SIGNA VITAE 2014; 9(2): 15 - 24

ORIGINAL

Near infrared spectroscopy tissue oxygenation in infants with bronchiolitis during mechanical ventilation and spontaneous breathing

MARTA ZNIDARSIC ERZEN • MARTINA JELIC • ANA GORNIK • MATEJ PODBREGAR • STEFAN GROSEK

STEFAN GROSEK (✉)
Department of Pediatric Surgery and Intensive Therapy
University Medical Centre Ljubljana
Surgical Service
Medical Faculty, University of Ljubljana
Bohoriceva 20. 1000 Ljubljana. Slovenia
GSM: ++ 386 (0)41 684 206
Phone: ++ 386 (0)1 522 48 29
Fax: ++ 386 (0)1 522 11 09
E-mail: stefan.grosek@mf.uni-lj.si
stefan.grosek@kclj.si
Web page: www.kclj.si

MARTA ZNIDARSIC ERZEN
Pediatric Clinical Department
Community Health Centre Ljubljana
Metelkova ulica 9. , 1000 Ljubljana, Slovenia

MARTINA JELIC
General Hospital Celje
Oblakova 30., 3000 Celje, Slovenia

ANA GORNIK
Hospital Sežana
Cankarjeva ulica 4., 6210 Sežana, Slovenia

MATEJ PODBREGAR
Department of Intensive Care Medicine
University Medical Centre Ljubljana
Zaloska c 7., 1000 Ljubljana, Slovenia

ABSTRACT

Introduction. Near-infrared spectroscopy (NIRS) was used in infants with acute bronchiolitis as a noninvasive indicator of tissue oxygenation to determine regional tissue oxygen saturation ($rStO_2$) and fractional tissue oxygen extraction (FTOE) during mechanical ventilation and spontaneous breathing.

Methods. Twenty-seven infants with bronchiolitis that needed mechanical ventilation were included in a prospective study. Regional StO_2 in brain, liver, kidney and skeletal muscle tissue was measured on admission to the Intensive Care Unit (ICU), on day 1 (D1); after two to three days of mechanical ventilation (D2); on the last day of mechanical ventilation (D3) and during spontaneous breathing (D4). Measurements were conducted by in-vivo optical spectroscopy. For research purposes we divided the infants according to C-reactive protein (CRP) levels, with a cut-off value of 10 mg/ml on admission, into low (l-CRP) and high (h-CRP) groups.

Results. During mechanical and spontaneous breathing we found lower StO_2 and higher FTOE for skeletal muscle at D4 compared to D1-D2 in the h-CRP group of patients. Differences between l- and h-CRP groups in $rStO_2$ were found for brain tissue on D3, D4, and in $rStO_2$ and FTOE for liver tissue on D3. A strong negative correlation was found between $rStO_2$ and FTOE in all tissues. A positive correlation was found between CRP and $rStO_2$ and negative between CRP and FTOE in skeletal muscle among all patients combined.

Conclusion. Only Infants with acute bronchiolitis in the h-CRP group have significant changes in $rStO_2$ and FTOE in skeletal muscles during mechanical ventilation and spontaneous breathing. Regional StO_2 and FTOE in all the other measured tissues never decreased below normal values.

Key words: bronchiolitis, near-infrared spectroscopy, fractional tissue oxygen extraction (FTOE), regional oxygen saturation ($rStO_2$)

Introduction

Noninvasive near-infrared spectroscopy (NIRS) has recently been widely introduced in operating theatres and intensive care units (ICUs). This is mainly for monitoring regional tissue oxygen saturation ($rStO_2$) in children during and after heart operations, although it is

Table 1. Normal means and ranges from the literature (8-11) for tissue oxygenation (rStO2) and oxygen extraction (FTOE) in the brain, liver, kidney and skeletal muscle of infants.

Tissue	$rStO_2$ [%]	FTOE
Brain (8)	66.2 ±10.2 (61.5-70.9)	.29 +/-.10 (.24-.3)
Liver (11)	59.23 ±9.66 (37.3-78.8)	NA* (NA
Kidney (9)	80.1 ±10.0 (75.4-84.4)	.11 ±.09 (.06-.16)
Skeletal muscle (9,10)	63.9 ±4.9†; 79 ± 9† (NA)	NA (NA)

Data are expressed as means ±standard deviation (range).
*NA, data not available
†Two different means from the literature

now used for many other clinical conditions. The low threshold values of $rStO_2$ under which tissue desaturation can be harmful for organs have been defined. (1) Oxygen consumption (VO_2) of the breathing and weaning processes in newborn infants can be reduced using certain modes of mechanical ventilation. (2)

Bronchiolitis is the most common viral infection of the lower respiratory tract in infants. With severe infections, respiratory failure can ensue, especially in infants with specific risk factors. (3) As well as direct damage to target organs, viral pathogens can elicit inflammatory responses, and severe infections can promote systemic inflammatory response syndrome. This syndrome modifies the microcirculation, with changes in oxygen delivery and uptake. (4)

No data are yet available regarding $rStO_2$ under NIRS and fractional tissue oxygen extraction (FTOE) in brain, liver, kidney and skeletal muscle tissue in infants with bronchiolitis and acute respiratory failure during mechanical ventilation and spontaneous breathing with mild or moderate inflammatory responses. We hypothesized that $rStO_2$ and FTOE might be disturbed in this group of patients.

