New indicator of postoperative delayed awakening after total aortic arch replacement†

Tonomori Shirasaka, Kenji Okada, Hiroya Kano, Masamichi Matsumori, Takeshi Inoue and Yutaka Okita*

Division of Cardiovascular Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Chuo-ku, Kobe, Hyogo, Japan

* Corresponding author. Division of Cardiovascular Surgery, Department of Surgery, Kobe University Graduate School of Medicine, 7-5-2, Kusunoki-Cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. Tel: +81-78-3825942; fax: +81-78-3825959; e-mail: yokita@med.kobe-u.ac.jp (Y. Okita).

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Abstract

OBJECTIVE: Impact of the decrease of regional cerebral oxygen saturation (rSO2) on postoperative delayed awakening after total aortic arch replacement (TAR) was validated.

METHODS: From 2008 to 2013, 143 consecutive patients underwent TAR using selective antegrade cerebral perfusion. rSO2 was monitored using near-infrared spectroscopy. We calculated a percent decrease of rSO2 (%-D) immediately after rewarming according to the following formula: %-%D = rSO2 (X1)−rSO2 (X2)/rSO2 (X1) × 100 (%), where rSO2 (X1) was measured at the beginning of rewarming, and rSO2 (X2) was measured 10 min later. Delayed awakening was defined as patients not waking up for more than 6 h after the termination of anaesthesia.

RESULTS: The average time to wake up was 3.6 ± 2.0 h. Fourteen patients showed delayed awakening. %-D showed a positive linear relationship to awakening time (y = 0.67x – 0.7, r = 0.23, P = 0.007) and receiver operating characteristic analysis showed %-D had a good predictive value for delayed awakening (area under the curve = 0.84). %-D was significantly different between the delayed awakening and the normal group (7.1 ± 5.1 vs 1.3 ± 6.6%, P = 0.002). Two patients (1.4%) who had multicomorbidity with higher %-D died in the hospital due to colon necrosis and sepsis. There were significant differences between patients with normal and delayed awakening in hospital mortality (P = 0.04) and transient neurological deficit (TND, P = 0.007).

CONCLUSION: The maintenance of rSO2 at the early phase of rewarming may be important to avoid delayed awakening or TND after TAR.

Keywords: Delayed awakening • Regional cerebral oxygen saturation • %-decrease of rSO2 • Near-infrared spectroscopy • Total arch replacement

INTRODUCTION

Delayed awakening after aortic surgery can indicate an intraoperative cerebrovascular event has occurred, which is still a concern in total aortic arch replacement (TAR), even though improved surgical strategies have decreased the postoperative complication rate [1].

Near-infrared spectroscopy (NIRS), which is widely used to monitor regional intraoperative cerebral oxygen saturation (rSO2) [2, 3], can help surgeons minimize the decrease in cerebral oxygenation that can occur during cardiovascular surgery. However, it is difficult to correlate clinical outcomes and rSO2 values measured during surgery, because the initial rSO2 level varies widely among patients, and because many factors are involved in determining the rSO2 level [4]. Many researchers have suggested that the risk of neurological complications might increase below a preliminary cut-off value for rSO2 [3–6], but this is still controversial.

The rewarming phase during extracorporeal circulation time requires close attention [7] because the rSO2 tends to drop as the brain becomes metabolically hyperactive [8]. Rapid rewarming can shorten the duration of cardiopulmonary bypass (CPB), but can also aggravate imbalances in the supply and demand of cerebral oxygen [9, 10].

This study was conducted to investigate relationships between the decreased cerebral oxygen saturation that occurs during the rewarming phase in TAR, and delayed awakening as a representative neurological adverse event.

PATIENTS AND METHODS

This study was approved by our Institutional Review Board (IRB: IRB number 1486), and the need for individual consent was waived.

