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ORIGINAL ARTICLE

Near-Infrared Spectroscopy for Evaluation of Cerebral Autoregulation During Orthotopic Liver Transplantation

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Abstract
Introduction The present study evaluated whether frontal lobe cerebral oxygenation (S_cO_2), as assessed by near-infrared spectroscopy (NIRS), can detect cerebral autoregulation in patients undergoing orthotopic liver transplantation.
Methods We studied changes in frontal lobe S_cO_2 assessed in 33 patients, 19 females, who underwent orthotopic liver transplantation (OLT). We evaluated whether S_cO_2 would remain stable over a wide range of MAP and whether an eventual drop in S_cO_2 could be related to a low MAP.
Results Among the 31 of 33 patients for whom a NIRS signal could be detected, S_cO_2 varied in parallel with mean arterial pressure (MAP) for 3 patients and, therefore, an autoregulation curve could not be established and yet, there was detected no change in S_cO_2 to a lowest MAP ranging from 42 to 66 mmHg for 20 patients, while for 8 patients a decrease in S_cO_2 was detected at a MAP of 69 (50–90) mmHg; (median and range). As detected by NIRS, the present study confirms that some patients undergoing liver transplantation do not demonstrate cerebral autoregulation but for the majority of the patients, S_cO_2 was stable over a wide range of MAP suggesting that S_cO_2 detects cerebral autoregulation.
Conclusion We find that NIRS is a ready available non-invasive technology for evaluation of cerebral autoregulation in patients undergoing orthotopic liver transplantation.

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Keywords Blood pressure · Cardiac output · Heart rate · Thoracic electric admittance · Venous oxygen saturation

Abbreviations

CBF	Cerebral blood flow
CBV	Central blood volume
CO	Cardiac output
MAP	Mean arterial pressure
NIRS	Near-infrared spectroscopy
OLT	Orthotopic liver transplantation
S_cO_2	Frontal lobe cerebral oxygenation
S_vO_2	Mixed venous oxygen saturation
TA	Thoracic electric admittance

Introduction

Cerebral autoregulation describes that cerebral blood flow (CBF) stays relatively stable within a mean arterial pressure (MAP) from approximately 60–150 mmHg [1] but for some patients with liver disease, there is no effective cerebral autoregulation [2, 3] and death from acute liver failure may be by a cerebral catastrophe related to cerebral hyperperfusion [2]. Also during orthotopic liver transplantation, cerebral autoregulation may be affected although the hepatectomy seems to correct the failing autoregulatory capacity of the brain circulation as detected by transcranial Doppler [4, 5] and similar observations are available with a ^{133}Xenon clearance determined CBF [2]. During the operation, however, neither an evaluation of cerebral perfusion with transcranial Doppler nor of CBF with ^{133}Xenon clearance are readily available as both techniques require a trained operator.

Furthermore, evaluation of CBF is a discontinuous measure and although information of CBF is important, we consider that the purpose of monitoring CBF is to secure

cerebral oxygenation (S_cO_2). Near-infrared spectroscopy (NIRS) is applicable for routine monitoring of the brain during surgery and S_cO_2 reflects changes in brain capillary saturation and mitochondrial oxygen tension [6].

In the present study, changes in frontal lobe S_cO_2 were assessed in patients who underwent orthotopic liver transplantation (OLT). We evaluated whether S_cO_2 would remain stable over a wide range of MAP and whether an eventual drop in S_cO_2 could be related to a low MAP. Such a correlation analysis for evaluation of cerebral autoregulation has been applied, based on internal jugular venous oxygen saturation, in healthy humans [7].

Methods

S_cO_2 was related to MAP in 33 patients, 19 females, undergoing liver transplantation at a Child-Pugh class A ($n = 4$), B ($n = 16$), and C ($n = 13$) (Table 1). Anesthesia was induced with fentanyl (0.3–0.5 mg) and propofol (1.5–2.5 mg/kg) and was maintained with remifentanil (1mcg/kg/min) and propofol (25–42 mcg/kg/min) infusions and oral intubation of the trachea was facilitated with cisatracurium (0.15 mg/kg). The patients were ventilated with an oxygen/air mixture to oxygen fraction of 0.8 [8] and ventilation was adjusted to maintain an end-tidal CO_2 tension ($etCO_2$) of 3.5–4.5 kPa. To attenuate bleeding, aprotinin (Trasylol® Bayer Healthcare Pharmaceutical, Montville, NJ) infusion was administered at 20 ml/h (40 ml/h during the anhepatic phase) and to prevent spasm in the hepatic artery, infusion of epoprostenol (Flolan® GlaxoSmithKline Pharma, Brentford, UK; 6 ml/h) was added before arterial reperfusion of the liver. Blood pressure was controlled by nitroglycerine, phenylephrine, or ephedrine and plasma calcium was kept within the normal range. Central blood volume (CBV) was maintained by infusion of plasma and saline–adenine–glucose–mannitol erythrocyte suspension to maintain a hematocrit of 33%. All patients, except for one had a venovenous bypass. The median anesthesia duration was 6 h 40 min, range 4–11 h 10 min.

