Regional Cerebral Oxygen Saturation Is a Sensitive Marker of Cerebral Hypoperfusion During Orthotopic Liver Transplantation

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Neurological complications contribute significantly to morbidity and mortality of patients after orthotopic liver transplantation (OLT). One possible cause of postoperative neurological complications is cerebral ischemia during the surgical procedure. In this study, we investigated the relationship between intraoperative changes in regional cerebral oxygen saturation (rSO₂) and postoperative values of neuron-specific enolase (NSE) and S-100, which are specific variables that indicate cerebral disturbances due to hypoxia/ischemia. The rSO₂ was monitored continuously by near-infrared spectroscopy in 16 patients undergoing OLT. In addition, NSE and S-100 were determined in arterial blood before surgery and 24 h after reperfusion of the donor liver. Interestingly, clamping of the recipient’s liver led to a significant decline in rSO₂ in eight patients, whereas the others tolerated clamping without major changes in rSO₂. The decrease in rSO₂ after clamping correlated significantly with postoperative increases in NSE (r² = 0.57) and S-100 (r² = 0.52). However, there were no significant differences between patients with and without rSO₂ decline concerning hemodynamic variables. There were no significant correlations between rSO₂ and cardiac output (r² = 0.20), NSE and cardiac output (r² = 0.37), or S-100 and cardiac output (r² = 0.24). Monitoring of rSO₂ may be a useful noninvasive tool to estimate disturbances in rSO₂ during OLT.

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There are many possible complications of orthotopic liver transplantation (OLT) that worsen patient outcome. Neurological disorders are among the most common of these; they may prevent total recovery in transplant patients and contribute significantly to morbidity and mortality (1).

There are several reasons for neurological damage during and after OLT. Causes for neuropsychiatric complications are the use of drugs such as cyclosporin A, electrolyte disturbances, air embolism, cerebral hemorrhage, and bacterial encephalitis (2–5). In addition, perioperative cerebral hypoperfusion may also contribute to the genesis of postoperative neurological complications.

A method for monitoring cerebral oxygenation is provided by near-infrared spectroscopy (NIRS) (INVOS 3100A; Somanetics). This technique is noninvasive and allows continuous registration of brain tissue oxygenation (6). Therefore, we investigated whether NIRS can sensitively indicate intraoperative cerebral hypoperfusion to prevent later irreversible damage.

We compared intraoperative changes in regional cerebral oxygen saturation (rSO₂) with postoperative increases in neuron-specific enolase (NSE) (LIA-mat® NSE Prolifigen; Byk-Sangtec, Germany) and Sangtec®100 (S-100) (LIA-mat® Sangtec®100; Byk-Sangtec). NSE, the neuronal isomer of the glycolytic enzyme 2-phosphoglycerate hydrolase, and Sangtec®100, which measures the central nervous system-specific isoforms of S-100, have been shown to be specific variables for the assessment of cerebral damage due to hypoxia/ischemia (7).

Methods

After institutional approval and informed, written consent, we investigated 16 patients—9 men and 7 women—undergoing OLT. All patients underwent transplantation because of chronic end-stage liver failure. The severity of the liver dysfunction was categorized as Child-Pugh B in 4 of the 16 patients and...
Child-Pugh C in 12 patients. None of the patients had preexisting hepatic encephalopathy. The underlying diseases were nutritive toxic cirrhosis in 8 cases, chronic active hepatitis in 6 patients, and primary biliary cirrhosis in 2 patients. NSE can be falsely increased in patients with small-cell lung cancer or benign pulmonary disease. Therefore, patients with benign pulmonary disease were excluded from the study. Patients with small-cell lung cancer did not undergo transplantation.

The patients’ ages ranged from 43 to 60 yr (48 ± 4 yr). The mean clamping time of the portal vein and vena cava (anhepatic period) was 115 ± 19 min. During the study, there were no major alterations in surgical technique. No patient had a venovenous bypass.

Anesthesia was induced with etomidate 0.2 mg/kg IV, midazolam 3–5 mg IV, and succinylcholine 1.0–1.5 mg/kg IV and was maintained with fentanyl or sufentanyl and midazolam as necessary. Pancuronium 1.5 mg/kg IV and was maintained with fentanyl or sufentanil and midazolam as necessary. Pancuronium –15 min, 90 min, and 24 h after reperfusion of the recipient’s liver, 20 min after cross-clamping of the recipient’s liver, before reperfusion of the donor liver, and 15 min, 90 min, and 24 h after reperfusion of the donor. OLT was performed according to the Heidelberg protocol, which includes cross-clamping of the caval vein. Intraoperative and postoperative blood loss was compensated for by autotransfusion using a cell-saver system, red blood cell packs, platelets, and fresh frozen plasma.