Participants and methods

Subject population

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia.

In this prospective study we included critically ill infants admitted with acute bronchiolitis between 2009 and 2011. They were treated in a Level III, multidisciplinary Neonatal and Paediatric ICU at the Department of Paediatric Surgery and Intensive Care, Surgical Service, University Medical Centre, Ljubljana (Slovenia). The inclusion criteria were acute bronchiolitis with respiratory failure during and after mechanical ventilation. On the basis of the C-reactive protein (CRP) cut-off value on admission, the infants were divided into two groups: those with low CRP (≤10 mg/ml; l-CRP group) and those with high CRP (>10 mg/ml; h-CRP group).

Clinical data

The infant demographic data, arterial blood pressure, breathing frequency, fraction of inspired O_2 in air, fraction of inspired oxygen (FiO_2), transfusion and drug support data were collected from hospital documentation. CRP, total blood leukocyte count, pH and hemoglobin (Hb) were collected from laboratory data. Arterial oxygen saturation (SaO_2) was continuously measured by transcutaneous pulse oxymetry on a limb. On the basis of radiological criteria, the infants were classified into groups with simple radiological pulmonary changes. (5)

Mechanical ventilation, sedation and analgesia

All of the infants were treated with conventional mechanical ventilation and/or volume controlled intermittent mandatory ventilation when needed. To avoid having problems with ventilators, pain and distress sedation and analgesia were provided by continuous infusion of benzodiazepine (midazolam) and opioids (fentanyl), following the protocol for our ICU.

Measurement of regional tissue oxygenation

During hospitalization, we measured $rStO_2$ of brain, liver and kidney tissue as well as skeletal muscle of the leg for all of the infants. We used a near-infrared spectrometer for in-vivo optical spectroscopy (5100B; Somanetics Corporation; Troy, Michigan), which allows non-invasive and continuous monitoring of $rStO_2$. (6) We pasted adhesive sensors onto the skin of the frontal part of the head, on the lumbar skin, under the right costal margin, and on the leg muscle. These sensors detected changes in oxygenation, deoxygenation and total Hb concentration. (6) Tissue oxygenation was determinated from the different signals that the sensors received, and expressed as percentages of venous oxygenated Hb. (7) To determine tissue oxygen uptake, we used $rStO_2$ in brain, kidney, liver and skeletal muscle, along with SaO_2. From the measured $rStaO_2$ and SaO_2, we calculated FTOE according to the formula: $(SaO_2 - rStO_2)/SaO_2$. These measurements were taken at four specific times: on admission to ICU, day 1 (D1); after two or three days of mechanical ventilation (D2); on the last day of mechanical ventilation (D3); and during spontaneous breathing, without extra oxygen supply (D4). Each measurement lasted 1 hour. These were compared with normal values from the literature for $rStO_2$ of brain, liver, kidney and skeletal muscle and

Table 2. Demographic clinical, radiological and laboratory data for all of the infants and between the l-CRP and h-CRP groups.

Baseline measure Median (IQR)	All infants (N = 27)	l-CRP group (n = 8)	h-CRP group (n = 19)	P*
Age (days)	53 (24-79)	39 (21-63)	57 (25-87)	.31
Body weight (grams)	4460 (3500-4860)	3640 (2983-4841)	4500 (3690-4870)	.20
Gender (male/female)	13/14	6/2	7/12	.16
Treatment duration (days)	6 (5-9)	7 (5-11)	6 (5-9)	.67
C-reactive protein (mg/l)	17 (5-52)	3 (3-5)	36 (16-64)	.000
Antibiotic treatment (n, %)	25 (93%)	6 (75%)	19 (100%)	.88
Dopamine use (n, %)	6 (22%)	2 (25%)	4 (21%)	.86
Noradrenaline use (n, %)	2 (7%)	1 (13%)	1 (5%)	.55
Blood transfusion (n, %)	18 (67%)	4 (50%)	14 (74%)	.84
Confirmed bronchiolitis†(n/N, %)	14/15 (93%)	5/6 (83%)	9/9 (100%)	.81

CRP, C-reactive protein; h, high; l, low.
*P calculated with Mann-Whitney U test for l – CRP group versus h – CRP group (asym. sig. 2-tailed) and chi-squared test
†following lung X-ray on admission

Table 3. Arterial oxygen saturation (SaO_2) for all of the infants and between the l-CRP and h-CRP groups, across the measurement days.

Measurement day Median (IQR)	SaO_2 (%) All infants (N = 27)	l-CRP group (n = 8)	h-CRP group (n = 19)	P*
D1	96 (94-98)	98 (95-100)	96 (93-97)	.18
D2	96 (94-97)	95 (93-97)	96 (95-97)	.20
D3	96 (95-98)	96 (94-99)	97 (95-98)	.71
D4	98 (95-99)†	98 (95-99)	97 (95-99)	.98