Table 1 Descriptive data for the investigated patients

	N or median	Range
Height, cm	173	151–187
Weight, kg	74	52–103
Age, years	49	19–63
MAP, mmHg	72	70–73
HR, bpm	82	80–83
Alcoholic liver disease	6	
Primary biliary cirrhosis	5	
Primary sclerosing cholangitis	4	
Retransplantation (thrombosis)	4	
Hepatitis C	4	
Acute liver failure	2	
Hepetocellular carcinoma	2	
Cryptogen cirrhoses	1	
Other	5	
Duration of surgery, min	400	240–640
Child-Pugh score	9	5–14

Arterial blood pressure was obtained from the right femoral artery and cardiac output (CO) is reported as estimated from the arterial pressure wave with the Modelflow method [9] that has been satisfactory compared to a thermodilution estimate in patients undergoing liver transplantation [10]. A pulmonary artery catheter (Swan-Ganz, 93A-831H-7.5F; Baxter Healthcare Corp., Irvine, CA.) was used for a thermodilution estimate of CO, pulmonary arterial mean pressure (PAMP), central venous pressure (CVP), and mixed venous oxygen saturation (S_vO_2). Heart rate (HR) and arterial oxygen saturation (S_aO_2) were monitored by an electrocardiogram and pulsoximetry, respectively.

Changes in the CBV were assessed by thoracic electrical admittance (TA) and expressed in Siemens (mS) (C-Guard, Danmeter, Odense, Denmark). At a low (1.5 kHz) and a high frequency (100 kHz) current, TA distinguishes between the extracellular ($TA_{1.5}$) and total water (TA_{100}) content. Accordingly, changes in the difference between $TA_{1.5}$ and TA_{100} were considered to reflect changes in the intracellular water content (TA_{ICW}) [11], i.e., red cell volume within the thoracic region [11, 12].

The S_cO_2 and muscle oxygen saturation (S_mO_2) were monitored by NIRS (INVOS Cerebral Oximeter, Somanetics, Troy, MI.) with optodes attached to the forehead and the skin over the left biceps muscle, respectively. Monitoring of frontal lobe oxygenation by NIRS is a non-invasive alternative to recording of changes in CBF [13]. Changes in S_cO_2 parallel those in internal jugular venous O_2 saturation and middle cerebral artery mean flow velocity [4, 14] and NIRS detects cerebral hypoperfusion during surgery [15]. The NIRS determined S_cO_2 is based on the absorption of light in the spectra for oxygenated and deoxygenated hemoglobin and reports S_cO_2 and S_mO_2 as a percentage of light absorption by oxygenated to total hemoglobin. An emitter generates light at 733 and 808 nm and the reflection is registered by two sensors placed at a distance of 3 and 4 cm from the emitter. This placement of the optodes allows for the subtraction of reflections derived from superficial tissues of the scalp and the skull for S_cO_2 [16] and subcutaneous tissue for S_mO_2. With increasing distance between the emitter and the optodes, light penetrates deeper into the tissues and with evaluation of absorption at two distances (spatial resolution), absorption

in deep tissue, i.e., brain and skeletal muscle, is appreciated. Thus, values reported for S_cO_2 and S_mO_2 account predominantly for hemoglobin oxygenation in the frontal lobe cortex and left biceps muscle, respectively. To take into account attenuation of S_cO_2 by individual high levels of bilirubin in the blood [17], NIRS data are presented as changes from baseline (ΔS_cO_2) defined as the first stable S_cO_2 recorded when the patient was fully monitored before surgery.