The rSO2 was continuously monitored by NIRS (INVOS 3100A) with the sensor positioned on the forehead of the patient. The optodes of the INVOS probe were 3.0 and 4.0 cm apart. The readings were recorded every 30 s and displayed graphically as well. NIRS light is generated by the INVOS 3100A at wavelengths of 725 and 797 nm. The NIRS light is reflected by tissues in a parabolic curve, and the oxygen saturation of cerebral tissue is calculated according to an algorithm described by McCormick et al. (6). Physiologically, vascular beds in cerebral tissue consist of 70% to 80% venous blood (8). Therefore, the oximeter reading is weighted toward venous blood oxygen saturation and represents the oxygen extraction by the cerebral tissue.

Arterial blood samples to determine NSE and S-100 serum levels were collected immediately before and 24 h after operation to calculate the perioperative changes in these variables. NSE (LIA-mat® NSE Prolifigen) and S-100 (LIA-mat® Sangtec®-100) were measured in the serum of these patients by using immunoluminometric assays.

Results

Immediately after clamping of the vena cava, there was a significant decrease in cardiac output in all patients. Cardiac output decreased to 49% compared with baseline values (9.6 ± 1.1 L/min). After reperfusion of the transplanted liver, there was a complete restoration of cardiac output to baseline levels. Mean arterial blood pressure decreased to 70 ± 5 mm Hg during the clamping period (baseline, 91 ± 7 mm Hg), and the mean heart rate increased to 120 ± 5 bpm (baseline, 93 ± 7 bpm). Both variables stabilized at baseline levels after reperfusion.

PaO2 was maintained at high normal ranges (>150 mm Hg) throughout the entire operation to prevent tissue hypoxia. In the early reperfusion period, PaCO2 was slightly increased (43 ± 3 mm Hg), and moderate acidosis (pH 7.27 ± 0.03) occurred. Both variables returned to normal in the late period of reperfusion. Hematocrit was stable with blood substitution as needed.

Interestingly, patients were in two subgroups with respect to rSO2 values after cross-clamping of the recipient’s liver (Fig. 1). Eight patients exhibited a significant decrease in rSO2, which was obtained 20 min after clamping of the vena cava and was totally reversible after declamping. Both groups of patients showed similar baseline rSO2 readings (70% ± 4% versus 68% ± 3% in patients without versus with a decline in rSO2, respectively) (Table 1).

For further information on the underlying mechanism for the dichotomous distribution of patients, hemodynamic data, variables of blood gas analysis, and laboratory data are given in Tables 2 and 3 for both groups. However, no significant difference was found in these variables between groups. In addition, in both groups, similar numbers of red blood cell packs (group without rSO2 decline, 8.7 ± 9.4 versus group with rSO2 decline, 8.1 ± 8.5) and amounts of fresh frozen plasma (group without rSO2 decline, 15.4 ± 10.2 versus group with rSO2 decline, 15.8 ± 10.9) were transfused. No significant differences in total bilirubin were observed at baseline (group without rSO2 decline, 2.7 ± 0.6 mg/dL versus group with rSO2 decline,
2.5 ± 0.9 mg/dL) or 24 h after transplantation (group without rSO2 decline, 3.3 ± 0.6 mg/dL versus group with rSO2 decline, 3.4 ± 0.7 mg/dL).

Baseline levels of NSE and S-100 were not significantly different in the two groups (Table 1). However, patients with a significant decline in rSO2 after clamping of the vena cava showed significant increases in NSE and S-100 24 h after reperfusion of the donor liver. Perioperative changes in NSE levels were calculated from plasma levels before surgery and 24 h postreperfusion (ΔNSE). During analysis, the mean value of rSO2 in the last 2 min before clamping was compared with the 2-min mean rSO2 readings at 20 min after cross-clamping the recipient's liver. We correlated ΔNSE with changes in ΔrSO2. There was an inverse correlation between ΔrSO2 and ΔNSE (baseline during the preparation period compared with the mean rSO2 value 20 min after clamping) (Fig. 1: $r^2 = 0.57; P \leq 0.05$).

S-100 levels also increased in patients with a significant reduction of rSO2 during the anhepatic period. Similar to NSE, patients with low intraoperative rSO2 readings also exhibited higher postoperative S-100 levels, and calculated differences between pre- and postsurgery (ΔS-100) were significantly increased. There was a significant correlation between changes in rSO2 and ΔS-100 (Fig. 1: $r^2 = 0.52; P \leq 0.05$).