CRP, C-reactive protein; D1, at admission; D2, after two or three days of mechanical ventilation; D3, on the last day of mechanical ventilation; D4, during spontaneous breathing, a day before discharge; h, high; l, low.
*P calculated with Mann-Whitney U test for l – CRP group versus h – CRP group
†P < .05 vs. D2 and D3, statistically significant difference calculated with Friedman ANOVA

from the literature for FTOE of the brain and kidney of infants (table 1). (8 -11)
Statistical analysis
The data are given as means ±SD and medians with 25 and 75 quartiles (interquartile range, IQR). The impact of lower and higher CRP levels on the main variables (heart rate, mean arterial pressure, SaO_2, breathing frequency, leukocytes, Hb, pH, partial oxygen pressure, FiO_2, $rStO_2$, FTOE) were tested with Mann – Whitney U-tests. Changes in the variables for D1, D2, D3 and D4 were analysed using analysis of variance (Friedman ANOVA). Pearson Chi-squared with Yates correction was used when gender and use of dopamine, antibiotics and pulmonary X-rays were compared. The Spearman correlation test was applied to determine the correlations between CRP, SaO_2, $rStO_2$ and FTOE. A $P < .05$ was considered as statistically significant. For the statistical analysis, SPSS version 22 (for WindowsTM, SPSS Inc., Chicago, IL, USA) was used.

Results

During the study period, 27 infants with acute bronchiolitis who were admitted

Table 4. Regional tissue oxygenation ($rStO_2$) for all of the infants and between the l-CRP and h-CRP groups across the measurement days, according to brain, liver, kidney and skeletal muscle.

Measurement day Median (IQR)	$rStO_2$ (%) All infants (N = 27)	l-CRP group (n = 8)	h-CRP group (n = 19)	P*
Brain				
D1	66.00 (57.00-74.00)	70.50 (59.25-77.75)	64.00 (56.00-74.00)	.52
D2	73.00 (67.00-81.00)†	78.00 (69.25-84.75)†‡‡	72.00 (66.00-79.00)	.21
D3	70.00 (63.00-85.00)	81.00 (70.25-83.25)	69.00 (62.00-76.00)	.03
D4	71.00 (65.00-74.00)	75.00 (67.00-84.00)	67.50 (64.25-72.75)	.04
Liver				
D1	69.00 (63.25-75.50)	69.50 (60.25-76.50)	69.00 (63.25-75.75)	.92
D2	71.00 (58.75-77.50)	71.00 (53.00-75.00)	71.00 (60.00-79.00)	.26
D3	75.00 (67.00-80.75)‡	66.00 (60.00-76.00)	79.00 (72.00-81.00)‡‡‡	.04
D4	69.00 (62.00-76.00)	69.00 (66.00-75.00)	68.00 (60.50-79.50)	.95
Kidney				
D1	77.00 (71.00-82.00)	78.50 (69.00-82.75)	77.00 (71.00-82.00)	.95
D2	79.00 (71.00-84.00)	81.00 (70.50-83.75)	78.00 (71.00-84.00)	.77
D3	82.00 (74.00-84.50)†‡	77.00 (73.00-83.50)	83.00 (74.00-85.50)	.27
D4	76.00 (71.00-84.00)	75.00 (71.00-80.00)	78.50 (71.75-86.50)	.44
Skeletal muscle				
D1	78.50 (64.50-83.00)	74.00 (60.50-85.00)	80.00 (67.50-83.00)	.71
D2	82.00 (75.00-86.00)‡‡	80.00 (70.75-83.50)	82.00 (75.00-87.00)	.33
D3	76.00 (69.50-85.75)	71.50 (61.00-82.75)	83.00 (73.25-87.50)†‡‡‡	.15
D4	73.00 (66.00-82.00)	77.00 (70.00-77.00)	72.00 (65.25-82.00)‡‡‡‡	.25

D1, on admission; D2, after two or three days of mechanical ventilation; D3, on the last day of mechanical ventilation; D4, during spontaneous breathing, a day before discharge; h, high; l, low.

*P calculated with Mann-Whitney U test for l – CRP group versus h – CRP group

† P < .05 vs.D1, statistically significant difference calculated with Friedman ANOVA

‡ P < .05 vs.D2, statistically significant difference calculated with Friedman ANOVA

†‡ P < .05 vs.D1, statistically significant difference calculated with Friedman ANOVA

‡‡ P < .05 vs.D3 and D4, statistically significant difference calculated with Friedman ANOVA

†‡ ‡P < . 05 vs.D1, statistically significant difference calculated with Friedman ANOVA

‡‡‡ P < . 05 vs.D1 and D2, statistically significant difference calculated with Friedman ANOVA

†‡‡‡ P < . 05 vs.D1 and D2, statistically significant difference calculated with Friedman ANOVA

‡‡‡‡ P < . 05 vs. D1, D2, D3 , statistically significant difference calculated with Friedman ANOVA

between 2009 and 2011 and mechanically ventilated in the 14-bed multidisciplinary Paediatric and Neonatal ICU were included in the NIRS measurements. According to the defined CRP cut-off values on admission, the infants were divided into the l-CRP group (≤10 mg/ml; l-CRP group; n = 8) and the h-CRP group (>10 mg/ml; h-CRP group; n = 19). Table 2 shows the demographic characteristics of these infants, both collectively and according to their CRP groups. In 23 of the infants (85%), the polymerase chain reaction analysis for Respiratory Syncytial Virus was positive. In the l-CRP group, Human Bocavirus and Enterovirus were detected for 1 infant, and virological testing for respiratory viruses remained negative for 1 infant. In the h-CRP group, Enterovirus and Rotavirus were detected. When there was suspicion of bacterial infection after cultures were taken, antibiotic treatment was started, according to antibiogram sensitivities. The bacteria isolated were as follows: Heamophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Pseudomonas aeruginosa, Escherichia coli, Enterobacter cloacae, Serratio

Table 5. Fractional tissue oxygen extraction (FTOE) for all of the infants and between the l-CRP and h-CRP groups across the measurement days, according to brain, liver, kidney and skeletal muscle.

