
16	Patent ductus arteriosus	52	42	0.81
17	Sepsis/seizures	60	31	0.51
18	Pre-op take down stoma	68	61	0.89
19	Vein of Galen malformation	38	50	1.32
20	Meconium aspiration	76	59	0.78
21	Status epilepticus	68	71	1.04
22	Inguinal hernia	65	64	0.98
23	Patent ductus arteriosus	66	63	0.95
24	Bronchiolitis	59	61	1.03
25	Acute renal failure	72	61	0.84
26	Status epilepticus	68	71	0.96
27	Aortopexy	76	70	0.92
28	NEC	60	50	0.83
29	Meconium aspiration syndrome	76	59	0.78
Ischaemia				
1	Small bowel atresia	70	32	0.46
2	Small bowel atresia	92	61	0.66
3	Peritonitis	78	51	0.65
4	Bladder extrophy	51	51	1.00
5	Bladder extrophy	70	30	0.43
6	NEC	56	38	0.69
7	NEC	59	26	0.44
8	NEC	62	47	0.75
9	NEC	89	38	0.42
10	NEC	60	41	0.68

abdomen, the pathlength of the particular part of bowel studied is not known. Thus absolute concentrations of oxyhaemoglobin and deoxyhaemoglobin cannot be quoted. In the absence of an abdominal pathlength it has not been possible to generate any quantitative data allowing comparison between different patient groups. Another concern was that insufficient infrared light would traverse overlying abdominal tissues and not actually penetrate bowel. However, we have demonstrated that an abdominal NIRS oxyhaemoglobin signal can be detected and take considerably longer to recover than peripheral arterial saturation after an hypoxic episode. This difference in response time suggests that NIRS applied to the abdomen can detect oxyhaemoglobin signals from bowel rather than just overlying abdominal skin [16].

Table 3 Two × two table of CSOR for patients with and without surgically confirmed intestinal ischaemia

	Ischaemic	Non-ischaemic	Total
CSOR < 0.75	9[a]	3[b]	12
CSOR > 0.75	1[c]	26[d]	27
Total	10	29	39

Odds ratio = (a/c)/(b/d) = 78

Another significant concern with the application of NIRS to the abdomen is the possibility of movement of the gut within the abdomen and also movement produced by peristalsis of the gut wall. These two movements can alter the scattering path of the near infrared light, resulting in absorption changes which would swamp the signal of interest. However, TOI now offers a method of comparing the haemoglobin redox status within the splanchnic circulation, which is not pathlength-dependent because it provides a simultaneous ratio of oxyhaemoglobin to deoxyhaemoglobin. Finally, by measuring the TOI of the brain, which is preferentially autoregulated with the splanchnic region under most physiological conditions, the resultant CSOR ratio gives absolute values which allow comparison between individual patients and allow a set of normal values to be established. We were able to confirm that neonates with normal bowel had a CSOR ratio of 0.96 (0.83–1.02) and found that those with compromised oxygen status had a lower value.

The acute abdomen group included five neonates with NEC, a condition for which there is very little available in terms of a monitor to help determine whether bowel ischaemia is improving or worsening. NEC is a common and potentially fatal condition seen in neonates. It has a significant mortality of 22 % even with aggressive treatment [17]. Medical therapy includes up to 10 days fasting, triple antibiotic therapy and total parental nutrition. Up to 50 % of neonates with NEC develop advanced disease which requires surgery. Although the precise aetiology and evolution of NEC is not known, it is clear that gut ischaemia becomes an important feature by the time infants come to surgical intervention [18]. Treatment is considered successful once enteral feeding and growth are established. Until significant and steady growth is achieved the neonate has an increased susceptibility to intermittent episodes of sepsis [17]. False positive diagnoses of NEC delay the progress of the infant and thus compromise their final outcome. A false negative diagnosis can have devastating consequences. Despite the prevalence of this condition, no diagnostic technique with sufficient sensitivity is available to aid