However, there were no significant differences between patients with and without NSE increases concerning hemodynamic variables during the transplantation (Tables 2 and 3), age, or underlying disease. There were no significant correlations between NSE and the decrease in cardiac output ($r^2 = 0.37$), ΔrSO2 and cardiac output ($r^2 = 0.20$), and S-100 and cardiac output ($r^2 = 0.24$). No patient underwent retransplantation.

**Discussion**

In this study we investigated the significance of monitoring cerebral tissue oxygenation by using NIRS in patients undergoing OLT. In these patients, neurological complications contribute significantly to perioperative morbidity and mortality. Cerebral hypoxia, particularly during the anhepatic period, may contribute to the development of neuropsychiatric complications of OLT. Philips et al. (9) investigated cerebral blood flow measured by a modified technique of Kety et al. (10) during OLT and found decreased cerebral blood flow in the anhepatic period, mainly because of reduced cerebral vascular reactivity.

In this study we demonstrate that there is no significant correlation between the decrease in rSO2 after clamping and changes in cardiac output. Thus, changes in cardiac output during the anhepatic period do not reflect disturbances in brain tissue oxygenation, as determined by NIRS. NIRS directly measures the brain tissue oxygenation in the frontal lobe and allows for direct detection of cerebral hypoxia in patients undergoing vascular clamping. The patients can be divided into two subgroups: one did tolerate clamping and one did not with respect to brain tissue oxygenation. The tolerating group had no significant changes in rSO2 and no increase in NSE levels. In contrast, the group with a decline in rSO2 during the anhepatic phase had significantly higher NSE levels 24 hours after transplantation. Thus, this method has the potential to differentiate between patients who are at particular risk of brain tissue hypoxia during the anhepatic period.

Several studies have demonstrated that changes in middle cerebral artery blood flow, as measured by transcranial Doppler sonography, were greatly dependent on changes in PaCO2 (11–13). Because this technique can give information only on the velocity of cerebral perfusion, but not on quantitative changes in...
perfusion, it cannot adequately detect disturbances in cerebral tissue oxygenation.

Our study presents evidence that changes in rSO₂ in patients correlate well with biochemical variables of brain tissue damage. Both NSE and S-100 are often accepted as specific markers of neurotissue disorders. However, S-100 is also present in significant amounts in neurons of the enteric nervous plexus and intestines and may therefore be affected by clamping of the portal and caval vein. In addition, S-100 was found in large amounts in shed wound blood of cardiac surgery patients, and early increases in serum S-100 correlated with markers of peripheral tissue injury (14). NSE can be falsely increased in patients with small-cell lung cancer or benign pulmonary disease (15). Therefore, these patients were excluded from our study. Also, a prolonged separation time of plasma and cell components of the blood samples may falsely increase measured NSE levels (16). Time until separation, however, was shortened by immediate centrifugation and separation. Nevertheless, Bottiger et al. (17) demonstrated that S-100 and NSE were significantly increased 24 hours after cardiac surgery in patients with brain damage. Therefore, we determined NSE and S-100 before surgery and in the intensive care

### Table 1. rSO₂, NSE, and S-100

<table>
<thead>
<tr>
<th>Variable</th>
<th>rSO₂ decline</th>
<th>B</th>
<th>C</th>
<th>A₂₀</th>
<th>R₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>rSO₂</td>
<td>–</td>
<td>70 ± 4</td>
<td>70 ± 3</td>
<td>69 ± 3</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>68 ± 3</td>
<td>68 ± 2</td>
<td>57 ± 2*</td>
<td>—</td>
</tr>
<tr>
<td>NSE</td>
<td>–</td>
<td>4.8 ± 0.6</td>
<td>—</td>
<td>—</td>
<td>5.4 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>4.3 ± 0.8</td>
<td>—</td>
<td>—</td>
<td>17.5 ± 1.1*</td>
</tr>
<tr>
<td>S-100</td>
<td>–</td>
<td>0.13 ± 0.03</td>
<td>—</td>
<td>—</td>
<td>0.56 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>0.11 ± 0.02</td>
<td>—</td>
<td>—</td>
<td>1.03 ± 0.12*</td>
</tr>
</tbody>
</table>

B = baseline; C = before cross-clamping of the recipient’s liver; A₂₀ = 20 min after cross-clamping of the recipient’s liver; R₄ = 24 h after reperfusion of the donor liver; rSO₂ = regional cerebral oxygen saturation; NSE = neuron-specific enolase.

Data are mean ± SEM.

* P < 0.05 between groups.