Measurement	FTOE			P*
day Median (IQR)	All infants (N = 27)	l-CRP group (n = 8)	h-CRP group (n = 19)	
Brain				
D1	0.29 (0.17-0.39)	0.29 (0.20-0.35)	0.32 (0.14-0.43)	.90
D2	0.22 (0.14-0.30)†	0.17 (0.10-0.27)‡‡	0.25 (0.14-0.31)	.24
D3	0.28 (0.15-0.34)	0.15 (0.14-0.28)	0.30 (0.21-0.36)	.06
D4	0.27 (0.23-0.33)	0.22 (0.12-0.32)	0.29 (0.25-0.33)	.08
Liver				
D1	0.26 (0.16-0.31)	0.29 (0.18-0.39)	0.25 (0.14-0.31)	.47
D2	0.24 (0.17-0.38)	0.25 (0.17-0.46)	0.22 (0.17-0.30)	.30
D3	0.21 (0.16-0.29)	0.31 (0.21-0.38)	0.20 (0.15-0.26)	.04
D4	0.27 (0.22-0.34)‡	0.27 (0.25-0.31)	0.28 (0.20-0.34)†‡‡	.74
Kidney				
D1	0.17 (0.08-0.28)	0.21 (0.10-0.29)	0.15 (0.07-0.28)	.40
D2	0.15 (0.09-0.26)	0.15 (0.11-0.25)	0.18 (0.09-0.26)	.96
D3	0.16 (0.11-0.22)	0.19 (0.16-0.25)	0.14 (0.10-0.21)	.18
D4	0.18 (0.14-0.24)	0.23 (0.16-0.29)	0.17 (0.11-0.22)	.20
Skeletal muscle				
D1	0.16 (0.12-0.29)	0.24 (0.10-0.39)	0.15 (0.12-0.22)	.31
D2	0.14 (0.04-0.20)†‡	0.16 (0.10-0.25)	0.12 (0.03-0.20)	.22
D3	0.20 (0.12-0.27)	0.25 (0.15-0.36)	0.15 (0.10-0.23)‡‡‡	.13
D4	0.22 (0.17-0.33)	0.21 (0.19-0.26)	0.23 (0.17-0.34)†‡‡‡	.50

CRP, C-reactive protein; D1, on admission; D2, after two or three days of mechanical ventilation; D3, on the last day of mechanical ventilation; D4, during spontaneous breathing, a day before discharge; h, high; l, low.

*P calculated with Mann-Whitney U test for l – CRP group versus h – CRP group

†,P < .05 vs. D1, statistically significant difference calculated with Friedman ANOVA

‡P < .005 vs. D3, statistically significant difference calculated with Friedman ANOVA

†‡ P < .05 vs. D3, D4, statistically significant difference calculated with Friedman ANOVA

‡‡ P < .05 vs. D1, statistically significant difference calculated with Friedman ANOVA

†‡‡ P < .05 vs. D3, statistically significant difference calculated with Friedman ANOVA

‡‡‡ P < .05 vs. D2, statistically significant difference calculated with Friedman ANOVA

†‡‡‡ P < .05 vs. D1, D2, statistically significant difference calculated with Friedman ANOVA

liquefaciens, Staphylococcus aureus, and Stenotrophomonas maltophilia. Between the CRP groups, there were no differences in antibiotic use.

Arterial oxygen saturation

There were no significant differences in SaO_2 between the l-CRP and h-CRP groups or according to the measurement days during admission to the ICU (D1-D4) for the l-CRP and h-CRP groups (table 3).

Tissue oxygenation ($rStO_2$) of brain, kidney, liver and skeletal muscle

For skeletal muscle in the h-CRP group, $rStO_2$ difference for D4 (during spontaneous breathing) compared with D1-D3 (during mechanical ventilation), was significant (P < .05). For the other three tissues in the study (brain, liver and kidney), there were no significant differences in $rStO_2$ between D4 and each of the measurement days when patients were mechanically ventilated (D1 - D3). However, considering the comparison between the l-CRP and h-CRP groups, there was a significantly lower $rStO_2$ in brain tissue on the last day of mechanical ventilation and spontaneous breathing (D3, D4) (P = .03; P = .04) and higher $rStO_2$ in liver tissue in the h-CRP group on the last day of mechanical ventilation (D3) (P = .04) (table 4).

Fractional tissue oxygen extraction (FTOE) in brain, liver, kidney and skeletal muscle

Table 5 shows the median FTOE for each of the measurement days for all of the infants together and for the l-CRP and h-CRP groups. In liver we found a significant higher FTOE on D4 compared to D3 (P < .05) in the h-CRP group. In skeletal muscle we also found a significantly higher FTOE on D4 compared to D1 and D2 (P < .05; P < .05), in the h-CRP group. On D3 and D4, in the brain there was a higher FTOE in the h-CRP group compared to the l-CRP group, but it did not reached signifi-

Table 6. Correlations between SaO_2 and FTOE in the brain, liver, kidney and skeletal muscle.