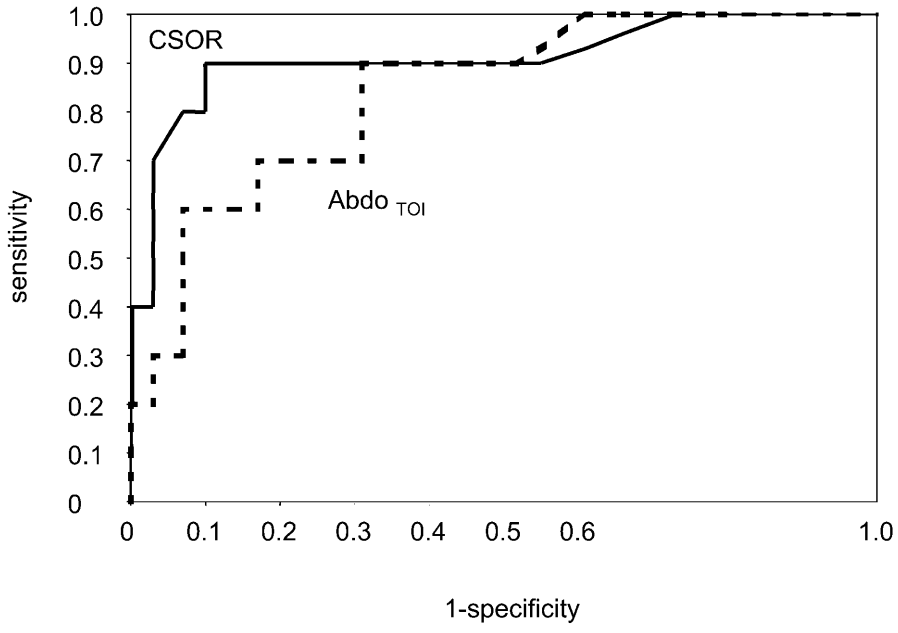

Fig. 4 Receiver operating characteristic (ROC) curve comparing CSOR and TOI_{abdo} for prediction of splanchnic ischaemia. The area under the curve was 0.91 (0.78–1.00) for CSOR and 0.83 (0.70–0.98) for TOI_{abdo}

in the diagnosis and management of suspected cases. Using abdominal NIRS we were able to detect a lower CSOR value in all five neonates with NEC. The diagnosis was confirmed at surgery and later with histological examination. Abdominal NIRS may therefore be potentially useful if it can corroborate a diagnosis of NEC. Furthermore, if it can monitor the progress of the early stages of the disease, which is often treated conservatively, it could be useful in detecting when to intervene surgically.

There was one false negative included in the analysis of the control group, and this baby was found to have NEC. The misleading CSOR may have arisen because the baby was systemically hypoxic (peripheral saturation 75 %) during the CSOR measurements. We postulate that with this level of systemic hypoxia a smaller difference between TOI_{abdo} and TOI_{brain} may be seen. This may represent a limitation of this technique, which warrants further study. All other patients with acute abdomens had systemic oxygen saturation greater than 90 %. There were also three CSOR measurements in the control group which would have been false positive results. The CSORs suggested significant splanchnic ischaemia in the presence of an apparently normal gut. However, one case had lower intestinal obstruction secondary to Hirschprung's disease and may have had altered gut haemodynamics secondary to his obstruction. A second had group B streptococcal sepsis on high dose dopamine, which may well have compromised gut perfusion. The third had severe abdominal wall oedema, which we have found degrades the signal measured from the gut.

One of the aims of this study was to make daily measurements of all the children in each group. The numbers of patients studied fell rapidly after the first day. This was due to a high turnover of neonates and their short length of stay on the unit. Patients who had abdominal surgery had their wounds covered with dressing and it was difficult to place the optodes on the skin directly.

In this study we have shown that measurement of TOI and then calculation of CSOR in neonates can be highly predictive of intra-abdominal pathology with a 90 % sensitivity and an 96 % specificity. Although these measures are less sensitive to prevalence of disease and group size than predictive values, we need to evaluate this technique further, with more subjects and a more heterogeneous population of neonates, before we can be confident of its usefulness. The technique is simple to use and measurements can be performed within 5 min without disrupting the routine care of the infant. It would be particularly interesting to apply this technique prospectively on all admissions to a general neonatal unit to see if it is able to provide any warning of impending splanchnic problems in advance of the development of the full clinical picture of an acute abdomen. NIRS also needs to be extended into the older age groups. In proposing the novel use of NIRS on the abdomen and in suggesting the use of CSOR as a means of detecting impending ischaemia, a number of assumptions have been made. The potential for developing a monitor of splanchnic oxygenation demands further investigation to try and resolve the theoretical concerns over the use of NIRS on the abdomen.

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