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Combined cerebral and somatic near-infrared spectroscopy oximetry monitoring during liver surgery: an observational and non-interventional study

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Background: Cerebral oximetry using near-infrared spectroscopy (NIRS) is used for monitoring cerebral oxygen saturation during cardiac surgery and is correlated with clinical outcomes. Our goal was to explore cerebral and somatic NIRS in liver resections as a predictor of post-operative complications.

Methods: Prospective observational and non-interventional study from a tertiary care university hospital including adult patients undergoing liver resection monitored using NIRS at four sites before and during surgery. Those sites were: frontotemporal left and right zones, right thigh, and right arm. Anesthesiologists and surgeons were blinded to oximetry values. Correlations were assessed between baseline oximetry values and cerebro-somatic desaturation load (threshold of 80% from baseline) values with peri-operative events and complications.

Results: Ninety patients were distributed equally among gender with a mean age of 59.7 ± 13.1 years. Lower baseline cerebral and/or somatic values were associated with increased risk of delirium, respiratory failure, surgical and renal complications, blood transfusions, and length of stay in the intensive care unit and in the hospital ($P < 0.05$). The severity of somatic desaturation below 80% was the only parameter associated with blood losses ($P = 0.030$) and length of hospital stay ($P = 0.047$).

Conclusions: Cerebral and somatic desaturation does occur in liver resection and can be used simultaneously during liver surgery. Both baseline cerebral and somatic NIRS values are correlated with complications and outcomes. However, thigh desaturation appears more sensitive than cerebral NIRS values in predicting some of these complications.

Keywords: Compartment syndromes; Hepatectomy; Intraoperative complications; Liver; Oximetry; Physiologic monitoring.

Introduction

Liver resections increase long-term survival in patients with colon cancer with liver metastasis [1]. Ongoing improvements in surgical and anesthetic techniques have significantly reduced mortality rates associated with liver resections. Nevertheless, it is still a major surgery that can lead to surgical bleeding and periods of hemodynamic instability. These hemodynamic fluctuations are a cause for medical concern because of their impact on tissue perfusion, which may lead to increased neurological and other postoperative complications. The incidence of postoperative complications after liver resections is approximately 31% [2].

Monitoring of cerebral oxygen saturation using near-infrared spectroscopy (NIRS) [3], a non-invasive optical technique, is an efficient way to evaluate regional blood flow and tissue oxygen transport [4]. The association between pre-operative and intraoperative reduction in NIRS value with post-operative mortality, renal failure, and delirium has been established [5–16]. Although most studies have focused on monitoring cerebral oxygen saturation, few studies have explored the role of somatic NIRS monitoring. In patients with septic shock, reduction in systemic tissue oxygen saturation was predictive of mortality [17–19]. In addition, tissue hemoglobin oxygen saturation or somatic NIRS monitoring is the best predictor of outcome in trauma patients with massive transfusion [20] and is associated with worse outcome when combined with cerebral saturation in congenital heart disease [21,22]. In patients having sustained severe trauma, reduced somatic NIRS value have been associated with mortality, subsequent organ dysfunction, the need for massive transfusion, or emergent surgery [23–26]. We have recently reported our experience using cerebral and somatic NIRS in liver transplantation [27,28] and proposed a combined cerebral and somatic algorithm [29]. However, no studies have examined intraoperative cerebral and somatic oxygen saturation as a predictor of postoperative complications after hepatic surgery. The primary objective of this observational study was to determine the association between the systemic and/or cerebral desaturation and the number of postoperative adverse events in hepatic surgery. In addition, we wanted to describe several cases showing the promising role of this form of regional tissue oxygenation monitoring in liver resection surgery. Our hypothesis is that reductions in both cerebral and somatic NIRS will correlate with post-operative complications.

Materials and Methods

This prospective single-site observational and non-interventional study was approved by the Ethics Committee of the Centre Hospitalier de l'Université de Montréal, CHUM Protocol No. 10.192, and written informed consent was obtained from all patients. The study was registered with clinicaltrials.gov (NCT 01458262) and reported using the STROBE Checklist guidelines (Appendix 1). The study was supported by an unrestricted equipment grant from Covidien (Covidien/Medtronic Inc., USA). Patients younger than 18 years old and patients with pre-existing neurological disease were excluded. Patients were recruited from January 2012 to July 2013.

The INVOS oximeter system (INVOS 5100-PB, Covidien-Medtronic, USA) was used for all patients. Before anesthesia induction, sensors were placed on both the frontotemporal zones of patients' heads and on the right thigh and right arm (opposite site of the intravenous line) and all four values displayed on a single screen on the NIRS monitor. The baseline values were obtained 1 min after sensors placing and signal stabilization. Validation of the use of both cerebral and somatic NIRS using this sensor was previously determined and reported in 53 healthy volunteers [30]. Normal left and right cerebral values were mean ± SD: 66.1 ± 9.4 and 66.6 ± 9.1 respectively, left and right arm: 74.1 ± 7.7 and 74.8 ± 8.5, and left and right thigh: 74.2 ± 8.0 and 74.1 ± 8.1. The same anesthesia induction technique (sufentanil, propofol, and rocuronium) was used for all patients. Anesthesia was maintained with desflurane in an air-oxygen mixture and rocuronium was administered as required. Monitoring included invasive arterial blood pressure monitoring, central venous pressure via central line, electrocardiogram, standard pulse oximetry, core temperature monitoring, and expired carbon dioxide measurement [31]. Every patient had indwelling urinary catheter and warming system. Only patients with hemoglobin ≥ 85 g/L, creatinine ≤ 104 μmol/L, and hemodynamic stability underwent phlebotomy before liver resection.

The technical details for the phlebotomy have been previously reported [32,33] and it was performed in 82 patients (91%) for an average of 273 ± 39 ml. All retrieved blood was re-transfused at the end. Vasopressors (phenylephrine and vasopressin) were used as required to manage blood pressure.

Patients were included if they underwent major liver resection that included right or left hepatectomy with at least three or more segments. Liver parenchyma transection was performed using advanced bipolar coagulation and/or stapler. Hepatic pedicles were controlled within the liver parenchyma using a surgical stapler. Intermittent hilar clamping was used with a ratio of 15 min of clamping to 5 min of reperfusion on a case-to-case basis. Liver parenchyma hemostasis was obtained using argon coagulation and/or fibrin sealant. All cases were performed by open surgery.

Cerebral and somatic NIRS data were collected continuously

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starting before induction until 1 h after surgery. Basic monitoring data were also recorded through the surgery up to 1 h after the surgery. The anesthesiologist and the surgeon as well as all clinical personnel were completely blinded to all oximetry measurements, so its data were not used in patient care plan. The monitoring system was positioned in such a way that the information was always hidden from the treating team. One of the investigators (TH) was present in the operating room during all the cases to take note of the events during the surgical procedure. The severity of desaturation (cerebro-somatic desaturation load) was obtained by obtaining the product of the area between the 80% desaturation threshold and the oximetry curve and time as previously described [34,35].

Data were anonymized and compiled into a database. Patient demographics, surgery duration, intensive care unit (ICU) stay, and length of hospital stay (LOS) were measured. For every subject, the pre-operative American Society of Anesthesiologists (ASA) class, the co-morbidities, international normalized ratio, albumin, hemoglobin, platelet, and creatinine levels were recorded. The patient was monitored daily in the post-operative period and no change in care plan was undertaken based on oximetry data. All complications defined pre-operatively (Appendix 2) were recorded and graded according to Dindo-Clavien scale [36].