Patient profiles

We retrospectively evaluated 143 consecutive patients (106 males and 37 females) who underwent TAR via median sternotomy from June 2008 to July 2013. The mean age was 72 ± 13 years, and there

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were 36 (25.2%) octogenarians. There were 8 patients (5.6%) with a history of carotid stenosis and 15 (10.5%) with a history of cerebral infarction. This series excluded emergency surgeries, hemiarch or partial arch replacement with reconstruction of only one or two branches, and surgeries with unusual approaches such as left thoracotomy [11] or the arch-first technique [12]. The patient profiles are summarized in Table 1.

Surgical approach

Our surgical procedure of TAR has previously been reported [1]. Patients were placed in a supine position; NIRS diodes (INVOS 5100C, Somanetics, Troy, MI, USA) were attached bilaterally on the forehead, and rSO2 was recorded every 30 s throughout the operation.

CPB was established in a routine manner. The patient was given betamethasone sodium phosphate (100 mg), and sivelestat sodium hydrate (100 mg) was added to the pump circuit when starting CPB. After the tympanic temperature had fallen to 23°C and the rectal temperature was 30°C or lower, the aortic arch aneurysm was opened and antegrade selective cerebral perfusion (SCP) was started. A 14-Fr or 16-Fr balloon-tipped cannula was inserted from inside the aorta into the brachiocephalic artery (BCA), and 12-Fr cannulas were positioned in the left common carotid and left subclavian arteries (lt.CCA/lt.SCA). Antegrade SCP flow was maintained at 10–12 ml/kg/min using an independent roller pump, and the balloon-tip pressure was maintained between 30 and 40 mmHg. During this period, the blood temperature of SCP was also maintained at 23 ± 1°C until the completion of the distal anastomosis. After completing the distal anastomosis, lower-body circulation was restored through a side branch of the graft, and rewarming was commenced.

On the early phase of rewarming, antegrade SCP flow was gradually increased while maintaining a baseline rSO2; the SCP flow was kept <1200 ml/min to prevent brain oedema. In this period, the blood temperature gradually went up to 33°C, maintaining a baseline rSO2 until the completion of the proximal anastomosis followed by coronary reperfusion and reconstruction of the triple neck vessels. In patients with severe carotid artery or intracranial artery stenosis or occlusion, the triple neck vessels (BCA, lt.CCA and lt.SCA) were reconstructed prior to rewarming.

Quantification of cerebral oxygen desaturation in the early period of rewarming

Typically, rSO2 peaks during the cooling phase of CPB and declines immediately after rewarming in response to the change in the balance of cerebral oxygen demand and supply.

We defined the rate of change in the rSO2 immediately after rewarming, reflecting metabolic activity in the brain caused by rewarming as % decrease of rSO2 (=%-D), which was calculated as follows: \( \%\text{-}\text{D} = \frac{\text{rSO}_2(\text{X}_1) - \text{rSO}_2(\text{X}_2)}{\text{rSO}_2(\text{X}_1)} \times 100 \% \), where rSO2(X1) is measured at the commencement of rewarming and rSO2(X2) is measured 10 min later (Fig. 1).
Definitions: delayed awakening, and transient or permanent neurological deficits

Generally, sedatives are discontinued at the end of surgery and the patient is transferred to the intensive care unit (ICU), where the patient is observed for awakening. The condition of ‘awakening’ was defined as a state in which the patient can open their eyes and respond spontaneously to calling from people without any physical contact or stimuli. Delayed awakening was defined as not having awakened 6 h after the termination of anaesthesia. A transient neurological deficit (TND) was defined as transient disorientation, slurred speech, agitation or poor response to commands, including a super-delayed awakening over more than 24 h. Permanent neurological deficit (PND) was defined as a deficit persisting at discharge, as reported by Ergin et al. [14].