Tissue	SaO_2 versus FTOE correlation					
	All infants (N = 27)		l-CRP group (n = 8)		h-CRP group (n = 19)	
	r†	P*	r	P	r	P
Brain	.172	.091	.117	.532	.157	.203
Liver	.199	.053	.334	.076	.160	.200
Kidney	.286	.004	.330	.070	.253	.039
Skeletal muscle	.214	.037	.246	.183	.220	.078

CRP, C-reactive protein; FTOE, fractional tissue oxygen extraction; h, high; l, low; SaO_2, arterial oxygen saturation.
P* statistical significance
r† Spearman's correlation coefficient

Table 7. Correlations between SaO_2 and $rStO_2$ in the brain, liver, kidney and skeletal muscle.

Tissue	SaO_2 versus $rStO_2$ correlation					
	All infants (N = 27)		l-CRP group (n = 8)		h-CRP group (n = 19)	
	r†	P*	r	P	r	P
Brain	.064	.532	.019	.919	.127	.306
Liver	.110	.287	-.146	.450	.200	.107
Kidney	.092	.365	-.133	.476	.173	.162
Skeletal muscle	.096	.354	-.033	.858	.117	.352

CRP, C-reactive protein; h, high; l, low; $rStO_2$, regional tissue oxygen saturation; SaO_2, arterial oxygen saturation.
P* statistical significance
r† Spearman's correlation coefficient

cance (P = .06; P = .08); conversely, in the liver, the lower FTOE in the h-CRP group compared to the l-CRP group at D3 reached significance (P = .04).

Correlations among CRP, SaO_2, $rStO_2$ and FTOE in brain, liver, kidney and skeletal muscle

Table 6 gives the correlations between the SaO_2 and FTOE. There were positive correlations in all tissues, though statistically significant positive correlations were found only for the h-CRP group of patients in kidney tissue (r = .253; P = .039).

Table 7 shows the correlations between the SaO_2 and $rStO_2$. No statistically significant correlations were found in all groups of patients.

There were strong negative correlations between the $rStO_2$ and FTOE for all of the tissues across all of the groups (P < .001) (table 8).

In tables 9 and 10 correlations between CRP and $rStO_2$, and CRP and FTOE in all of the tissues are presented. A positive correlation between CRP and $rStO_2$ (r = .297; P = .004) and negative between CRP and FTOE (r = -.360; P = .000) was found in skeletal muscle in all infants combined. No significant correlations were found in the other three tissues.

Discussion

The main finding of our study is that in infants with acute bronchiolitis (during and after mechanical ventilation), and mild or moderate inflammatory responses on admission and thereafter, the $rStO_2$ and FTOE levels in the tissues measured never decreased below normal values. The second particular finding is that for all of the infants combined , and for the h-CRP subgroup in particular, the $rStO_2$ of skeletal muscle during spontaneous breathing before discharge from the ICU (D4) was lower and FTOE was higher compared to the first and third day of mechanical ventilation (D1, D2). In liver tissue, a higher FTOE at D4 compared to D3 was also found. Moreover, there were higher $rStO_2$ and lower FTOE in liver in the h-CRP group compared to l-CRP group during the last day of mechanical ventilation (D3). Furthermore, there were lower $rStO_2$ and higher FTOE in brain tissue in the h-CRP group compared to l-CRP group during the last day of mechanical ventilation and spontaneous breathing (D3, D4). There were also highly significant negative correlations between $rStO_2$ and FTOE in skeletal muscle, as well as in the other three tissues, for all of the infants together and for both of the CRP groups. But, on the other hand, positive correlations between CRP and $rStO_2$ and negative between CRP and FTOE in skeletal muscle in the combined group of infants, as well as in the l-CRP and h-CRP groups of patients, might indicate that tissue oxygen delivery and extraction were not critically but only mildly disturbed.

Table 8. Correlations between FTOE and $rStO_2$ in the brain, liver, kidney and skeletal muscle.

Tissue	FTOE versus $rStO_2$ correlation					
	All infants (N = 27)		l-CRP group (n = 8)		h-CRP group (n = 19)	
	r†	P*	r	P	r	P
Brain	-.915	<.001	-.984	<.001	-.886	<.001
Liver	-.879	<.001	-.969	<.001	-.834	<.001
Kidney	-.841	<.001	-.966	<.001	-.794	<.001
Skeletal muscle	-.897	<.001	-.970	<.001	-.865	<.001

CRP, C-reactive protein; FTOE, fractional tissue oxygen extraction; h, high; l, low; $rStO_2$, regional tissue oxygen saturation.
P* statistical significance
r† Spearman's correlation coefficient

However, in interpreting these results we have to be cautious because when we use the mathematical coupling between $rStO_2$ and FTOE we should be aware that interpretation of preserved or impaired tissue auto-regulation is very difficult and even speculative by using just these two variables without additional data i.e. Doppler flow as has been shown by Walsh TS. (12) Combining only these two methods may give reliable results and interpretation of preserved or impaired tissue auto-regulation. (13)

