Redox behavior of cytochrome oxidase and neurological prognosis in 66 patients who underwent thoracic aortic surgery

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Abstract

Objective: Using near-infrared spectroscopy (NIRS), we have developed a new approach to the measurement of the redox state of cytochrome oxidase (cyt. ox.) in the brain. Our previous animal study showed that oxygen-dependent redox changes in cyt. ox. occur only when oxygen delivery is badly impaired. Therefore, in this study, we retrospectively examined the relationship between the redox behavior of cyt. ox. (measured by NIRS) during an operation and the neurological outcome in patients.

Methods: We studied 66 patients undergoing thoracic aortic surgery with cardiopulmonary bypass. Cerebral oxygenation was monitored by NIRS, and relative values for the concentrations of oxy-Hb, deoxy-Hb, and the redox state of cyt. ox. in the brain were calculated using our developed algorithm.

Results: Retrospective assessment revealed three different types of cyt. ox. behavior: (1) no change (type-A) in 34 cases (51.5%), (2) a temporary reduction, with a subsequent return to the pre-surgery baseline level (type-B) in 29 cases (43.9%), or (3) a marked and prolonged reduction (type-C) in only three cases (4.5%). Nine of the 66 patients (13.6%; one type-A, five type-B, and all three type-C patients) showed evidence of postoperative brain injury (in the type-A patient, the injury proved to be localized and far from the monitoring site). The relationship between the occurrence of such an injury and the type of cyt. ox. behavior seen during the operation was highly significant (P < 0.0001; chi-square test for independence).

Conclusions: Our data suggest that the redox behavior of cyt. ox. during an operation is a good (though not perfect) predictor of postoperative cerebral outcome, and that overall tissue oxygen sufficiency can be confirmed by near-infrared measurement of cyt. ox. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Thoracic aortic surgery; Cerebral monitoring; Near-infrared spectroscopy; Cytochrome oxidase; Hemoglobin oxygenation; Cardiopulmonary bypass

1. Introduction

Since cerebral injury continues to be a major source of morbidity and mortality after thoracic aortic surgery, protection of the brain is a primary concern during the operative and pre-operative periods [1–3]. The presence of a level of cerebral perfusion that is inadequate to meet the cerebral metabolic demands during cardiopulmonary bypass (CPB) and/or selective cerebral perfusion (SCP), even though the patient is under deep hypothermia, has been incriminated as a major factor in this complication. Consequently, during thoracic aortic surgery it is not the level of cerebral blood flow per se, but an appropriate balance between cerebral perfusion and cerebral oxygen consumption that is likely to be important.

Near-infrared spectroscopy (NIRS), although relatively new, is now in widespread use in such clinical fields as anesthesiology, neurosurgery, and pediatrics [4–6]. NIRS is a non-invasive technique that enables physicians to monitor continuously the alterations in the oxygenation of hemoglobin (Hb) and the redox state of cytochrome oxidase (cyt. ox.) in living tissue. Although measurement of the level of oxygenation of Hb by NIRS has been widely used as an indicator of cerebral oxygenation in the clinic, it is difficult to judge the level of critical factors, such as decreased production of ATP, without other forms of monitoring. On the other hand, the redox state of cyt. ox., one of the respiratory-chain enzymes, can potentially be used to monitor not only cerebral tissue oxygenation but also alterations in energy production within the brain [7–9]. Our previous animal study showed that oxygen-dependent redox changes in cyt. ox. occur only when oxygen delivery is badly impaired [10]. Therefore, in this study, in order to evaluate
whether the redox state of cyt. ox. during the operation, as measured by NIRS, is an accurate predictor of postoperative cerebral outcome, we retrospectively examined the relationship between these two parameters in 66 patients who underwent thoracic aortic surgery. In this paper, we also discuss some limitations of NIRS in the clinical field.

2. Methods

After institutional approval and informed consent had been obtained, we studied 66 patients (64.6 ± 9.9 years; 43 males and 23 females) undergoing repair of a thoracic aortic aneurysm (TAA) under CPB together with SCP and/or deep hypothermic circulatory arrest (DHCA). The types of TAA comprised 51 dissecting thoracic aneurysms [Stanford type-A (n = 46), Stanford type-B (n = 5)] and 15 non-dissecting thoracic aneurysms. Twenty-nine of the 66 cases underwent emergency procedures. Fourteen patients with a pre-existing neurological dysfunction – such as a pre-operative history of cerebral injury and/or cerebral infarction detected in a pre-operative examination by computed tomography (CT) scan or magnetic resonance imaging (MRI) – were included in this study. Anesthesia was induced intravenously with fentanyl (2–5 μg/kg) and midazolam (0.05–0.1 mg/kg), and intubation was facilitated by the use of vecuronium bromide (0.1 mg/kg). Anesthesia was thereafter maintained with 0.4–1.5% isoflurane in air plus oxygen. Additional doses of fentanyl and vecuronium were given when necessary. A heart–lung machine (HAD-101; Mera, Tokyo, Japan) was used in non-pulsatile flow mode (2.0–3.0 l/min/m²) together with a membrane oxygenator (SX10R; Terumo, Tokyo, Japan), and Paco₂ (uncorrected for temperature) was adjusted to normocapnic levels (α-stat regulation). Nasopharyngeal and rectal temperatures were continuously monitored throughout the operation.