Statistical analysis

Data were processed with the JMP 9 software (SAS Institute, Inc., Cary, NC, USA). All values were expressed as the mean ± standard deviation. It may be possible that the occurrence of postoperative delayed awakening differs by age; the mean values of 2 groups were also adjusted for octogenarians with analysis of covariance (ANCOVA). Continuous variables were analysed by Welch’s test. Categorical variables were analysed by a χ² test. A logistic regression model was constructed considering the stepwise selection method for confirming the correlation between %-decrease and awakening time. Calculation of the area under the curve (AUC) of the receiver operating characteristics (ROCs), with 95% confidence interval, was used to evaluate the diagnostic accuracy of %-decrease for delayed awakening. The cut-off value was identified. Differences with P < 0.05 were considered statistically significant.

RESULTS

The average time from entering into the ICU to awakening was 3.6 ± 2.0 h. The duration for CPB, myocardial ischaemia, lower-body circulatory arrest (lower CA) and SCP was 179 ± 51, 82 ± 36, 42 ± 18 and 101 ± 33 min, respectively (Table 2). The minimum tympanic temperature was 22 ± 1.9°C. Of 143 patients, 14 (9.8%) had a delayed awakening (delayed group). The lowest preoperative haemoglobin (Hb) in the delayed and the normal group were 8.3 ± 0.4 g/dl and 8.7 ± 0.5 g/dl, respectively. CPB time was significantly longer and Hb at the start of rewarming was significantly smaller in the delayed group than in the normal group.

CPB: cardiopulmonary bypass time; CA: circulatory arrest of the lower body; SCP: selective cerebral perfusion; BT: body temperature; Hb: haemoglobin.

Table 2: Intraoperative variables

<table>
<thead>
<tr>
<th>Intraoperative variables</th>
<th>All (n = 143)</th>
<th>Delayed awakening (-) (N = 129)</th>
<th>Delayed awakening (+) (n = 14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB time (min)</td>
<td>179 ± 51</td>
<td>175 ± 48</td>
<td>221 ± 66</td>
<td>0.03</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>82 ± 36</td>
<td>80 ± 33</td>
<td>103 ± 51</td>
<td>0.10</td>
</tr>
<tr>
<td>Lower CA time (min)</td>
<td>42 ± 18</td>
<td>42 ± 18</td>
<td>44 ± 24</td>
<td>0.58</td>
</tr>
<tr>
<td>SCP time (min)</td>
<td>101 ± 33</td>
<td>100 ± 33</td>
<td>108 ± 30</td>
<td>0.27</td>
</tr>
<tr>
<td>SCP at rewarming (ml/kg/min)</td>
<td>16 ± 1.9</td>
<td>16 ± 1.9</td>
<td>16 ± 1.7</td>
<td>0.76</td>
</tr>
<tr>
<td>Minimal BT (tympanic, °C)</td>
<td>22 ± 1.9</td>
<td>21 ± 1.9</td>
<td>21 ± 1.3</td>
<td>0.08</td>
</tr>
<tr>
<td>/BT at rewarming (tympanic, °C)</td>
<td>22 ± 2.6</td>
<td>22 ± 2.8</td>
<td>22 ± 0.5</td>
<td>0.23</td>
</tr>
<tr>
<td>/BT (tympanic, °C)</td>
<td>2.7 ± 2.4</td>
<td>2.9 ± 1.5</td>
<td>2.3 ± 1.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Hb at rewarming (g/dl)</td>
<td>8.3 ± 0.4</td>
<td>8.7 ± 0.5</td>
<td>7.5 ± 0.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CPB time was significantly longer and Hb at the start of rewarming was significantly smaller in the delayed group than in the normal group.

Figure 2: A strong tendency to have a positive value of %-D in the delayed awakening group. (A). %-D shows a significant positive linear relationship with postoperative wakening time. (B). %-D in the delayed group was significantly higher than in the normal group.
There was no correlation between the rSO2 value at various time points (at the start or end of CPB and SCP) during the surgery and the awakening time. However, %D had a positive linear relationship with awakening time (%D: y = 0.67x - 0.7, r = 0.23, P = 0.007, Fig. 2A). There were significant differences in %D between patients with delayed or normal awakening (%D: delayed group, 7.1 ± 5.1 vs normal group, 1.3 ± 6.6%, P = 0.002, Fig. 2B). The cut-off value of %D for delayed awakening evaluated by ROC curve analysis was 4.6% (AUC = 0.84, Fig. 3).