Many studies have attempted to define the clinical significance and value of measuring tissue oxygenation saturation by NIRS in various tissues. While the values of brain oxygen desaturation at which we can expect neurological deficit have been estimated at between 40% and 50%, the NIRS values in the somatic organs have not been so clearly defined. Stapleton et al. (14) studied the optimal values of oxygen saturation in the mesenterial area. They reported that when regional oxygen desaturation of the splanchnic area in infants with pulmonary atresia and intact ventricular septum with adequate and stable pulmonary flow dropped to 24.5%, this was related to the appearance of necrotizing enterocolitis. Hoffman et al. (15) showed that measurements of kidney saturation can predict acute renal failure after heart operations in neonates. In children with pernicious anemia, Raj et al. (16) reported that measurements of $rStO_2$ can predict those patients who are at increased risk of brain hypoxia during the awake and sleep states. In our infants, there was a strong negative correlation between $rStO_2$ and FTOE, which indicated that during the lowering of $rStO_2$, FTOE in all four of these observed tissues increased, and therefore oxygen delivery and consumption are not likely to be critically disturbed.

Petrova and Mehta (8) showed that a reduction in cerebral and kidney oxygenation during which arterial saturation decreases from 70% to 80% has an increased FTOE in kidney, while its use in cerebral tissue did not significantly change. In our study, SaO_2 positively correlated with FTOE in both cerebral and kidney tissues (table 6). How mechanical ventilation and spontaneous breathing under different clinical conditions during brain hypoxia might affect $rStO_2$ and FTOE were also investigated by Chien et al. in animal studies. They showed that in the animal model with and without hypoxia induced by decreasing the frequency of mechanical ventilation from 40 per min to 20 per min, $rStO_2$ of the brain decreased, but FTOE increased in both groups of animals. (17)

During the third days of mechanical ventilation (D2), CRP was the highest for all of the infants together as well as in both of the CRP groups, which indicated mild-to-moderate inflammatory responses with some signs of systemic inflammatory response syndrome. Afterwards, the CRP decreased significantly in these infants, until they started breathing spontaneously. While we found for all of the infants and for the h-CRP group that during mechanical breathing there was decreased FTOE in skeletal muscle, as compared to spontaneous breathing, these changes were not seen for the l-CRP group. We were not able to measure the consequent serum lactate levels in all blood samples, but blood samples, which were occasionally taken on our patients, had lactate levels within reference values.

Moreover, the pH values taken at the same time when these other measurements were carried out were all in the normal range.

Because of a decreased FTOE that was found in skeletal muscle in the h-CRP group on D1 and D2 compared to D4, we speculate that the infants in the h-CRP group might have had stronger inflammatory responses than those in the l-CRP group, which could affect the microcirculation in the tissues.

In systemic inflammatory response syndrome, the microcirculation can be affected in several ways. There is an increase in the number of nonperfused capillaries and systemic vascular permeability, and in addition there is disruption of autoregulation of the local blood flow. (9) Part of the tissue, where there is a reduced flow of blood through the capillaries, can become hypoxic, which will result in a reduction in FTOE in the affected tissues. (18) At the same time, the blood flow in the tissues increases, which is why tissue saturation does not change, or might even increase. (6) So we would expect that $rStO_2$ between the l-CRP and h-CRP groups will not be different. This has been demonstrated

Table 9. Correlations between CRP and $rStO_2$ in the brain, liver, kidney and skeletal muscle.

Tissue	CRP versus $rStO_2$ correlation					
	All infants (N = 27)		l-CRP group (n = 8)		h-CRP group (n = 19)	
	r†	P*	r	P	r	P
Brain	-.0.03	.773	-.225	.241	.150	.242
Liver	-.013	<.905	-.207	.300	-.043	.739
Kidney	-.052	<.632	.281	.140	-.055	.666
Skeletal muscle	-.297	<.004	.352	.061	.246	.056

CRP, C-reactive protein; h, high; l, low; $rStO_2$, regional tissue oxygen saturation.
P* statistical significance
r† Spearman's correlation coefficient

Table 10. Correlations between CRP and FTOE in the brain, liver, kidney and skeletal muscle.

Tissue	CRPversus FTOE correlation					
	All infants (N = 27)		l-CRP group (n = 8)		h-CRP group (n = 19)	
	r†	P*	r	P	r	P
Brain	-.066	.531	-.251	.190	-.147	.252
Liver	-.060	.579	.173	.389	-.008	.949
Kidney	-.155	.140	-.333	.077	-.027	.836
Skeletal muscle	-.360	<.000	-.350	.063	-.299	<.019