### Table 2. Hemodynamic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>rSO₂ decline</th>
<th>B</th>
<th>C</th>
<th>A₂₀</th>
<th>Aₓ</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>–</td>
<td>92 ± 6</td>
<td>87 ± 7</td>
<td>71 ± 5</td>
<td>70 ± 6</td>
<td>72 ± 7</td>
<td>84 ± 3</td>
<td>92 ± 6</td>
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<tr>
<td></td>
<td>+</td>
<td>88 ± 3</td>
<td>85 ± 5</td>
<td>72 ± 3</td>
<td>75 ± 2</td>
<td>68 ± 4</td>
<td>80 ± 5</td>
<td>90 ± 2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>–</td>
<td>91 ± 5</td>
<td>99 ± 1</td>
<td>111 ± 5</td>
<td>111 ± 5</td>
<td>114 ± 5</td>
<td>105 ± 4</td>
<td>96 ± 5</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>87 ± 5</td>
<td>104 ± 4</td>
<td>110 ± 3</td>
<td>114 ± 5</td>
<td>111 ± 5</td>
<td>105 ± 6</td>
<td>96 ± 4</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>–</td>
<td>9 ± 1</td>
<td>10 ± 1</td>
<td>10 ± 3</td>
<td>7 ± 1</td>
<td>14 ± 1</td>
<td>9 ± 1</td>
<td>7 ± 2</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>9 ± 1</td>
<td>11 ± 1</td>
<td>9 ± 2</td>
<td>8 ± 2</td>
<td>13 ± 1</td>
<td>10 ± 1</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>–</td>
<td>9.6 ± 1.1</td>
<td>9.7 ± 1.2</td>
<td>4.3 ± 0.4</td>
<td>4.3 ± 0.5</td>
<td>8.5 ± 1.1</td>
<td>8.0 ± 0.8</td>
<td>7.3 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>9.1 ± 1.1</td>
<td>9.3 ± 1.5</td>
<td>4.6 ± 0.5</td>
<td>4.5 ± 0.5</td>
<td>11.1 ± 1.7</td>
<td>9.0 ± 0.9</td>
<td>7.9 ± 1.6</td>
</tr>
</tbody>
</table>

B = baseline; C = before cross-clamping of the recipient’s liver; A₂₀ = 20 min after cross-clamping of the recipient’s liver; Aₓ = before reperfusion of the donor liver; R₁, R₂, R₃ = 15 min, 90 min, and 24 h after reperfusion of the donor liver; MAP = mean arterial blood pressure; HR = heart rate; CVP = central venous pressure; CO = cardiac output; rSO₂ = regional cerebral oxygen saturation.

Data are mean ± SEM. There were no significant differences between groups.

### Table 3. Blood Gas Analysis and Laboratory Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>rSO₂ decline</th>
<th>B</th>
<th>C</th>
<th>A₂₀</th>
<th>Aₓ</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH</td>
<td>–</td>
<td>7.44 ± 0.03</td>
<td>7.37 ± 0.03</td>
<td>7.35 ± 0.03</td>
<td>7.36 ± 0.02</td>
<td>7.28 ± 0.01</td>
<td>7.38 ± 0.03</td>
<td>7.45 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>7.42 ± 0.03</td>
<td>7.39 ± 0.01</td>
<td>7.34 ± 0.01</td>
<td>7.31 ± 0.02</td>
<td>7.24 ± 0.03</td>
<td>7.38 ± 0.03</td>
<td>7.44 ± 0.02</td>
</tr>
<tr>
<td>Pao₂ (mm Hg)</td>
<td>–</td>
<td>160 ± 18</td>
<td>171 ± 19</td>
<td>189 ± 12</td>
<td>197 ± 20</td>
<td>194 ± 23</td>
<td>178 ± 19</td>
<td>111 ± 18</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>171 ± 18</td>
<td>171 ± 10</td>
<td>186 ± 12</td>
<td>201 ± 13</td>
<td>186 ± 12</td>
<td>176 ± 9</td>
<td>116 ± 11</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>–</td>
<td>39 ± 2</td>
<td>38 ± 1</td>
<td>38 ± 2</td>
<td>38 ± 1</td>
<td>48 ± 1</td>
<td>42 ± 1</td>
<td>41 ± 3</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>38 ± 2</td>
<td>38 ± 2</td>
<td>39 ± 2</td>
<td>40 ± 2</td>
<td>49 ± 3</td>
<td>40 ± 3</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>aHk (%)</td>
<td>–</td>
<td>29 ± 1</td>
<td>29 ± 1</td>
<td>30 ± 1</td>
<td>31 ± 2</td>
<td>27 ± 1</td>
<td>29 ± 2</td>
<td>32 ± 1</td>
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<td></td>
<td>+</td>
<td>30 ± 1</td>
<td>32 ± 1</td>
<td>32 ± 1</td>
<td>33 ± 1</td>
<td>29 ± 1</td>
<td>30 ± 2</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>Na⁺ (mmol/L)</td>
<td>–</td>
<td>135 ± 2</td>
<td>136 ± 2</td>
<td>134 ± 3</td>
<td>135 ± 2</td>
<td>135 ± 3</td>
<td>142 ± 3</td>
<td>141 ± 2</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>137 ± 1</td>
<td>136 ± 1</td>
<td>134 ± 3</td>
<td>136 ± 2</td>
<td>134 ± 3</td>
<td>140 ± 4</td>
<td>141 ± 2</td>
</tr>
</tbody>
</table>