Statistical analysis

The primary outcome was to define the correlation coefficient between the number of systemic and/or cerebral desaturation phases and the number of postoperative adverse events. Continuous variables are presented as mean ± SD or as median and interquartile range (IQR) according to the normality of the distribution of the variables, while categorical variables are presented as frequency (percentages). The distribution of the continuous variables was assessed using plots (histograms, stem-and-leaf plots), normality tests (Shapiro-Wilk, Kolmogorov-Smirnov), and skewness and kurtosis indexes. Pearson's (for normally distributed variables) and Spearman's (for non-normal distribution) correlation coefficients were used to assess the relation between oximetry variables and continuous parameters of interest. Student t-tests and Mann-Whitney-Wilcoxon tests were used to compare oximetry measurements between categories of specific population baseline characteristics (sex, hypertension, smoking, etc.) and peri-operative variables (use of Pringle, etc.), and also between the presence versus absence of different complications (dichotomous variables for neurological, cardiac, respiratory, surgical, infectious, and hematological complications). Binary logistic regression was also used to study the relation between baseline oximetry values and the risk of these various complications. The same statistical analyses were performed accordingly to assess the relation between the severity of desaturation and the other parameters of interest. Measurement of cerebro-somatic desaturation load between the four sites of assessment were compared using a one-way repeated measures ANOVA and contrasts between groups (if the overall group test is statistically significant). Odds ratio (OR) and 95% CI were calculated. The original sample size calculation was based on a primary analysis involving a multiple linear regression model and requiring a total of 90 subjects. The primary analysis was then simplified and based on a simple Pearson correlation coefficient to assess the relation between oximetry variables and continuous parameters of interest. A sample size of 90 was still sufficient to detect a coefficient r of 0.3 (medium effect size) with a statistical power of 80% and a two-sided alpha of 0.05. For all tests, a two-sided $P < 0.05$ was considered significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., USA).

Results

Ninety patients (45 males and 45 females) scheduled for major liver resections (three or more segments) were included in the study. The mean age was 59.7 ± 13.1 years. Table 1 describes the baseline cerebral and somatic oximetry values, co-morbidities, and surgical indications of the patient population. Cerebral right (CR) and cerebral left (CL), somatic arm, and thigh NIRS values were successfully obtained and analyzed in most patients (90, 87, 89, and 89 patients). ASA 1 and 2 patients represent 84% of the cohort. Co-morbidities were present in 63 patients (70%). A total of 73 patients (81%) had previous abdominal surgery. The surgeries in this study included 32 right hepatectomies, 21 left hepatectomies, and 37 partial liver resections (of at least three segments). Median (Q1, Q3) operative time was 180 (140, 225) min and median blood loss was 350 (150, 600) ml. Median LOS was 7 (5, 10) days and median ICU stay was 2 (0, 2) days.

In the postoperative course, one patient died. Overall, 11 patients had severe complications (Dindo 3 or higher, 12.2%), 41 patients had mild complications (Dindo 1 or 2, 45.6%), and 38 patients (42.2%) had no complications. There were 9 neurological, 6 cardiac, 16 respiratory, 35 surgical, 30 infectious, 5 renal, 10 hematologic, and 4 various complications (some patients had more than one complication; complications are detailed in Appendix 3).

Table 2 summarizes the relation between baseline NIRS value and population characteristics. Higher baseline somatic arm NIRS was observed in younger patients (correlation coefficient: –0.265, $P = 0.013$), patients with lower ASA (correlation coefficient:

Table 1. Baseline Characteristics, Co-morbidities and Surgical Indications in the Population

Demographic	Results
Age	59.7 ± 13.1
Gender (M/F)	45/45
Weight (kg)	76.7 ± 18.2
Height (cm)	168 ± 9.6
ASA I–II	0.841
Baseline oximetry	
CR	67 ± 9
CL	67 ± 8
Arm	75 ± 8
Thigh	74 ± 8
Comorbidities	63 (70)
Cirrhosis	5 (5.6)
Hypertension	24 (26.7)
Diabetes	9 (10.0)
Chronic obstructive lung disease	8 (8.9)
Coronary artery disease	8 (8.9)
Dyslipidemia	15 (16.7)
Previous abdominal surgery	73 (81)
Surgical indications	
Malignancy*	71 (78.9)
Gallbladder	6 (8.5)
Hepatocellular carcinoma	5 (7.0)
Cholangiocarcinoma	4 (5.6)
Colorectal liver metastases	51 (71.8)
Breast cancer liver metastases	1 (1.4)
Melanoma liver metastases	1 (1.4)
Neuroendocrine liver metastases	2 (2.8)
Oncocytoma	1 (1.4)
Benign*	19 (21.1)
Liver abscess	1 (5.3)
Ischemic cholangitis	1 (5.3)
Hepatolithiasis	3 (15.8)
Adenoma, focal nodular hyperplasia, hemangioma	14 (73.7)

Values are presented as mean ± SD or number of patients or mean (%). *Percentages are presented over the section sub-total. Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. ASA: American Society Anesthesiology class, CR: cerebral right, CL: cerebral left.

–0.215, P = 0.047), and patients without co-morbidities (no co-morbidities NIRS = 77.4 ± 8.1%; presence NIRS = 73.4 ± 8.2%, P = 0.036). There was a significant difference in baseline values between men and women for arm (women: 77.4 ± 7.9%, men: 71.7 ± 7.9%, P = 0.001) and thigh (women: 76.5 ± 6.9%, men: 72.6 ± 8.2%, P = 0.018) measurements, but not for cerebral values.

The baseline values and the associated significant post-operative complications are shown in Table 3. Delirium was associated with lower baseline left cerebral saturation value (61.6 ± 6.3 vs. 67.7 ± 8.4, P = 0.041). Respiratory failure was associated with reduced bilateral cerebral and thigh saturations (CR and CL of 59.4 ± 8.2 and 59.7 ± 6.5 vs. 68.4 ± 8.8 and 68.2 ± 8.1, P = 0.004 and 0.002; thigh values: 69.5 ± 9.6 vs. 75.2 ± 7.3, P = 0.014). Both somatic values were lower in patients developing surgical complications (arm: 72.3 ± 8.6 vs. 76 ± 8.0, P = 0.049; thigh 71.6 ± 7.8 vs. 76.4 ± 7.3, P = 0.004) and renal complications (arm: 66.2 ± 4.8 vs. 75.1 ± 8.3, P = 0.014; thigh: 68.6 ± 4.1 vs. 74.9 ± 7.9, P = 0.032). Finally, a composite of all post-operative complications were only associated with reduced baseline thigh saturation values (72.5 ± 7.9 vs. 77 ± 7; P = 0.003).

Significant correlations between baseline NIRS values and peri-operative data are shown in Table 4. Baseline arm NIRS values were inversely associated with operating room bleeding values (P = 0.027), blood transfusion requirement values (P = 0.026), blood losses values (P = 0.046), and ICU LOS (P = 0.014). Lower baseline CR NIRS measurements were also associated with length of stay in ICU (P = 0.042). Lower baseline CL (P = 0.013) and thigh NIRS values (P = 0.009) correlated also with length of stay in ICU.

The cerebral desaturation load in relation to the peri-operative parameters and complications is shown in Table 5. Thigh desaturation (68 ± 328 %min) was more pronounced than cerebral (CR: 32 ± 151 %min; P = 0.005 and CL: 19 ± 84 %min; P = 0.021) or arm (37 ± 201 %min; P = 0.044) desaturation. The severity of thigh desaturation correlated directly with blood losses (P = 0.030) and LOS (P = 0.047) in the hospital. In addition, higher thigh desaturation load was associated with ileus (66 ± 366 vs. 72 ± 111; P = 0.005). No other correlation between the cerebral or somatic desaturation load and peri-operative parameters or complications was observed.