CRP, C-reactive protein; FTOE, fractional tissue oxygen extraction; h, high; l, low.
P* statistical significance
r† Spearman's correlation coefficient

in kidney and skeletal muscle. For the latter, our results are in agreement with the study by Strahovnik and Podbregar. (6) Statistically significant differences were seen between l-CRP and h-CRP groups of patients for brain tissue on D3 and D4 and for liver tissue on the last day of mechanical ventilation (D3). In the l-CRP group, the brain $rStO_2$ during D3 and D4 was 81.00% and 75.00%, consecutively and in the h-CRP group, 69.00% and 67.00%, consecutively. The liver $rStO_2$ during D3 in the l-CRP group was 66.0%, while in the h-CRP group, it was higher, 79.00 percent. We expected that maybe under the stronger inflammatory response, there would be differences in FTOE in kidney and skeletal muscle between the two CRP groups, and that the FTOE values of the h-CRP group would be higher consequently. Comparing FTOE between the two CRP groups, we observed that the FTOE values in the h-CRP group were on average higher than in the l-CRP group in the brain at D3 and D4, but lower in the liver at D3. At the same time, no differences for kidney and skeletal muscle were found between the two CRP groups. Why was there a difference in $rStO_2$ and FTOE only in brain and liver tissue, but not in the kidney and skeletal muscle and why, apart from skeletal muscle and liver, was there no difference between spontaneous breathing and mechanical ventilation in neither the l-CRP nor in the h-CRP subgroups of patients? At present, we are not able to specifically explain these data. What we can confirm from our data is that CRP positively correlates with $rStO_2$ and negatively with FTOE in skeletal muscle (tables 9 and 10), but not for the other three studied tissues and this might be the cause for differences found in skeletal muscle.

In regard to the liver, we can only speculate that the systemic inflammatory response in the infants in the h-CRP group increased the blood flow to the liver and the lower FTOE was just compensated for by higher blood flow, but no correlations were found between CRP and $rStO_2$ and CRP and FTOE to explain this speculation. As we already mentioned above, we should be aware

that interpretation of preserved or impaired tissue auto-regulation is very difficult and even speculative by using just these two variables without additional data i.e. Doppler flow. (12,13) The other possibility might be the use of vasopressors, which have influence on the blood flow to the organs. Indeed, the use of vasopressor drugs can significantly affect the transport and uptake of oxygen not only in muscle, but also in other organs, as well as during systemic inflammatory response syndrome itself. Catecholamines (e.g., dopamine, norepinephrine) have various effects on the distribution of oxygen through their vasoactive actions. (19-22) In addition to these vasoactive actions of the catecholamines, as adrenergic agonists they also have metabolic effects on tissues, which can result in increased oxygen consumption, VO_2 due to the increased energy needs of the tissues. Increased demand of peripheral tissue due to increased metabolism might prevail over the catecholamine effects of increased peripheral delivery of O_2-rich blood. (20) It is therefore difficult to evaluate any critical assessment of the impact of catecholamines on the hepatosplanchnic circulation in our patients, as so far in different published studies there have been conflicting opinions of vasoactive and metabolic effects of dopamine and norepinephrine in the hepatosplanchnic vascular network. (19,23-25)

From the number of studies and the different results obtained relating to the effects of dopamine and norepinephrine on the hepatosplanchnic circulation, these suggest a complex mechanism for the regulation of blood flow in the hepatosplanchnic area. Differential effects of dopamine and norepinephrine might depend on the intensity of the clinical course, due to the different sensitivities of the adrenergic receptors and/or to the different doses of drugs used. (20) However, only a few of the infants in our study had dopamine (22%) or norepinephrine (7%) support, with no differences between these for the l-CRP and h-CRP groups; therefore, we can exclude possible effects of vasopressors in our group of infants.

Finally, in the interpretation of our data, we need to consider the significance of transfusion in the oxygenation of tissues, although we did not find any differences in the number of transfusions between the l-CRP and h-CRP groups. A number of studies have questioned the possible contributions of transfusions to increased tissue oxygenation. (9,16,18,26) If the transfusion does not contribute to the improvement of tissue oxygenation, the potential causes might be the disruption of the microcirculation or modified features of the red blood cells (e.g., their age, any endogenous deformation). (27) From the above data, we can exclude blood transfusion as the cause for the differences in tissue oxygenation seen here.

A weakness of our study is that we failed to obtain any sudden oxygen desaturation, which can appear in the first few days in infants with acute bronchiolitis. One of the limitations of our study is the small number of participants, although the group was very homogeneous, as all of the infants weighed less than 5 kg, and the levels of CRP in the two groups at entry into the study showed an evident difference for these infants, in terms of the l-CRP and h-CRP groups. The last but not least weakness is that we did not measure Doppler flow and therefore interpretation of preserved or impaired tissue auto-regulation is very difficult and even speculative.

In conclusion we can say that we have shown that during mechanical ventilation of infants with acute bronchiolitis, there were no major disturbances in $rStO_2$ and FTOE during the period of observation.

ACKNOWLEDGMENTS

We would like to thank the medical staff at the Department of Paediatric Surgery and Intensive Care, University Medical Centre Ljubljana, particularly the nurses who participated in the care and treatment of infants with bronchiolitis.
This work was conducted at the Department of Pediatric Surgery and Intensive Care, University Medical Centre Ljubljana, Bohoriceva 20, 1525 Ljubljana, Slovenia as part of the TERCIAR Clinical Study, project no. 70243, University Medical Centre Ljubljana.