There were no significant differences in all intraoperative variables but CPB duration and Hb value at the commencement of rewarming between the delayed group and the normal group (CPB time, 221 ± 66 vs 175 ± 48 min, P = 0.03; Hb value at the commencement of rewarming, 7.5 ± 0.5 vs 8.7 ± 0.5 g/dl, P = 0.0001; Table 2). Tympanic temperature at the commencement of rewarming (BTr) and the degree of change in the tympanic temperature in the early period of rewarming (ΔBTr, 10 min since the commencement of rewarming) were 22 ± 2.6°C and 2.7 ± 2.4°C, respectively. And there was no significant differences in both of them between these two groups (BTr, delayed group: 22 ± 0.5 vs normal group, 22 ± 2.8°C, P = 0.23; ΔBTr, 2.3 ± 1.6 vs 2.9 ± 1.5°C, P = 0.19; Table 2). Total SCP flow at the commencement of SCP, at the commencement of rewarming, at the reconstruction of the left subclavian artery and at the reconstruction of the left common carotid artery was not significantly different between these two groups (data not shown).

Two patients (1.4%) died in the hospital. Both of them belonged to the delayed group (awakening time were 12 and 11 h, respectively). One of them was an 80-year-old male who had chronic kidney disease (CKD, stage IV), and a higher EuroSCORE II (8.3). He died of colon necrosis. His %D was 6.3%. Another patient was a 76-year-old male who had CKD (stage IV) and a higher score of EuroSCORE II (8.6). He died of sepsis. His %D was 6.8%.

There were 15 patients with TND (10.5%) and 1 with PND (0.7%). The %D was significantly higher in patients with TND (P = 0.007) but not with PND (P = 0.10). There were significant differences between patients with normal and delayed awakening with regard to in-hospital mortality (P = 0.04), the occurrence of TND, the period of ICU stay (P = 0.04) and hospital-to-home discharge rate (P = 0.03), but not with regard to the occurrence of PND (Table 3).

**DISCUSSION**

Delayed awakening involves diverse factors such as the patient’s physiological background, haemodilution and microembolism. Advances in aortic arch surgery, such as shorter CPB and lower CA time, and the use of SCP and new anaesthetic agents such as remifentanil [15, 16], can reduce the instances of delayed awakening and other neurological disturbances. Our present study found that our patients showed a shorter time to awakening after TAR than previously reported by other studies [17, 18].

Although relationships between neurological complications and rSO2 values or a current baseline rSO2 ratio have been reported [3, 5, 6], these results are difficult to reproduce because rSO2 is affected by many factors, including body temperature, Hb or haematocrit concentration and neuroprotective drugs. Moreover, the absolute

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**Table 3: Postoperative complications**

<table>
<thead>
<tr>
<th>Variables</th>
<th>All (n = 143)</th>
<th>Delayed awakening (-) (N = 129)</th>
<th>Delayed awakening (+) (n = 14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>2</td>
<td>0</td>
<td>2 (14.3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke*, symptomatic</td>
<td>1</td>
<td>0</td>
<td>1 (7.1%)</td>
<td>0.15</td>
</tr>
<tr>
<td>TNDb</td>
<td>15</td>
<td>10 (7.8%)</td>
<td>5 (35.7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Delirium</td>
<td>12</td>
<td>9 (7.0%)</td>
<td>3 (21.4%)</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>1</td>
<td>0</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>1</td>
<td>1 (0.8%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Monoplegia</td>
<td>1</td>
<td>0</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>PND</td>
<td>1</td>
<td>0</td>
<td>1 (7.1%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>1</td>
<td>0</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>5 ± 5</td>
<td>4 ± 5</td>
<td>7 ± 7</td>
<td>0.04</td>
</tr>
<tr>
<td>In-hospital stay (days)</td>
<td>29 ± 29</td>
<td>29 ± 30</td>
<td>29 ± 13</td>
<td>0.95</td>
</tr>
<tr>
<td>Hospital-to-home discharge rate (%)</td>
<td>87 ± 91</td>
<td></td>
<td>57</td>
<td>0.03</td>
</tr>
</tbody>
</table>