Using logistic regression, respiratory complications were associated with baseline CL (OR: 0.913, 95% CI [0.840, 0.992], P = 0.031) and thigh NIRS values (OR: 0.927, 95% CI [0.861, 0.999], P = 0.046). Surgical complications were associated only with baseline thigh NIRS values (OR: 0.925, 95% CI [0.869, 0.984], P = 0.013).

Examples of the directional and paradoxical changes observed in cerebral and somatic NIRS are shown in Figs. 1A and 1B. Parallel changes in all NIRS signals were seen during induction of anesthesia with pre-oxygenation (Fig. 1A) and bleeding and transfusion (Fig. 1B). Intraoperative hepatectomy, skin closure, and abdominal pressure were mostly associated with a reduction in thigh NIRS values (Figs. 2A and 2B). Acute respiratory failure was associated with more pronounced cerebral than somatic desaturation (Fig. 3). Examples of patients without (Figs. 4A and 4B) and

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Table 2. Baseline Oximetry Measurements and Population Description Parameters

Characteristics	CR [P value]	CL [P value]	Arm [P value]	Thigh [P value]
Age (correlation coefficient)*	0.015 [0.891]	0.082 [0.451]	−0.265 [0.013]	−0.093 [0.384]
Gender (Mean M:F)	66.4:68.3 [0.332]	65.9:68.4 [0.158]	71.7:77.4 [0.001]	72.6:76.5 [0.018]
ASA score (correlation coefficient)	0.012 [0.914]	0.043 [0.699]	−0.215 [0.047]	0.040 [0.714]
Pre-op albumin (g/L) (correlation coefficient)	0.217 [0.040]	0.323 [0.002]	−0.049 [0.649]	0.093 [0.385]
Bilirubin (μmol/L) (correlation coefficient)	−0.046 [0.666]	−0.076 [0.484]	−0.287 [0.007]	−0.098 [0.359]
PALC (correlation coefficient)	−0.258 [0.014]	−0.266 [0.013]	−0.017 [0.874]	−0.102 [0.342]
Cancer (n = 69) (Mean N:Y)	66.5:67.5 [0.673]	65.9:67.5 [0.498]	76.8:74.0 [0.190]	76.2:74.1 [0.410]
Any co-morbidity (n = 63) (Mean N:Y)	67.0:67.4 [0.848]	67.7:66.9 [0.662]	77.4:73.4 [0.036]	75.0:74.3 [0.709]
Hypertension (n = 24) (Mean N:Y)	66.9:68.3 [0.532]	66.5:69.0 [0.220]	74.7:74.3 [0.844]	74.5:74.5 [0.984]
COPD (n = 8) (Mean N:Y)	67.6:64.8 [0.410]	67.4:64.3 [0.350]	74.7:74.0 [0.833]	74.7:72.7 [0.526]
Coronary artery disease (n = 8) (Mean N:Y)	67.9:61.8 [0.072]	67.6:63.1 [0.156]	75.1:69.8 [0.086]	75.0:69.5 [0.056]
Diabetes (n = 9) (Mean N:Y)	67.1:69.0 [0.566]	67.2:66.9 [0.922]	75.1:70.2 [0.098]	74.9:71.0 [0.155]
Chronic renal failure (n = 2) (Mean N:Y)	67.4:66.0 [0.838]	67.1:69.5 [0.691]	74.8:65.0 [0.101]	74.7:67.0 [0.170]
Cirrhosis (n = 5) (Mean N:Y)	67.1:70.6 [0.415]	67.2:67.0 [0.968]	75.0:68.8 [0.111]	74.6:73.6 [0.787]
Smoking (n = 15) (Mean N:Y)	68.1:63.4 [0.070]	67.9:63.5 [0.067]	75.3:71.4 [0.104]	75.4:70.4 [0.024]
Dyslipidemia (n = 15) (Mean N:Y)	67.4:66.9 [0.835]	67.4:65.7 [0.488]	75.3:70.8 [0.063]	75.1:71.8 [0.139]

Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. *Except for Age, means are expressed as % of saturation. CR: cerebral right, CL: cerebral left, ASA: American Society of Anesthesiologists, PALC: phosphatase alkaline, COPD: chronic obstructive pulmonary disease, n: number, N: no, Y: yes.

Table 3. Baseline Cerebral and Somatic Oximetry Values and Significant Post-operative Complications

Complications	Number		CR	CL	Arm	Thigh
Delirium	81	No	67.8 ± 9.1	67.7 ± 8.4	74.8 ± 8.1	74.8 ± 8.0
	9	Yes	63.1 ± 9.1	61.6 ± 6.3	72.5 ± 11.2	72.0 ± 5.5
		Diff (95% CI)	4.7 (−2.5, 11.9)	6.1 (0.6, 11.5)	2.3 (−7.1, 11.8)	2.8 (−1.6, 7.2)
		P value	0.178	0.041	0.508	0.164
Respiratory failure	79	No	68.4 ± 8.8	68.2 ± 8.1	74.9 ± 8.4	75.2 ± 7.3
	11	Yes	59.4 ± 8.2	59.7 ± 6.5	72.4 ± 8.2	69.5 ± 9.6
		Diff (95% CI)	8.9 (3.2, 14.7)	8.5 (3.9, 13.1)	2.5 (−3.1, 8.3)	5.7 (−0.9, 12.3)
		P value	0.004	0.002	0.452	0.014
Surgical complications	56	No	68.2 ± 8.2	68.0 ± 7.7	76.0 ± 8.0	76.4 ± 7.3
	34	Yes	65.9 ± 10.6	65.8 ± 9.4	72.3 ± 8.6	71.6 ± 7.8
		Diff (95% CI)	2.3 (−1.9, 6.5)	2.1 (−1.7, 6.0)	3.7 (−0.0, 7.4)	4.8 (1.5, 8.1)
		P value	0.125	0.198	0.049	0.004
Renal complications	85	No	67.8 ± 9.1	67.4 ± 8.4	75.1 ± 8.3	74.9 ± 7.9
	5	Yes	59.6 ± 8.5	63.6 ± 7.4	66.2 ± 4.8	68.6 ± 4.1
		Diff (95% CI)	8.2 (−2.2, 18.5)	3.8 (−5.2, 12.8)	8.9 (3.1, 14.7)	6.3 (1.3, 11.2)
		P value	0.082	0.401	0.014	0.032
All complications	40	No	69.4 ± 7.7	68.9 ± 7.7	75.6 ± 8.7	77.0 ± 7.0
	50	Yes	65.7 ± 10.0	65.7 ± 8.7	73.8 ± 8.1	72.5 ± 7.9
		Diff (95% CI)	3.7 (0.0, 7.4)	3.2 (−0.3, 6.7)	1.9 (−1.7, 5.5)	4.5 (1.3, 7.6)
		P value	0.059	0.095	0.429	0.003

Values are presented as number of patients or mean ± SD. Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. CR: cerebral right, CL: cerebral left, Diff: Values are presented as mean ± SD. Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. CR: cerebral right, CL: cerebral left, Diff: difference.