Regional cerebral oxygenation was monitored during surgery by means of an NIR monitor (OM-110; Shimadzu Inc., Kyoto, Japan). The basic principle of the NIRS apparatus used in this study has been published in detail elsewhere [10,11]. Briefly, NIR light from a halogen lamp is passed through a lens system with a rotating disk containing four interference filters (wavelengths 700, 730, 750, and 805 nm), and from thence directed into the forehead via a single optic fiber. The source probe and the detector probe were fixed on to the forehead 4 cm apart. The values obtained before starting any surgical procedures were taken as the baseline control values.

A decrease in [oxy-Hb] and an increase in [deoxy-Hb] suggests a decrease in oxygenated blood supply and/or an increase in cerebral oxygen metabolism, resulting in cerebral tissue hypoxia. In our study we used the cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) and the redox state of cyt. ox. to evaluate whether the pattern of cerebral Hb oxygenation and the redox behavior, as detected by NIRS during the operation, predict the postoperative cerebral outcome.

To test for significant differences among groups, we used Fisher’s exact probability test or the chi-square test for independence (I × m contingency table), a P value less than 0.05 being considered statistically significant.

3. Results

The mean duration of CPB, which was instituted in all cases, was 168 ± 52.3 min (n = 66). In 43 of the 66 cases, SCP was performed, and its mean duration was 86.6 ± 52.1 min. DHCA was employed in 11 of the 66 cases, the mean duration being 26.4 ± 9.16 min. In this study, nine of the 66 patients (13.6%) suffered from post-operative brain injury (Table 1). This resulted in severe coma (four cases), hemiparesis (three cases), convulsion (one case), or a sight deficit (one case). No significant relationship was detected between the occurrence of a brain injury and the use of SCP or of DHCA (Fisher’s exact probability test).

In all 66 patients, Hb oxygenation and the redox state of cyt. ox. during the operation was assessed retrospectively. In all cases, changes occurred in [oxy-Hb], [deoxy-Hb], and [total-Hb] at the initiation of CPB, and during the periods of hypothermia and rewarming. Although the changes in the cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) in the 66 cases could not be classified into particular patterns during the operation, at the end of the operation the index showed an increase (25 cases; 37.9%), decrease (28 cases; 42.4%), or return to the control values (13 cases; 19.7%) obtained before we started any surgical procedures. There was no significant relationship between the occurrence of a brain injury and the magnitude of the cerebral oxygen index at the end of the operation.

On the other hand, when, in the entire group of patients, the redox behavior of cyt. ox. during the operation was retrospectively assessed in detail, we realized that there were three different types of cyt. ox. behavior. In terms of time course, we classed these as (1) no change (type-A), (2) a temporary, marked reduction with a subsequent return to baseline (type-B), or (3) a marked and prolonged reduction (type-C) (Fig. 1).

Fig. 2 shows the changes in cerebral oxygenation observed in a case representative of type-A; 34 of the 66 cases (51.5%) were of this type. The characteristics of the type-A pattern are that the redox state of cyt. ox. remains at its initial level (no change) throughout the operation even though marked changes occur in [oxy-Hb], [deoxy-Hb], and [total-Hb] at the initiation of CPB and/or during the periods of hypothermia and rewarming. In the type-B pattern, a transient reduction of cyt. ox. is observed, but recovery to baseline occurs by the end of the operation (Fig. 3). Twenty-nine of the 66 cases (43.9%) showed this pattern. Fig. 4 shows the changes in cerebral oxygenation in a case representative of type-C; only three of the 66 cases (4.5%) were of this type. The characteristics of type-C are that the redox
Table 1