To evaluate whether S_cO_2 could detect cerebral autoregulation, for each patient, S_cO_2 was related to MAP by computer-assisted iteration of crossing between a line based on the lowest versus the highest MAP values [7]. If an insertion could be detected between the two lines, the MAP at the insertion was taken to define the lower limit of cerebral autoregulation [7]. Conversely, if no such insertion could be defined between the two lines, cerebral autoregulation was not considered to be detected by S_cO_2, or if there was no significant change in S_cO_2 over the range of manifested MAP, cerebral autoregulation was considered to be maintained to the lowest recorded level of MAP.

For presentation of the data, surgical procedures were divided into the dissection phase (from the beginning of surgery until clamps were placed on the portal and the inferior caval veins), the anhepatic phase (where the liver was bypassed and ending when flow through the inferior caval and portal veins was re-established), the early reperfusion phase (with full portal flow) followed by the late reperfusion phase (to the end of surgery). Mean values for each phase were compared by one-way ANOVA for repeated measures on ranks and Dunn's test evaluated post-hoc comparisons. Statistical significance was set at the 95% confidence limit ($P < 0.05$) and data are presented as median with range.

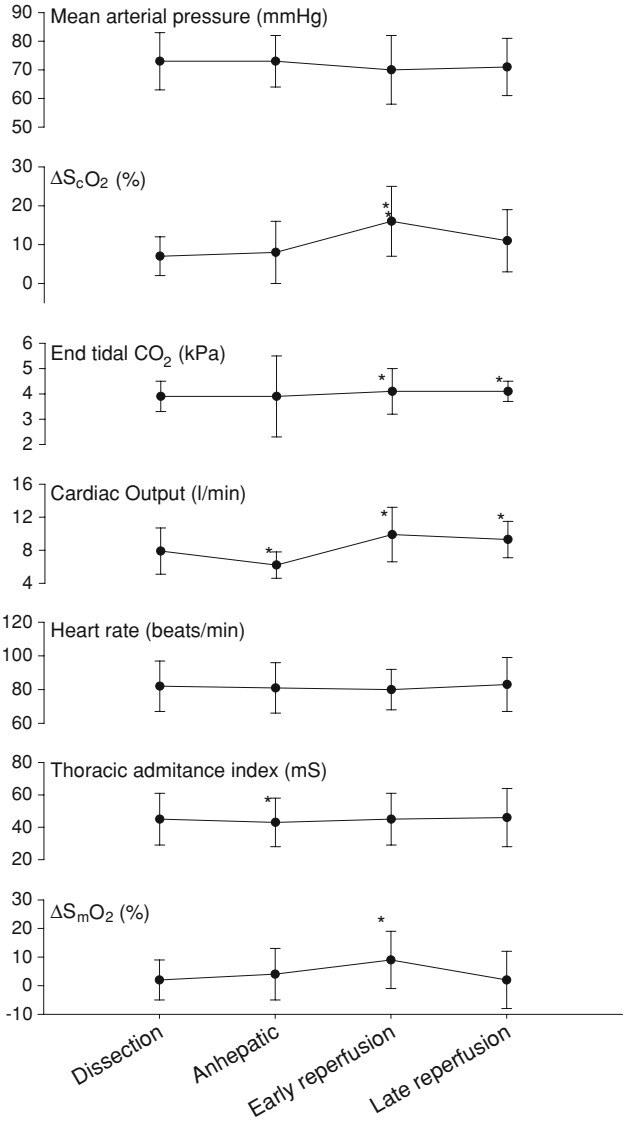

Fig. 1 Intraoperative variables during the four phases of liver transplantation. *MAP* mean arterial pressure; S_cO_2 cerebral oxygen saturation; CO_2 carbon dioxide; S_mO_2 muscle oxygen saturation. * Difference as compared with the dissection phase $P < 0.05$

Results

The dissection phase lasted 131 (40–312) min, the anhepatic phase 80 (30–180) min, the early reperfusion phase 22 (20–30) min, and the late reperfusion phase 125 (50–350) min. High levels of bilirubin rendered the NIRS measurements impossible in two patients who, therefore, were excluded from the study. During the four phases of surgery, no significant changes in MAP (72 (70–73) mmHg) and HR (82 (80–83) beats/min) were detected (Fig. 1). Following clamping of the portal and the inferior caval veins in the anhepatic phase of surgery, blood flow to the heart was impeded. Thus, as expected, when compared with the dissection phase, CO and TA_{ICW} decreased (from 7.9 (3.5–16.7) to 6.2 (3.1–10.2) l/min and 45 (21–76) to 43 (19–73) mS, respectively). Despite the decrease in CO and TA_{ICW}, ΔS_cO_2 remained stable at 7 (−1–20)% vs. 8 (−9–30)%, as did ΔS_mO_2 at 2 (−12–22)% vs. 4 (−24–18)% and $etCO_2$ was 3.9 (3.1–5.9) vs. 3.9 (3.0–7.4) kPa.