Table 4. Baseline Saturation Values and Peri-operative Parameters

Parameters	CR [P value]	CL [P value]	Arm [P value]	Thigh [P value]
Surgical time (correlation coefficient)	–0.002 [0.985]	0.035 [0.748]	0.048 [0.661]	0.083 [0.443]
Use of Pringle (OR)	0.986 [0.565]	0.962 [0.178]	0.998 [0.950]	0.985 [0.595]
Total Pringle time (correlation coefficient)	–0.058 [0.767]	0.177 [0.377]	–0.024 [0.906]	0.084 [0.666]
Operating room blood transfusion (correlation coefficient)	–0.117 [0.273]	–0.071 [0.516]	–0.236 [0.027]	–0.060 [0.577]
Blood transfusion (hospital) (correlation coefficient)	–0.101 [0.344]	–0.051 [0.639]	–0.238 [0.026]	–0.140 [0.190]
Blood loss (correlation coefficient)	–0.196 [0.065]	–0.192 [0.074]	–0.213 [0.046]	–0.160 [0.135]
Length of stay in ICU (correlation coefficient)	–0.215 [0.042]	–0.141 [0.194]	–0.260 [0.014]	–0.075 [0.486]
LOS (correlation coefficient)	–0.196 [0.064]	–0.266 [0.013]	–0.072 [0.503]	–0.273 [0.009]

Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. The relation between baseline values and various peri-operative parameters is presented. OR or correlation coefficient are presented when appropriate. CR: cerebral right, CL: cerebral left, OR: odds ratio, ICU: intensive care unit, LOS: length of hospital stay.

Table 5. Cerebro-somatic Desaturation Load Values, Peri-operative Parameters and Complications

Parameters and Complications	CR [P value]	CL [P value]	Arm [P value]	Thigh [P value]
Cerebro-somatic desaturation load below 80% (%min)	32 ± 151 (n = 90)	19 ± 84 (n = 87)	37 ± 201 (n = 88)	68 ± 328* (n = 89)
Surgical clamping time (correlation coefficient)	–0.177 [0.358]	0.021[0.918]	–0.510 [0.007]	–0.005 [0.980]
Blood loss (correlation coefficient)	0.104 [0.329]	0.049 [0.652]	0.013 [0.905]	0.230 [0.030]
Length of stay in ICU (correlation coefficient)	0.128 [0.229]	–0.046 [0.675]	–0.056 [0.606]	–0.030 [0.765]
LOS (correlation coefficient)	–0.110 [0.302]	–0.030 [0.768]	0.071 [0.508]	0.211 [0.047]
Complications (OR [95% CI])				
Neurological	0.831 (0.275, 2.508) [0.742]	1.000 (0.994, 1.008) [0.728]	0.992 (0.959, 1.026) [0.646]	1.000 (0.998, 1.002) [0.849]
Cardiac	0.829 (0.209, 3.279) [0.789]	1.000 (0.995, 1.010) [0.565]	0.870 (0.381, 1.987) [0.741]	0.967 (0.836, 1.118) [0.648]
Respiratory	1.000 (0.999, 1.005) [0.149]	0.997 (0.986, 1.009) [0.633]	0.998 (0.991, 1.006) [0.670]	1.000 (0.998, 1.002) [0.981]
Surgical	1.000 (0.998, 1.003) [0.702]	1.000 (0.995, 1.006) [0.838]	1.000 (0.998, 1.007) [0.300]	1.000 (0.998, 1.001) [0.652]
Infectious	1.000 (0.997, 1.003) [0.897]	0.997 (0.990, 1.005) [0.481]	1.000 (0.997, 1.015) [0.184]	1.000 (0.999, 1.001) [0.948]
Hematological	1.000 (0.999, 1.005) [0.213]	1.000 (0.995, 1.008) [0.638]	0.975 (0.869, 1.094) [0.665]	1.000 (0.998, 1.002) [0.953]

Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. *The somatic load desaturation was higher than the CR (P = 0.005), CL (P = 0.021), and arm (P = 0.044). CR: cerebral right, CL: cerebral left, ICU: intensive care unit, LOS: length of hospital stay, OR: odds ratio.

with (Figs. 5A and 5B) post-operative complications are shown. In those patients with complications, greater signal variations, more frequent reductions below baseline NIRS values, and paradoxical cerebral and somatic changes were more frequently observed. Fig. 6 summarizes the most common patterns of cerebral and somatic desaturation observed in the current study.

Discussion

To our knowledge, this is the first observational and non-interventional study on the potential usefulness of combined cerebral and somatic NIRS in the setting of liver resections. It adds to previous observations we made in 10 liver transplantation patients [27]. We observed that both baseline cerebral and somatic values were associated with pre- operative variables, but also with post-operative complications. Somatic baseline values were higher than cerebral NIRS as previously reported [30]. In addition, higher somatic values were associated with younger age, lower ASA class, and lower co-morbidity burden. No gender difference was observed in cerebral NIRS values, in contrary to somatic arm and thigh values. Smokers had lower thigh NIRS values. An association with vascular disease could explain this difference as patients with coronary artery disease had a tendency for lower thigh values (P = 0.056). Patients developing post-operative neurological,

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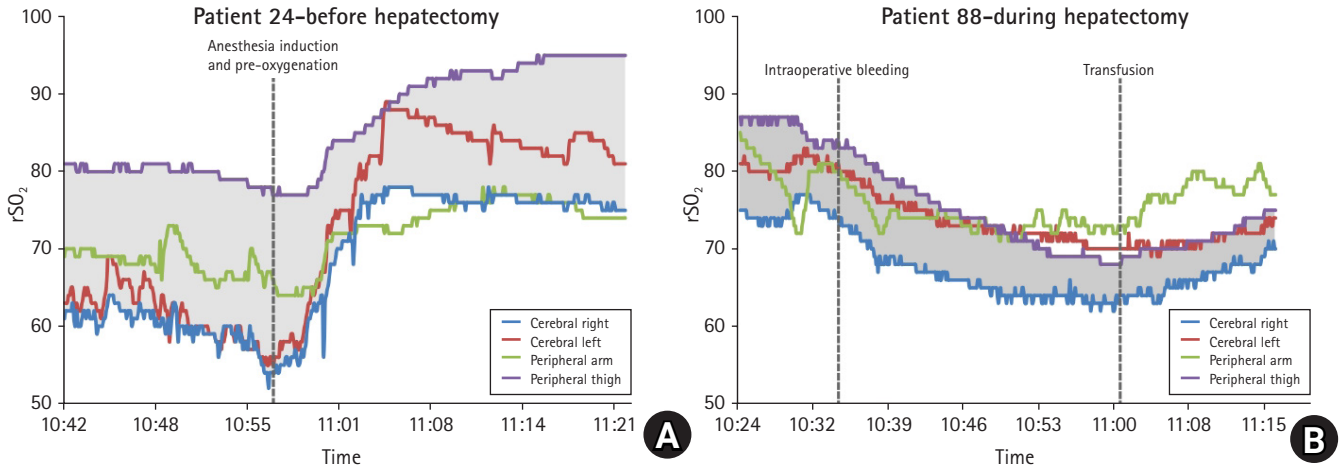

Fig. 1. Cerebral and somatic regional oxygen saturation (rSO_2) during oxygenation and bleeding (A) Prior to hepatectomy in a 64-year-old man (patient #24), a significant increase in both cerebral and somatic rSO_2 signals was observed shortly following the induction of anesthesia and pre-oxygenation. (B) Intraoperative bleeding in a 78-year-old woman (patient #88) during right hepatectomy. Note the proportional reduction on all rSO_2 signals and their increase during transfusion.