Characteristics of the nine patients who suffered stroke

<table>
<thead>
<tr>
<th>Lowest age (year)/sex</th>
<th>Pre-op. neuro. finding</th>
<th>Surgical procedure</th>
<th>Cannulation A/V</th>
<th>CPB (min)</th>
<th>Ao clamp (min)</th>
<th>SCP (min)</th>
<th>DHCA (min)</th>
<th>Lowest temp. (°C)</th>
<th>Emer Type of Cyt. ox.</th>
<th>Neurological Outcome</th>
<th>Post-op CT or MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 66/M</td>
<td>Descending Ao</td>
<td>FA/RA</td>
<td>207</td>
<td>151</td>
<td>135</td>
<td>18.4</td>
<td>A</td>
<td>Blindness</td>
<td>B</td>
<td>Occipital, Cerebellar infarct</td>
<td></td>
</tr>
<tr>
<td>2 77/M</td>
<td>Lacunar infarct.</td>
<td>Hemiarch + CABG</td>
<td>Axilla. A/RA</td>
<td>277</td>
<td>96</td>
<td>14</td>
<td>17.6</td>
<td>B</td>
<td>Convulsion</td>
<td>RCI</td>
<td></td>
</tr>
<tr>
<td>3 68/M</td>
<td>Ao arch</td>
<td>FA/RA</td>
<td>221</td>
<td>156</td>
<td>107</td>
<td>19.2</td>
<td>(E)</td>
<td>B</td>
<td>Hemiplegia</td>
<td>Watershed infarct</td>
<td></td>
</tr>
<tr>
<td>4 61/M</td>
<td>Ascending Ao</td>
<td>FA/RA</td>
<td>162</td>
<td>125</td>
<td>35</td>
<td>19.5</td>
<td>(E)</td>
<td>B</td>
<td>Hemiplegia</td>
<td>Watershed infarct</td>
<td></td>
</tr>
<tr>
<td>5 72/M</td>
<td>Ao arch</td>
<td>Ascend. Ao/RA</td>
<td>178</td>
<td>57</td>
<td>84</td>
<td>17.0</td>
<td>B</td>
<td>RCI</td>
<td>Watershed infarct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 48/F</td>
<td>CA embolism</td>
<td>Hemiarch</td>
<td>FA/RA</td>
<td>149</td>
<td>78</td>
<td>65</td>
<td>17.0</td>
<td>B</td>
<td>Coma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 65/M</td>
<td>Cerebral infarct. (parietal lobe)</td>
<td>Descending Ao</td>
<td>FA/RA</td>
<td>230</td>
<td>87</td>
<td>43</td>
<td>13.0 (E)</td>
<td>C</td>
<td>Coma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 70/F</td>
<td>Ao arch</td>
<td>FA/RA</td>
<td>238</td>
<td>128</td>
<td>169</td>
<td>15.8</td>
<td>C</td>
<td>Coma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 63/F</td>
<td>Post-SAH (5 years ago)</td>
<td>Ao arch</td>
<td>FA/RA</td>
<td>332</td>
<td>229</td>
<td>260</td>
<td>14.8</td>
<td>(E)</td>
<td>C</td>
<td>Coma</td>
<td></td>
</tr>
</tbody>
</table>

* CA = carotid artery; Cannulation A/V = position of delivery cannula and venous cannula; FA = femoral artery; RA = right appendage; Axilla. A = axillary artery; CPB = duration of cardiopulmonary bypass; Ao Clamp = duration of aorta clamping; SCP = duration of selective cerebral perfusion; DHCA = duration of deep hypothermic circulatory arrest; Lowest Temp. = lowest nasopharyngeal temperature during operation; Emerg. = Emergency; RCI = regional cerebral infarction; SAH = subarachnoid hemorrhage.
behavior of cyt. ox. shows a marked and prolonged reduction both during the operation and after it.

All patients (three cases) who exhibited type-C cyt. ox. behavior suffered from brain coma after their operation. Among the 29 type-B patients, brain coma (one case), hemiparesis (three cases), and convolution (one case) were observed postoperatively. Only one of the 34 type-A patients suffered a postoperative deficit (visual loss). The relationship between the occurrence of a brain injury and the type of cyt. ox. behavior was highly significant ($P < 0.0001$; chi-square test for independence ($1 \times m$ contingency table)) (Table 2).

4. Discussion

NIRS, a relatively new technique, enables us to monitor changes in Hb oxygenation and in the redox state of cyt. ox. in living tissues in a non-invasive manner. This technique has found wide clinical application, and its usefulness in the measurement of regional cerebral oxygenation during SCP and DHCA has been reported [12–15].

Since cyt. ox. is the terminal enzyme in the respiratory chain in mitochondria, its redox state is directly related to the intracellular oxygenation state and to the energy state of the cell.

Table 2

<table>
<thead>
<tr>
<th>Postoperative brain injury</th>
<th>Behaviour of cyt. ox. during operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>A-type 1</td>
</tr>
<tr>
<td>No</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>34</td>
</tr>
</tbody>
</table>

* Occurrence of brain injury vs. type of cyt. ox. behaviour: $<0.0001$ (chi-square test for independence, $1 \times m$ contingency table).
concentration for oxy-Hb and deoxy-Hb, and oxidation of cyt. ox.