In the early reperfusion phase, ΔS_cO_2 increased to 16 (−6–36)%, ΔS_mO_2 to 9 (−27–24)% and $etCO_2$ to 4.3 (3.4–5.2) kPa. That was the cases as CO increased to 9.9 (4.3–18.8) l/min and TA_{ICW} returned to the level of the dissection phase (45 (22–78) mS).

ΔS_cO_2 and ΔS_mO_2 tended to decrease in the late reperfusion phase, 11 (−6–25)% and 2 (−20–28)%, respectively, although $etCO_2$ and CO remained higher than during the dissection phase (4.2 (3.2–5) kPa and 9.3 (5.1–13.2) l/min, respectively). Compared with the dissection phase at 46 (22–99) mS., the TA_{ICW} was not significantly different.

Table 2 Correlations between frontal lobe oxygenation as determined by near-infrared spectroscopy (S_cO_2) and mean arterial pressure (MAP) with associated lower limit of cerebral autoregulation

Patient (no)	Observations (*n*)	MAP, range	Correlation between S_cO_2 and MAP	Lower limit of cerebral autoregulation (MAP, mmHg)
1	41	49–90	0.351 ($P = 0.024$)	67
4	41	55–90	0.889 ($P < 0.001$)	71
7	47	51–71	0.371 ($P = 0.010$)	62
11	28	50–84	0.489 ($P = 0.008$)	75
15	48	57–91	0.446 ($P = 0.001$)	–
19	41	54–81	0.366 ($P = 0.020$)	71
20	36	47–92	0.632 ($P < 0.001$)	–
29	54	44–87	0.731 ($P < 0.001$)	62
30	49	61–114	0.556 ($P < 0.001$)	90
31	41	40–90	0.609 ($P < 0.001$)	–
32	31	38–74	0.464 ($P = 0.010$)	50
			Mean (range)	69 (50–90)

For patient # 15, 20, and 31 it was not possible to define a lower limit of cerebral autoregulation

Even though MAP, on an average, remained stable during surgery, some patients demonstrated hypotensive episodes. To evaluate whether there was any individual change in S_cO_2 in response to a lowering of MAP, for each patient S_cO_2 was related to MAP. From that perspective eight patients exhibited cerebral autoregulation with a defined lower level of ~69 (range 50–90) mmHg (Table 2 and Fig. 2a). In contrast, for three patients, a positive regression between S_cO_2 and MAP continued for the full range of MAP recorded (Fig. 2b). No statistical significant correlation between S_cO_2 and MAP could be established for 20 patients who demonstrated a lowest MAP of 55 (range 42–66) mmHg (Fig. 2c).

Discussion

On an average MAP did not change significantly during the operation while S_cO_2 increased in the early reperfusion phase, indicating hyperperfusion of the brain [2, 14] and also S_mO_2 increased. Despite the stable MAP, individual variation in S_cO_2 between patients was significant and 3 patients exhibited a linear relation between S_cO_2 and MAP, indicating that brain perfusion was not autoregulated. Conversely, a lower limit of cerebral autoregulation was defined in 8 patients while the lowest recorded MAP did not affect S_cO_2 for 20 patients.

During OLT, S_cO_2 detects changes in cerebral perfusion related to the arterial carbon dioxide tension ($PaCO_2$) [14] and affected mental function after the operation has been related to a sudden drop in S_cO_2 probably because of an embolus [18]. Also the NIRS signal becomes affected by enhanced bilirubin concentration in blood likely to be elevated for the liver transplant patient, although even low values appear to respond to changes in the $PaCO_2$ [17]. However, plasma bilirubin may be so high (>370 mM) that no NIRS signal can be detected.