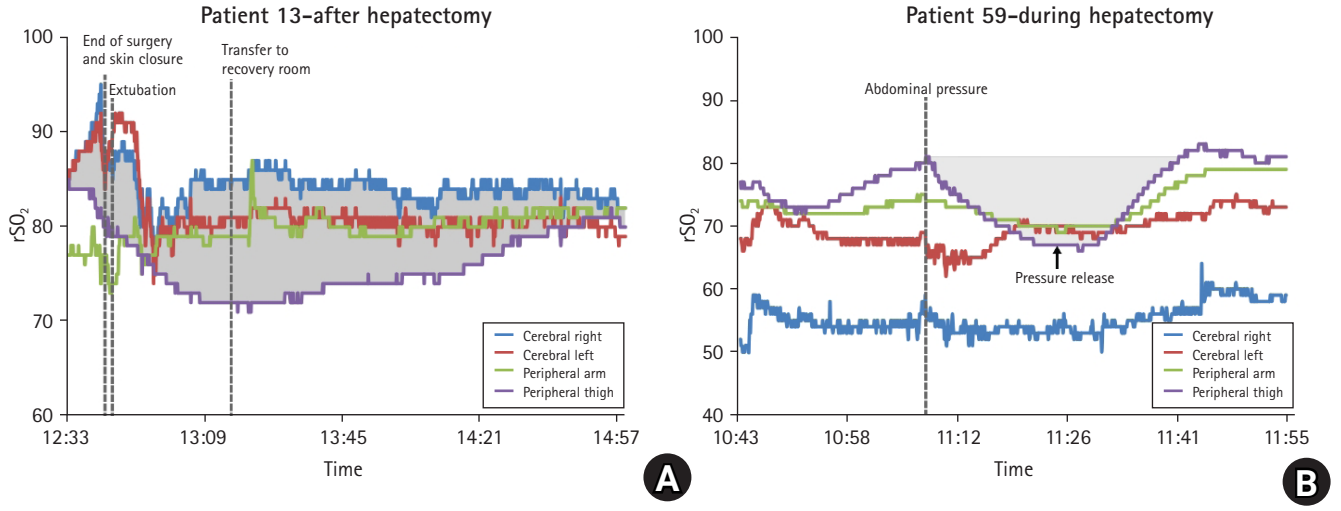

Fig. 2. Cerebral and somatic regional oxygen saturation (rSO_2) during extubation and abdominal pressure (A) rSO_2 signals following skin closure in a 67-year-old woman (patient #13) with previous abdominal surgery following cholecystectomy and hepatectomy of segments 4, 5, and 8. More pronounced reduction in thigh oximetry was observed compared to arm and cerebral signals following skin closure and extubation. The difference normalized within 2 h. (B) Localized changes in thigh oximetry during abdominal pressure in a 72-year-old woman (patient #59) during hepatectomy of segment 1. Note the minimal changes in the other oximetry signals.

respiratory, renal, and surgical complications had lower baseline cerebral as reported previously [10,11,13,37] but also lower somatic NIRS values that have not been reported. Interestingly, in patients undergoing liver resection, lower somatic NIRS values were more commonly associated than cerebral NIRS values in patients developing those complications, which have not been reported in the literature before. Finally, in terms of the severity of intraoperative desaturation, thigh desaturation was more commonly observed and was the only NIRS variable associated with blood losses and prolonged LOS in the hospital. Therefore, this study suggests that, when considering only desaturation load during surgery, somatic oximetry may be superior to cerebral oximetry for the prediction of post-operative outcomes in some types of non-cardiac surgeries such as liver surgery.

While very few papers have studied the use of cerebral NIRS monitoring during liver surgery or transplantation [12,38–41], most clinical studies with NIRS monitoring comes from the cardiac surgical environment [5,6,9–13,34,42–44]. The mean cumulative cerebral desaturation load during liver surgery in this study (Left: 19 ± 84 %min, Right: 32 ± 151 %min) appeared to be

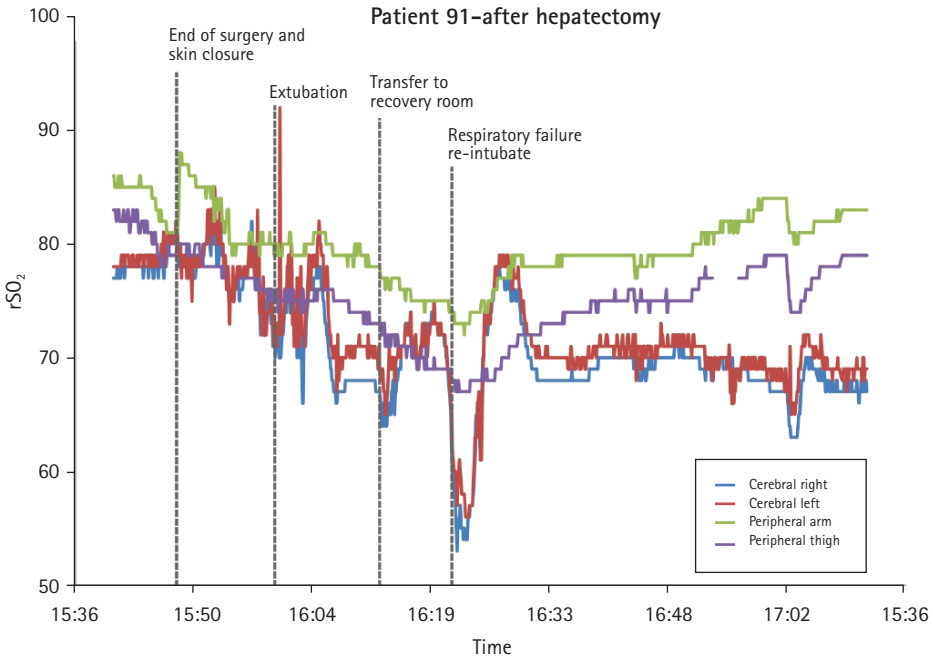

Fig. 3. Cerebral and somatic regional oxygen saturation (rSO_2) during respiratory failure, Post-operative brain desaturation in a 66-year-old woman (patient #91) with portal hypertension with acute respiratory failure requiring re-intubation. The patient had a hepatectomy of segments 5, 6, 7, and 8. Note that the change in brain desaturation was more pronounced than the somatic signals during respiratory failure.

greatly inferior to what was previously observed in cardiac surgery (100–400 %min) [35]. In patients undergoing liver resection, an association between baseline cerebral desaturation, neurological and respiratory complications, ICU length of stay as well as the total LOS was observed. Hypothetically, this could be explained by the baseline cerebral oximetry measurement, which will be influenced by the physiological cardiopulmonary and hematological reserve of the patient, with sicker patients staying longer in the hospital after liver resection. Another variable that could play a role would be altered autoregulation of patients with liver disease [38,39]; however, only five patients had cirrhosis in our group.

The most interesting findings of our study were the dynamic patterns observed with combined use of cerebral and somatic sensors positioned at the arm and thigh in relationship with clinical events. The combined use of both somatic and cerebral NIRS parameters has been reported in cardiac surgical patients for fluid challenge [45] and as a predictor of post-operative delirium [46]. Most of its use has been in pediatric cardiac surgical patients [21,47,48]. Combining cerebral and somatic NIRS is useful to discriminate if a reduction in ScO_2 results from a central or peripheral process as we previously proposed [29,49]. For instance, if brain and somatic desaturation are present simultaneously, the etiology is unlikely to be cerebral in nature and could be hemorrhagic shock as we observed in Fig. 1B.

In our study, baseline systemic values (arm and/or thigh) predicted more post-operative complications, especially direct surgical complications, compared to cerebral values. During a state of relative hypoperfusion, blood flow will be preferentially maintained to organs such as the brain, heart, liver, and kidney at the expense of muscles. Therefore, early in shock, cerebral autoregulation will be maintained, but signs of hypoperfusion could be detected earlier in the muscles that are monitored with somatic NIRS. In addition, NIRS signals are very sensitive to cerebral venous congestion [50] and right ventricular diastolic dysfunction [51]. In the presence of venous congestion or hypervolemia, complications such as delirium, respiratory insufficiency, ileus, and cardio-renal failure will be observed [50,52]. This may explain why liver manipulation and abdominal pressure, by causing transient vena cava occlusion, will lead to lower limb congestion and the Pringle maneuver will similarly cause bowel venous congestion (Figs. 2A and 2B). Bowel congestion could lead to an inflammatory reaction similar to what is described in the cardio-intestinal syndrome [53]. The frequent observation of reduced thigh NIRS value during caval obstruction as reported previously in liver transplantation [54] and the increase in lower extremity NIRS during treatment of abdominal compartment syndrome [49] could support this hypothesis. In our patient population, an association with reduced somatic NIRS and post-operative complications was present. If such complications occur, then longer ICU and hospital LOS may be observed.