B = baseline; C = before cross-clamping of the recipient’s liver; A₂₀ = 20 min after cross-clamping of the recipient’s liver; Aₓ = before reperfusion of the donor liver; R₁, R₂, R₃ = 15 min, 90 min, and 24 h after reperfusion of the donor liver; Pao₂ = arterial oxygen tension; Paco₂ = arterial carbon dioxide tension; aHk = arterial hematocrit; Na⁺ = sodium levels in plasma; rSO₂ = regional cerebral oxygen saturation.

Data are mean ± SEM. There were no significant differences between groups.
unit on the first postoperative day. Furthermore, we investigated whether decreased intraoperative rSO$_2$ readings were significantly correlated with increases in NSE and S-100. In this study, NSE and S-100 levels were highly correlated with decreased rSO$_2$ readings, further confirming our findings.

Fifty percent of the patients exhibited decreased rSO$_2$ readings during the clamping period. These patients were characterized by postoperative increased levels of NSE and S-100. Patients with almost unchanged rSO$_2$ readings did not show significant changes in either neuromarker. Because all patients showed a significant decrease in cardiac output, it is not clear why there was no significant correlation between cardiac output and the decline in rSO$_2$. Obviously, predispositions such as preexisting encephalopathy or vascular disease may be more relevant with respect to changes in cerebral oxygenation. Similar results were found in an animal study by Thorniley et al. (18), who measured decreased rSO$_2$ readings in the anhepatic period and an immediate return to baseline levels after declamping. Decreased levels were seen in animals with poor grafts.

One of the limitations of measuring rSO$_2$ is the assumed fixed relationship between arterial and venous blood. Therefore, rSO$_2$ does not reflect volume shifts, which are very likely during OLT, especially during the anhepatic phase. Even if there are no large changes in central venous pressure, this phenomenon has, nevertheless, to be taken into consideration.

In addition, the accuracy of monitoring cerebral tissue oxygenation with the INVOS device has been questioned in some studies. However, in earlier studies, the authors used a sensor with optodes 1.0 and 2.7 cm apart (19). In contrast, we used INVOS probes with optodes 3.0 and 4.0 cm apart. A study of Reents et al. (20) showed that the INVOS device failed to predict postoperative cognitive function in patients after coronary artery bypass grafting. The positive predictive value was low for detecting cerebral ischemia during carotid endarterectomy, according to a study of Samra et al. (21). Furthermore, it was shown by Madsen et al. (22) that bilirubinemia can decrease rSO$_2$ readings; however, even at high bilirubin levels, relative changes in oxygenation were still detectable. In this study bilirubin levels were rather constant, and relative changes in rSO$_2$ were taken for correlation with NSE and S-100. Thus, despite these limitations, there was a significant correlation between the neuromarkers and the decline in rSO$_2$.

A weakness of this study is the lack of distinct neuropsychiatric examination. Because neuropsychometric tests are strongly dependent on liver function, we used the biochemical variables NSE and S-100 as markers of cerebral tissue injury. No patient had preexisting hepatic encephalopathy, and no postoperative stroke occurred.

From the results of our study, a decrease in cardiac output alone does not predict neurologic damage. Therefore, direct monitoring of cerebral tissue oxygenation by rSO$_2$ is a sensitive, direct, and noninvasive method to detect cerebral hypoxia. The inverse correlation between the increase in NSE and the decrease in rSO$_2$ during the clamping period points to the significance of the NIRS as a predictive method to detect impaired cerebral perfusion under the conditions of OLT.

In conclusion, the results of this study show a close correlation between decreased rSO$_2$ readings and increased markers of neurological damage during the anhepatic period. Cerebral NIRS is a noninvasive and easy to use monitoring technique. It predicts the risk of cerebral hypoxia at a time when therapeutic interventions are possible with the aim of improving cerebral oxygenation.

References