The capability of NIRS to determine adequate cerebral perfusion has been shown in other studies [19–21]. From the present study, we consider the findings to indicate that NIRS detects cerebral autoregulation for most patients undergoing liver transplantation, the exception being those patients with so high a bilirubin level that a reading of S_cO_2 by NIRS, at least with the applied apparatus, becomes impossible as was the case for 2 of the 33 studied patients (6%). For those patients for whom a NIRS signal could be detected, two responses in S_cO_2 to a low MAP were detected. For the majority of the patients a low level of MAP was of no consequence for S_cO_2. On the other hand, for the remaining of the patients, a low MAP was associated with a reduction in S_cO_2 and the difference between the two groups of patients appeared, although the central blood volume was not affected, as detected with transthoracic electric admittance and S_mO_2 indicated no periferal vasoconstriction [13]. Under circumstances were MAP is reduced by lowering of the central blood volume by lower body negative pressure [22], head-up tilt [23, 24], and hemorrhage [13], jugular venous saturation and S_cO_2 are affected, while the same MAP may be of no consequence for S_cO_2 if CBV is maintained [25]. Yet the present results indicate that for some patients cerebral oxygenation becomes affected with even a small reduction in MAP at a maintained central blood volume.

During anesthesia MAP is often the only indirect measure to indicate whether CBF is preserved. CBF is held relatively stable by cerebral autoregulation, and only if MAP exceeds the lower limit of cerebral autoregulation CBF is considered to decrease [1]. Conversely, with a maintained central blood volume cerebral autoregulation may still be intact with a MAP of 37 mmHg as indicated by S_cO_2 [25]. For the present patients, MAP offered little if any indication for whether S_cO_2 was maintained in that there was a substantial overlap between the lowest MAP recorded for the patients with maintained S_cO_2 and the

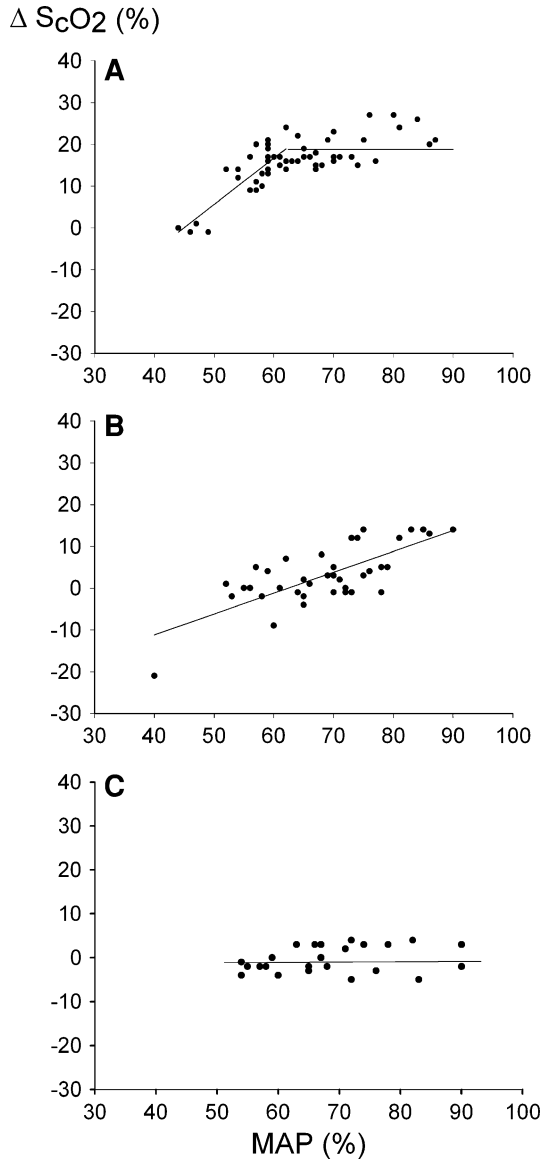

Fig. 2 Changes in frontal lobe cerebral oxygenation (ΔS_cO_2) in relation to mean arterial pressure (MAP). **a** Cerebral autoregulation for patient # 29. The intersection between the regression and the horizontal line indicates a lower limit of cerebral autoregulation at 62 mmHg. **b** Impaired cerebral autoregulation for patient # 31. ΔS_cO_2 is positively related to MAP throughout the full range of MAP. **c** No lower limit of cerebral autoregulation could be established for patient # 13