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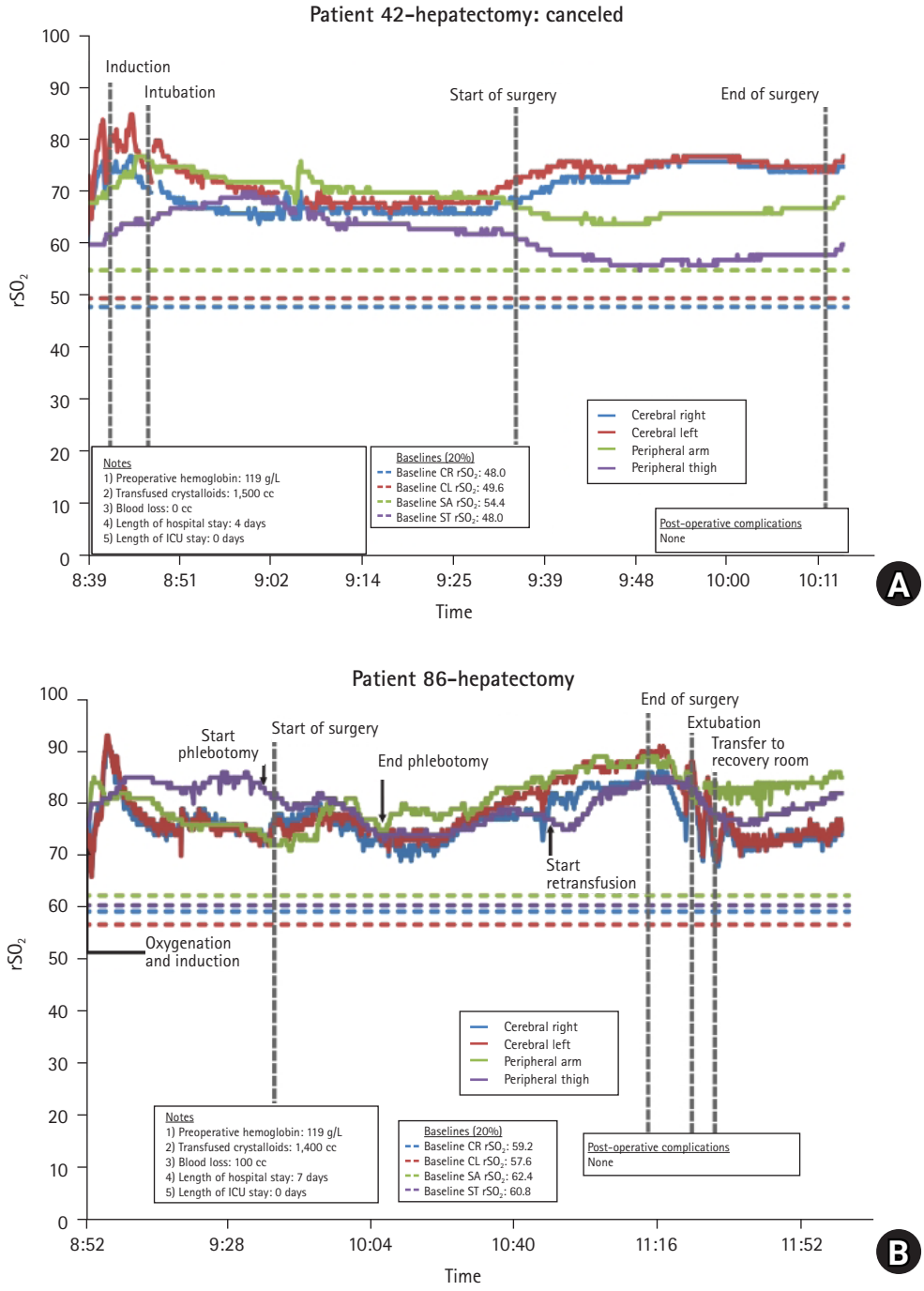

Fig. 4. Unchanged cerebral and somatic regional oxygen saturation (rSO_2) (A) 69-year-old man (patient #42) in whom surgical findings led to a cancellation of the hepatectomy. The patient did not develop any post-op complications. (B) 53-year-old woman (patient #86) with hepatectomy of segments 2, 3, 4, and 7. The patient did not develop any complications post-operatively. A: arm, CL: cerebral left, CR: cerebral right, ICU: intensive care unit, T: thigh.

There are several limitations from our study. This is a single center study with a limited sample size that limits the validity of the findings. Our study is however the first and largest observational and non-interventional study in liver resection that lay the basis for future potential interventional trials. As shown by other authors, we observed an association with reduced baseline oximetry values, intraoperative desaturation, and outcome. The impact of brain and somatic desaturation correction remains debatable [55–58]. The determination of the number of patients in whom cerebral and somatic desaturation would occur in liver resection was undetermined and never reported. Therefore, our study can be used as a pilot study to determine in more detail the number of