PND: permanent neurological deficit; ICU: intensive care unit; TND: transient neurological deficit.
*Stroke: symptomatic cerebral infarction, excluding atrial fibrillation induced cerebral infarction.
*TND: including transient loss of orientation, agitation, slurred speech, much prolonged (over 24 h) delayed awakening.
rSO₂ values differ so widely among individuals that they cannot be used as a reliable indicator of ongoing adverse neurological events. Actually, the significant difference in the absolute values of rSO₂ between the normal and delayed groups was not found all through the operation in our present study (data not shown).

The presence of patients whose %D was higher than the cut-off value (4.6%), but with no significant postoperative neurological problems implies that it is not always easy to discriminate delayed awakening patients only by %D. We found that they had less comorbidity compared with the people in the delayed group. At least, we could predict that the patients with %D lower than 0 would wake early. On the other hand, the patients who had TND or delayed awakening showed a strong tendency to have a positive value of %D. We think it important to realize that %D responds to the actual in

influence of rewarming that aggravate imbalances in the O₂ demand and supply for their brain although it is not always clinically visible. Based on this, it may safely be said that the patients with multicomorbidity and higher %D in TAR might show TND or delayed awakening more frequently.

The new finding of this study was that the rewarming phase in aortic arch surgery was related to awakening time. Basically, early rewarming is important because it contributes to minimizing CPB time [1]. However, rapid rewarming sometimes becomes too aggressive for the patients whose brain cannot tolerate the imbalance of oxygen demand and supply. The degree of change of rSO₂ or %D-decrease, would reflect the influence on the brain and hence might be a good indicator of the perfusion to the brain during rewarming. Many reports have documented that rapid rewarming increases the risk of metabolic brain damage. Ueda et al. reported that rapid rewarming causes functional abnormalities in both endothelial and vascular smooth muscle cells in an experimental model, including diminished responses to acetylcholine, hypercapnia, pinacidil and sodium nitroprusside [8]. The hypothesis that rapid rewarming during the post-hypothermic phase on a brain with damage caused by trauma, ischaemia and any other forms of injury may induce adverse consequences seems consistent with other recent reports where the avoidance of rapid rewarming after hypothermia was recommended [9, 10].

As rewarming begins, the SCP flow is usually increased to 10–12 ml/min/m² to prevent rapid drops in rSO₂, although the total SCP flow is maintained <1200 ml/min to avoid brain oedema [1]. The rSO₂ curve tends to rise in response to this flow in most cases. Based on typical patterns of rSO₂ values, we hypothesized that a steep decrease in rSO₂, which is induced by rapid rewarming and reflects progressive oxygen desaturation in the brain, might be related to neurological disturbance. If rSO₂ values keep dropping after rewarming, we recheck the values of Hb and haematocrit, and flow of SCP as well as the position of the tip of cannula of SCP. If we cannot find the primary reason for the radical drop in rSO₂ during that phase, we stop the rewarming temporarily.

Limitation

This retrospective study investigated patients from a single surgical centre. The monitoring of rSO₂ can miss cerebral adverse events in the non-sampling area and hence cannot inform the causes of unexpected decrease in the absolute value of rSO₂, especially under hypothermia.

In conclusion, the maintenance of rSO₂ at the early phase of rewarming may be important to avoid delayed awakening and TND after TAR.

Conflict of interest: none declared.

REFERENCES