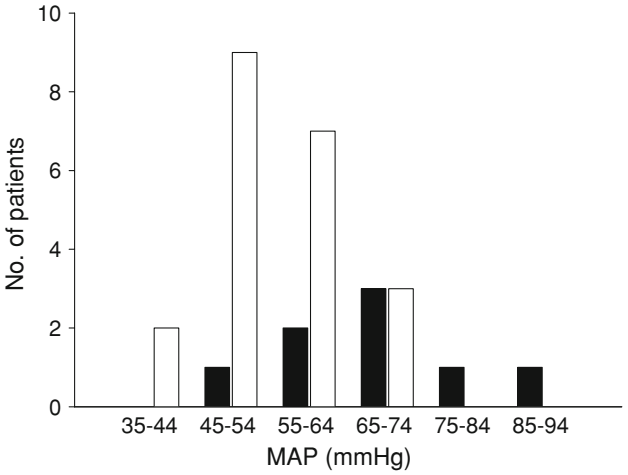

Fig. 3 *Filled bars*, number of patients demonstrating a lower limit of cerebral oxygenation as detected by near-infrared frontal lobe oxygenation (S_cO_2) during orthotopic liver transplantation plotted at the mean arterial pressure (MAP) of the limit. *Open bars*, number of patients for whom S_cO_2 was independent of MAP plotted against the lowest recorded MAP during the operation

MAP at which a lower limit of cerebral autoregulation appeared to be detected in other patients (Fig. 3). It has furthermore been demonstrated that administration of epinephrine through its α_1-adrenergic agonist vasopressure actions may produce increased perfusion pressure and flow in large vessels, but nevertheless decreases the cerebral microcirculatory blood flow [26].

For three patients it was not possible to determine a plateau where S_cO_2 remained stable. S_cO_2 kept rising through the full range of MAP recorded indicating that cerebral autoregulation was impaired. In contrast to the patients for whom an autoregulatory plateau could be established, not only a low MAP challenges cerebral perfusion, but also in case of a high MAP, the brain circulation will not be protected and, in turn, constitute a risk of cerebral hyperperfusion that may lead to cerebral edema [27].

It has been reported that postoperative neurological complications is seen in up to 33% of the patients undergoing OLT [28]. During surgery the S_cO_2 should not be allowed to decrease more than 10% from baseline as this is the level associated with brain dysfunction [13] and for (cardiac) surgery preserved S_cO_2 appears to reduce postoperative complications [29]. Only one patient exceeded the 10% limit drop in S_cO_2 and thus may have had an episode of cerebral hypoperfusion to a level where brain dysfunction would be suspected [23]. The drop in S_cO_2 was by 21% during reperfusion of the liver and associated with a concomitant decrease in MAP and CO, although TA_{ICW} remained stable. S_cO_2, MAP, and CO normalized within 20 min and S_cO_2 remained stable around baseline for the remaining part of the operation. Accordingly, some cardio-inhibiting factor of consequence for not only CO but also for cerebral perfusion, may have been released when normal splanchnic circulation was reestablished.

When there was a S_cO_2 determined cerebral autoregulation, it was possible to approximate the lower limit of cerebral autoregulation. For the eight patients we found the lower limit was at a MAP of ~69 mmHg but there was considerable variation among the patients. Variation in $PaCO_2$ during the operation could influence the lower limit of cerebral autoregulation as hypercapnia leads to cerebral vasodilatation and hypocapnia to vasoconstriction producing, not only changes

in CBF [30], but also different levels of S_cO_2 for the same MAP [13]. Hypercapnia in the reperfusion phase could have shifted the autoregulatory curve upwards and the lower limit towards a higher MAP because of the dilated cerebral vessels.

In conclusion, S_cO_2 was kept at an acceptable level during surgery even though the lower limit of cerebral autoregulation was exceeded or autoregulation was impaired for some patients. Only one patient (#31) exhibited a critical drop in S_cO_2 not associated with a drop in TA but with a reduction in MAP, CO, and S_vO_2 in the early reperfusion phase and S_cO_2, as well as the other parameters returned to the normal level after 20 min.

This study indicates that S_cO_2 detect effective cerebral autoregulation for most patients undergoing liver transplantation, but with a highly variable lower limit, i.e., S_cO_2 may be maintained at lowest MAP of 42 mmHg, while for another patient S_cO_2 decreased when MAP became lower than 90 mmHg. The implication of the present observations is that it remains unknown whether S_cO_2 is maintained during the operation unless it is measured when MAP is lower than 90 mmHg. We therefore recommend that regional cerebral oxygenation be monitored throughout the operation.

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