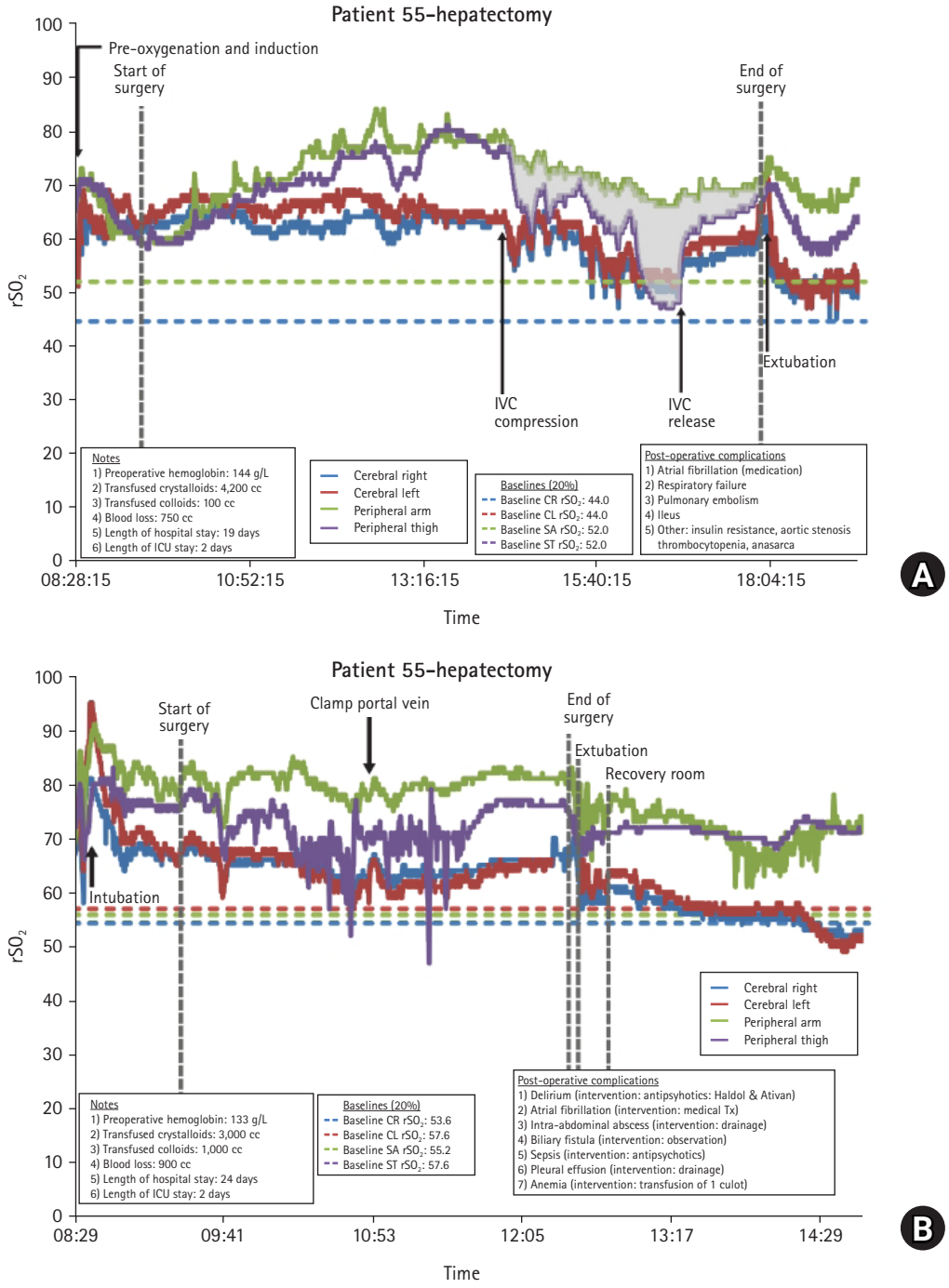

Fig. 5. Cerebral and somatic regional oxygen saturation (rSO_2) during IVC clamping and in a patient with post-op complications (A) 69-year-old man (patient #55) with previous hepatectomy who underwent hepatectomy of segment 1. The patient developed significant post-operative complications. Note the increase in the variability of the signals, the gradients between cerebral and somatic values and cross-over of the signals differences. (B) 80-year-old man (patient #4) with vascular disease who had hepatectomy of segments 5, 6, 7, and 8. The patient developed significant post-operative complications. Note the increase in the variability of the signals, the gradients between cerebral and somatic values and cross-over of the signals' differences between patients with or without complications. A: arm, IVC: inferior vena cava, CL: cerebral left, CR: cerebral right, ICU: intensive care unit, T: thigh.

patients in order to perform a more precisely powered study. Furthermore, because we did not systematically assess the clinical implications of desaturation patterns associated with intra-operative events, the qualitative observations reported remain only hypothesis-generating and will require validation. Therefore, the benefit and clinical impact of monitoring cerebral and somatic NIRS in

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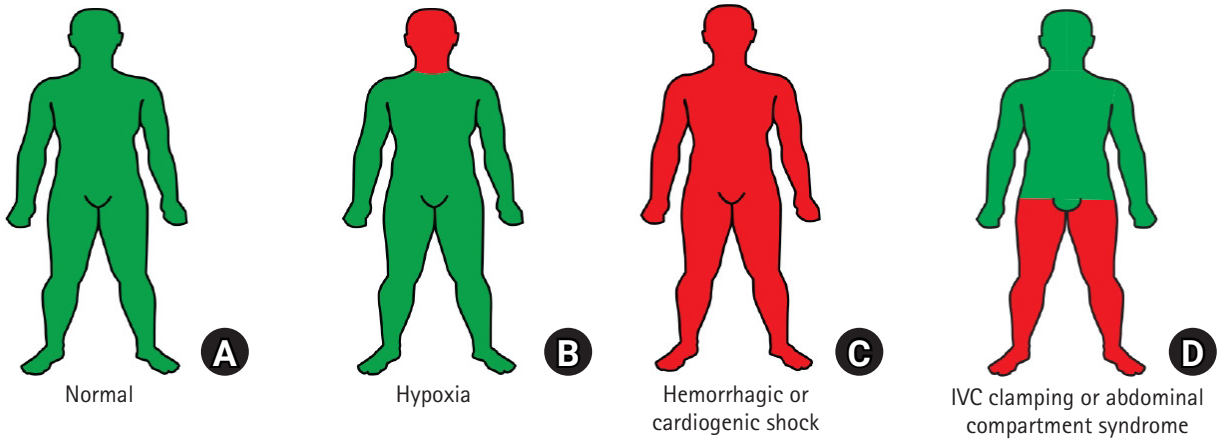

Fig. 6. Commonly observed cerebral and somatic oximetry patterns in patients undergoing liver resection. (A) Normal, (B) Hypoxia, (C) Hemorrhagic or cardiogenic shock, (D) IVC clamping or abdominal compartment syndrome. IVC: inferior vena cava.

non-cardiac surgery remain to be proven. While our data does not provide causative explanation for the findings because of the observational nature of this study, it certainly provides interesting findings justifying more research in the field. In fact, our work seems to suggest that both cerebral and somatic NIRS could be used at baseline before surgery to establish some patients at risk. Our findings suggest that somatic monitoring may be as important, if not more, than cerebral monitoring to predict surgical outcome in liver surgery. It is also possible that lower baseline cerebral or somatic saturation are associated with sicker patients at higher risk of complications such as delirium as reported for cerebral saturation [11,46]. We did not explore in detail the mechanism of reduced NIRS values, but it may represent a relatively easy method to identify those high-risk patients at the bedside. A multicenter trial with a larger cohort of patient would be required in order to identify the most important determinants that influence cerebro-somatic NIRS measurement in liver surgery.

In conclusion, combining cerebral and somatic oxygenation monitoring with NIRS is a promising tool for liver resection cases. Baseline NIRS values and intraoperative somatic desaturations may have a prognosis value for post-operative outcomes. It may identify higher risk patients. The extent to which interventions can correct cerebral and somatic desaturation in liver resection and its possible impact on clinical outcomes is still to be elucidated.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Tina Hu (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing)
André Denault (Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing)
Annik Fortier (Conceptualization; Formal analysis; Methodology; Writing – review & editing)
William Beaubien-Souligny (Formal analysis; Writing – original draft; Writing – review & editing)
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Appendix 1. STROBE Statement—Checklist of Items That Should Be Included in Reports of Observational Studies

	Item No	Recommendation	PAGE
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6–7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 8-9	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	
		Case-control study—For matched studies, give matching criteria and the number of controls per case	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9–10 + Appendix 2
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8–11
Bias	9	Describe any efforts to address potential sources of bias	8–10
Study size	10	Explain how the study size was arrived at	8–9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9–10
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	9–10
		Case-control study—If applicable, explain how matching of cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12 + Tables 1 and 2
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	12

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Appendix 1. Continued

	Item No	Recommendation	PAGE
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12 + Appendix 3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 4 and 5
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17–18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16–18
Generalisability	21	Discuss the generalisability (external validity) of the study results	16–18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and 7 unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at Combined Cerebral and Somatic Near-Infrared Spectroscopy Oximetry during Liver Surgery: an Observational and NonInterventional Study Collin *et al.*

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Appendix 2. Definitions of Variables