REFERENCES

1. Bernal NP, Hoffman GM, GhanayemNS, Arca MJ. Cerebral and somatic near infrared spectroscopy in normal newborns. J Pediatr Surg 2010;45(6):1306-10.
2. Rozé JC, Liet JM, Gournay V, Debillon T, Gaultier C. Oxygen cost of breathing and weaning process in newborn infants. Eur Resp J 1997;10:2583-5.
3. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child1986;Jun;140(6):543-6.
4. Pittard AJ, Hawkins WJ, Webster NR. The role of the microcirculation in the multi-organ dysfunction syndrome. Clin Intensive Care 1994;5(4):186-90.
5. Schuh S, Lalani A, Upton A, Manson D, Babyn P, Derek S, et al. Evaluation of the Utility of Radiography in Acute Bronchiolitis. J Pediatr 2007;150:429-33.
6. Strahovnik I, Podbregar M. Measurement of skeletal muscle tissue oxygenation in the critically ill. Signa Vitae 2008;3(1):43–50.
7. Roche-Labarbe N, Zaaimi B, Berquin P, Nehliq A, Grebe R, Wallois F. NIRS-measured oxy- and deoxyhemoglobin changes associated with EEG spike-and-wave discharges in children. Epilepsia 2008;49(11):1871–80.
8. Petrova A, Mehta R. Near – infrared spectroscopy in the detection of regional tissue oxygenation during hypoxic events in preterm infants undergoing critical care. Ped Crit Care Med 2006;6(5):449–54.
10. Parežnik R, Knezevic R,Voga G, Podbregar M. Changes of the muscle tissue deoxygenation during stagnant ischemia in septic patients. Intensive Care Med 2006;32(1):87–92.
11. Schulz G, Weiss M, Bauersfeld U, Teller J, Haensse D, Bucher HU, et al. Liver tissue oxygenation as measured by near-infrared spectroscopy in the critically ill child in correlation with central venous oxygen saturation. Intensive Care Med 2002;8(2):184–9.
12. Walsh TS, Lee A. Mathematical coupling in medical research: lessons from studies of oxygen kinetics. Brit J Anesth 1998;81:118-20.
13. Pfister D, Siegemund M, Dell-Kuster S, Smielewski P, Ruegg S, Strebel SP, et al. Cerebral perfusion in sepsis-associated delirium. Crit Care 2008;12(3):R63. Doi: 10.1186/cc6891. Epub 2008 May 5.
14. Stapleton GE, Eble BK, Dickerson HA, Andropoulos DB, Chang AC. Mesenteric oxygen desaturation in an infant with congenital heart disease and necrotizing enterocolitis. Tex Heart Inst J 2007;34(4):442–4.
15. Hoffman GM, Ghanayem NS, Mussatto KA, Musa N. Perioperative Perfusion Assessed by Somatic NIRS Predicts Postoperative Renal Dysfunction. Anesthesiology 2005;103:A1327.
16. Raj AB, O'brien LM, Bertolone SJ, Gozal D, EdmondsHL Jr. Cerebral oximetry improves detection of sickle cell patients at risk for nocturnal cerebral hypoxia. Pediatr Pulmonol 2006;41(11):1088–94.
17. Chien JC, Jeng MJ, Chang LH, Lee YS, Soong WJ, Hwang B. Cerebral oxygenation during hypoxia and resuscitation by using near-infrared spectroscopy in newborn piglets. J Chin Med Assoc 2007;Vol.70 No.2:47–55.
18. Vincent J, De Backer D. Oxygen transport – the oxygen delivery controversy. Intensive Care Med 2004;30:1990–6.
19. De Blasi R, Palmisani S, Alampi D, Mercieri M, Romano R, Collini S, et al. Microvascular dysfunction and skeletal muscle oxygenation assessed by phase-modulation near-infrared spectroscopy in patients with septic shock. Intensive Care Med 2005;31:1661–8.
19. Jakob M, Ruokonen E, Takala J. Effects of dopamine on systemic and regional blood flow and metabolism in septic and cardiac surgery patients. Shock 2002 ;Vol.18 No.1:8–13.
20. Guerin JP, Levraut J, Samat-Long C, Leverve X, Grimaud D, Ichai C. Effects of Dopamine And Norepinephrine on Systemic and Hepatosplanchnic Hemodynamics, Oxygen Exchange, And Energy Balance in Vasoplegic Septic Patients. Shock 2005;23(1):18–24.
21. Murphey ED, Traber DL. Cardiopulmonary and splanchnic blood flow during 48 hours of a continuous infusion of endotoxin in conscious pigs: a model of hyperdynamic shock. Shock 2000;13:224–9.
22. Ruokonen E, Takala J, Kari A, Saxen H, Mertsola J, Hansen EJ. Regional blood flow and oxygen transport in septic shock. Crit Care Med 1993;21:1296–303.
23. Träger K, Radermacher P, Rieger KM, Vlatten A, Vogt J, Iber T, et al. Norepinephrine and N*-monomethyl-L- arginine in porcine septic shock. Effects on hepatic O2 exchange and energy balance. Am J Respir Crit Care Med 1999;159:1758–65.
24. Cheung PY, Barrington KJ, Pearson RJ, Bigam DL, Finer NN, Van Aerde JE. Systemic, pulmonary and mesenteric perfusion and oxygenation effects of dopamine and epinephrine. Am J Respir Crit Care Med 1997;155:32–7.
25. Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. JAMA 1994;272: 1354–7.
26. Malik P, Sibbald W. Effect of Stored-Blood Transfusion on Oxygen Delivery in Patients With Sepsis. JAMA 1993;269:3024–9.
27. Mclellan in Walsh. Oxygen delivery and haemoglobin. Contin Educ Anaesth Crit Care Pain 2004;4:124.