However, the specific concentration required for a half-maximal reduction of cyt. ox. during cerebral hypoxia and/or hypoperfusion, and indeed increases in PCr and ATP in the brain are observed during cooling [21,22]. When a new algorithm, earlier developed by us [10], was used to measure the redox state of cyt. ox. in the present study, the redox state of cyt. ox. showed oxidation during the cooling phase, and there was an increase in cerebral Hb oxygenation in this phase. In this respect, the NIRS findings in our study are not consistent with the changes in cyt. ox. behavior in humans undergoing CPB–DHCA reported previously by another group [19].

None of the 34 type-A patients showed any significant changes in the redox state of cyt. ox. during the operation. This shows that our present measurement method can selectively detect redox changes in cyt. ox. in cerebral tissue at times when there may be large changes in cerebral Hb oxygenation (as indicated by changes in [oxy-Hb] minus [deoxy-Hb]). The overwhelming majority (33/34; 97.3%) of the type-A patients exhibited no neurophysiological complications after their operation. In the one type-A patient who did suffer such a complication (visual loss), a local regional cerebral infarction in the occipital region, far from the monitoring site, was found by CT scanning after the operation.

Unlike those in type-A, the type-B patients showed an immediate reduction of cyt. ox. at the initiation of CPB and/or in the rewarming period, with a recovery to the original level by the end of the operation. Our data strongly suggest that severe ischemia leading to extreme tissue hypoxia occurred at some time during the operation, because five of the 29 (17.2%) type-B patients exhibited a neurological complication (coma, convulsion, or hemiparesis) after the operation. Furthermore, the fact that the three type-C patients showed a marked and prolonged reduction of cyt. ox. during and after the operation suggests that they experienced severe tissue hypoxia during and after the operation, and that this resulted in the occurrence of severe coma in all three of these patients.

The cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) showed various changes under hemodilution, cooling, rewarming, blood transfusion, and changes in FiO₂. We cannot explain exactly why there was no significant relationship between the occurrence of a brain injury and the magnitude of the cerebral oxygen index at the end of the operation. Hyperoxia of the internal jugular venous blood has been reported in patients who suffered coma or brain death; this was thought to be because the external carotid regions had received ‘luxury perfusion’, resulting in hyperoxia of the venous blood returning from the extracerebral tissues [23]. Since Hb signals from external or internal carotid regions cannot be separated by NIRS, we may possibly detect an increase in Hb oxygenation even under conditions of severe brain-tissue hypoxia, such as lead to coma or brain death. Thus, the degree of cerebral hypoxia cannot be judged by near-infrared measurement of Hb oxygenation alone. However, our data demonstrate that the redox behavior of cyt. ox. (as measured by NIRS) can provide direct, real-time information about crises in cerebral oxygen metabolism associated with fairly widespread hypoxia and/or ischemia, and that acquiring such information enables us both to assess the likely degree of cerebral damage and to predict the postoperative cerebral outcome.

What was the etiology of the brain damage, particularly in cases with coma or hemiplegia? In this study, two patients who underwent DHCA suffered from coma and convulsions in the postoperative period. Although we could not obtain anatomical information by CT or MRI because of unstable.
postoperative hemodynamics, the main cause may have been an inadequate cerebral oxygen balance during the period of DHCA. It would appear that global cerebral hypoxia and/or ischemia induced by lower cerebral perfusion can be detected by NIRS via probes positioned at the forehead. On the other hand, four patients under SCP suffered from either slight deficit (one case) or hemiplegia (three cases); these were presumably related to the regional cerebral infarction shown up by CT and/or MRI. Hence, we need to consider embolic episodes as a cause of stroke, particularly in patients who undergo SCP. NIRS can only assess cerebral oxygenation in the parts of the brain that can be reached by the light, which means that changes in local regions far from the monitoring site may elude detection. In other words, we must always be mindful that NIRS may be reached by the light, which means that changes in local regions far from the monitoring site may elude detection. The positioning of the probes is therefore of considerable importance.

From our data, we conclude that the redox behavior of cyt. ox. during an operation is likely to be a good predictor of the postoperative cerebral outcome. Our data imply that although changes in local regions far from the monitoring site may elude detection, oxygen sufficiency or deficiency of brain tissue on a more global scale can be evaluated by near-infrared measurement of the redox state of cyt. ox. At the time we carried out the operations detailed in this study, we were not confident of the reliability of NIRS as a predictor of the neurological outcome. Now, however, we feel confident enough of its reliability to alter our surgical strategy during an operation if the NIRS data gives us reason to think that the patient is experiencing deficient cerebral oxygenation.

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References