Demographic Factors	
Body mass index (kg/m^2)	Weight/(Height)^2.
Preoperative Variables	
American Society of Anesthesiologists class	Risk score ranges from 1 (healthy and low risk) to 5 (high risk). (1)
Reduced ejection fraction	Left ventricular ejection fraction < 30%; left ventricular ejection fraction was the last measured value reported before surgery by left ventriculography, echocardiography, or nuclear medicine (lowest value was selected). (2)
Child-Pugh score	Scores are used to assess the severity of liver disease and are calculated based on total bilirubin, serum albumin, INR, ascites, and hepatic encephalopathy. Scores between 5–6 are associated with high survival rates (Stage A, 1-year survival rate is 100%), scores between 7–9 are associated with intermediate survival rates (Stage B, 1-year survival rate is 81%) while scores above 10 are associated with low survival rates (Stage C, 1-year survival rate is 45%).(3)
Model for End-Stage Liver Disease (MELD) score	Scores are used to assess the severity of liver disease and are calculated based on serum bilirubin, serum creatinine, and prothrombin time as calculated by the International Normalized Ratio (INR). Scores range from < 9 (1.9% mortality at 3 months) to > 40 (71.3% mortality at 3 months). (4)
Perioperative Variables	
Cerebral desaturation	20% decrease of the baseline rSO_2 value for 15 seconds. (5)
Cerebral desaturation load (%min)	Area under the threshold spent beneath the absolute threshold limit of 80% of the baseline rSO_2 value multiplied by time. (6)
Postoperative Variables	
Neurological	
Delirium	Disturbance of consciousness and cognition that develops over a short period of time (hours to days) and requires the use of antipsychotics. (7)
Cerebrovascular accident	Clinically manifested by persistent focal neurological deficits radiologically confirmed by CT scan lasting > 24 hours. (2)
Seizures	Paroxysmal alteration of behaviour and/or ECG changes resulting from excessive neuronal activity. (8)
Cardiac complications	
Atrial fibrillation	Supraventricular tachyarrhythmia characterized by uncoordinated atrial activation as shown on an electrocardiogram and requires electrical or pharmacological cardioversion. (9)
Hypotension	Vasoactive requirement post-operatively.
Myocardial infarction with persistent Q wave	Presence of increase in CK-MB > 100U, new Q waves in 2 contiguous electrocardiographic leads, or confirmed graft occlusion within 30 days after surgery. (2)
Cardiac arrest/cardiogenic shock	Need for vasopressors and inotropic agents, intra-aortic balloon-pump, or ventricular-assist device for > 48 hours.
Respiratory complications	
Pulmonary embolism	Embolus identified as obstructing a vessel as diagnosed by pulmonary angiography. (10)
Empyema	Documented pleural effusion with positive cultures.
Respiratory failure	Intubation ≥ 48 hours post-surgery, reintubation for a pulmonary cause, acute lung injury (PaO_2/FiO_2 < 300), or acute respiratory distress syndrome (PaO_2/FiO_2 < 200). (2)
Pneumonia	Pulmonary infiltrates and documented broncho-tracheal culture.
Pneumothorax	Pleural air requiring chest tube or percutaneous drainage.
Surgical complications	
Liver failure	Increased MELD score > 9.
Biliary fistula	Presence of bile in drainage fluid, drainage ≥ 50 mL/day on the third day after the operation, and drainage for 3 days consistently. (11)
Ileus	Impairment in gastrointestinal mobility for over 6 days after the surgery. (12)
Revision surgery	Follow-up surgery is required.

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Appendix 2. Continued

Infectious complications	
Wound infection	Infection from surgical procedure requiring antibiotic therapy.
Clostridium Difficile	Documented infection using toxin assay.
Intra-abdominal abscess	Localized collection of pus or gastrointestinal content inside abdominal cavity requiring antibiotics or percutaneous drainage. (13)
Infected ascites	Documented peritoneal fluid with positive culture.
Peritonitis	Presence of free pus or gastrointestinal content in the peritoneal cavity requiring antibiotics or surgical treatment. (13)
Urinary tract infection	Documented urine with positive culture.
Sepsis and septic shock	Non-specific systemic inflammatory symptoms with evidence of microbial basis. (14) Severe sepsis is defined as sepsis with organ dysfunction and septic shock is defined as sepsis with hypotension despite adequate volume resuscitation. (14)
Fungemia	Positive fungal blood culture.
Hematological complications	
Bleeding	Blood loss requiring red blood cells, fresh frozen plasma, cryoprecipitate, and platelets. Massive blood loss is defined as the loss of one blood volume = 70 ml/kg or 5 liters in an adult patient within 24 hours or the loss of 0.5 blood volumes within 3 hours. (15)
Thrombophlebitis	Inflammation of a cannulated vein requiring heparin, antibiotics, or anti-inflammatory medications. (16)
Renal failure	Dialysis requirement or doubling of baseline serum creatinine level, or serum creatinine level > 150 μmol/L (1.7 mg/dl). (2)
Other complications	
Excessive weight gain	≥ 20 kg compared to pre-operative weight.
Upper gastrointestinal bleeding	Blood loss from upper gastrointestinal tract documented by gastroscopy.
Miscellaneous Variables	
Length of time in the ICU	Length of time from date of surgery to the date when patient left the ICU.
Length of hospital stay	Length of time from date of surgery to the date when patient left the hospital.
Clavien-Dindo classification of postoperative complications	All complications were given a grade, which ranged from Grade I (a deviation from the normal postoperative course without the need of pharmacological treatment or surgical interventions), Grade II (requiring pharmacological treatment), Grade III (requiring surgical, endoscopic, or radiological intervention), Grade IV (life-threatening complication), and Grade V (death of patient). (17)

CK: creatinine kinase, CT: computed tomography, FiO_2: inspired fraction of oxygen, ICU: intensive care unit, PaO_2: arterial oxygen partial pressure, rSO_2: regional brain or somatic saturation.

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Appendix 3. Detailed Complications Observed in the Studied Population

Variable	Absence	DINDO 1-2	DINDO 3 or more
Neurological complications	81 (90)	9 (10)	
Delirium	81 (90)	9 (10)	
Convulsion	89 (99)	1 (1)	
Cardiovascular complications	84 (93)	6 (7)	
Arrhythmia	87 (97)	3 (3)	
Myocardial infarction	89 (99)	1 (1)	
Hypotension	88 (98)	2 (2)	
Respiratory complications	74 (82)	11 (12)	5 (6)
Pulmonary embolism	87 (97)	3 (3)	
Empyema	89 (99)	1 (1)	
Respiratory failure	79 (88)	9 (10)	2 (2)
Gastro-intestinal complications	52 (58)	36 (40)	2 (2)
Hepatic insufficiency	89 (99)	1 (1)	
Biliary leak	76 (84)	12 (13)	2 (2)
Stress ulcer	88 (98)	2 (2)	
Infected ascites	89 (99)	1 (1)	
Ileus	71 (79)	19 (21)	
Portal vein thrombosis	89 (99)	1 (1)	
Infectious complications	60 (67)	27 (30)	3 (3)
Urinary tract infection	88 (98)	2 (2)	
Abdominal abscess	88 (98)	2 (2)	
Wound infection	81 (90)	9 (10)	
Clostridium Difficile infection	87 (97)	3 (3)	
Sepsis	87 (97)	3 (3)	
Septic shock	89 (99)	1 (1)	
Fungemia	88 (98)	2 (2)	
DCS1	89 (99)	1 (1)	
Hematological complications	80 (89)	9 (10)	1 (1)
Pancytopenia	89 (99)	1 (1)	
Deep vein thrombosis	89 (99)	1 (1)	
Renal complications	85 (94)	5 (6)	
Volume overload	80 (89)	9 (10)	1 (1)
Renal failure	86 (96)	4 (4)	
Surgical complications	55 (61)	30 (33)	5 (6)
Various complications	86 (96)	4 (4)	
Total number of patients with complications	38 (42.2)	41 (45.5)	11 (12.2)*

*Patient may have more than one complication.

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