Influence of the Descending Thoracic Aortic Cross Clamping on Bispectral Index Value and Plasma Propofol Concentration in Humans

Manabu Kakinohana, M.D., Ph.D.,* Seiya Nakamura, M.D., Ph.D., † Tatsuya Fuchigami, M.D., Ph.D., ††
Yuji Miyata, M.D., Ph.D., †† Kazuhiro Sugahara, M.D., Ph.D., ‡

Background: In this study, the authors investigated changes in Bispectral Index (BIS) values and plasma propofol concentrations (Cp) after aortic cross clamping in the descending thoracic aortic aneurysm repair surgery during propofol anesthesia.

Methods: Prospectively, in 10 patients undergoing thoracic aortic surgery during total intravenous anesthesia with propofol, BIS values were recorded during cross clamping of the descending thoracic aorta. In this study, the rate of propofol infusion was controlled to keep the BIS value between 30 and 60 throughout surgery. Simultaneously, Cp values in the blood samples taken from the right radial artery (area proximal to cross clamping) and the left femoral artery (area distal to cross clamping) were measured.

Results: Approximately 15 min after initiating aortic cross clamping, BIS values in all cases started to decrease abruptly. Cp values of samples taken from the radial artery after cross clamping of the aorta were significantly (P < 0.05) increased compared with pre–cross clamp values (1.8 ± 0.4 µg/ml), and the mean Cp after aortic cross clamping varied between 3.0 and 5.3 µg/ml. In addition, there were significant differences in the Cp values between radial arterial and femoral arterial blood samples throughout aortic cross clamping. Cp values in samples from the radial artery were approximately two to seven times higher than those from the femoral artery.

Conclusions: This study showed that Cp values increased and BIS values decreased rapidly after aortic cross clamping in thoracic aortic aneurysm repair surgery during propofol anesthesia. These findings suggested that all anesthesiologists should control the infusion rate carefully, taking the abrupt changes in its pharmacokinetics into consideration, especially during cross clamping of the descending thoracic aorta.

Cross clamping of the descending thoracic aorta (DTA) required in DTA or thoracoabdominal aortic surgery causes marked hemodynamic alterations and alteration of organ perfusion. After cross clamping of the DTA, especially, perfusion of organs below the level of the aortic cross clamp, spinal cord, kidney, intestine, and liver was reduced drastically without distal circulatory support, leading to ischemic spinal cord injury, renal failure, and other problems. In addition, placement of the cross clamp on the thoracic aorta during DTA or the thoracoabdominal aortic surgery significantly affects hemodynamics not only by increasing vascular resistance, but also by reducing circulating volume in the area proximal to the aortic cross clamp. In those circumstances, it should be considered that pharmacokinetics of some drugs administered during cross clamping of the DTA are probably altered because of changes in distribution volume and elimination. We experienced a case in which plasma propofol concentrations increased and Bispectral Index (BIS) values decreased rapidly after aortic cross clamping in thoracic aortic aneurysm repair surgery during propofol anesthesia. This phenomenon, however, was not reported until our case was published. Therefore, it is unclear whether this phenomenon observed in our case is consistent in patients undergoing cross clamping of the DTA. In this study, we investigated changes in plasma propofol concentrations and BIS values after aortic cross clamping in thoracic aortic aneurysm repair surgery during propofol anesthesia.

Materials and Methods

After obtaining departmental approval (Department of Anesthesiology, University of the Ryukyus, Okinawa, Japan) and informed consent, we studied 10 patients (American Society of Anesthesiologists physical status II, aged 36–70 yr) undergoing elective thoracic or thoracoabdominal aneurysm repair surgery with femoral vein to femoral artery cardiopulmonary bypass using a pump oxygenator.

After routine monitoring of vital signs was supplemented with Bispectral Index (BIS®) monitoring (Aspect A-2000; Aspect Medical Systems, Newton, MA), anesthesia was induced with 1 mg/kg propofol, 1 mg/kg ketamine, and 1.5–3 µg/kg fentanyl and maintained with infusions of propofol and ketamine and intermittent injections of fentanyl via an upper limb vein. Patients were intubated using a double-lumen endotracheal tube after intravenous infusion of 1 mg/kg suxamethonium. Vecuronium, 0.5 mg/kg, was administered after a compound myogenic action potential by transcranial electrical stimulation was recorded as the control value for transcranial myogenic action potential. All patients were mechanically ventilated to maintain an end-tidal carbon dioxide concentration of 30–35 mmHg. Acetated Ringer’s solution was infused intravenously at 5–8 ml·kg⁻¹·h⁻¹ throughout surgery. Anesthesia was initially maintained with the propofol infusion at a rate of 100 µg·kg⁻¹·min⁻¹ and the ketamine at a rate of 1 mg·kg⁻¹·h⁻¹. The infusion...
rate of propofol was varied to maintain the BIS value between 50 and 60. Patients were placed in a right decubitus position with the lower half of the body rotated posteriorly to facilitate right femoral vessel cannulation. After isolation of both the right femoral artery and vein, the arterial cannula was inserted and then attached to the pump oxygenator. A long venous cannula (Long Cannula RK-28M; Toyobo, Osaka, Japan) was introduced into the right femoral vein, and the tip of this catheter was advanced between the inferior vena cava and right atrium. The tip was confirmed to be correctly positioned by transthoracic echocardiography (ProSound SSD-5500SV; Aloka Co., Mitaka, Tokyo). A Stony incision was used as the surgical approach to the aneurysm. The entire aneurysm was exposed, with tapes applied for multisegmental aortic clamping at intervals of approximately every three vertebral lengths. A full dose of heparin (300 U/kg) was administered. Adjuncts for aortic clamping consisted of normothermic partial femoral vein-femoral artery bypass. The cardiopulmonary bypass circuit was an open system and included a reservoir, oxygenator, and heat exchanger. During the stage of cardiopulmonary bypass for distal perfusion, left ventricular cavity size and function were monitored by transesophageal echocardiography to allow adequacy of preload and optimal fluid resuscitation for maintenance of both upper and lower body perfusion.

In our protocol for anesthesia in this study, the rate of propofol infusion was controlled to keep the BIS value between 50 and 60. Patients were placed in a right decubitus position with the lower half of the body rotated posteriorly to facilitate right femoral vessel cannulation. After isolation of both the right femoral artery and vein, the arterial cannula was inserted and then attached to the pump oxygenator. A long venous cannula (Long Cannula RK-28M; Toyobo, Osaka, Japan) was introduced into the right femoral vein, and the tip of this catheter was advanced between the inferior vena cava and right atrium. The tip was confirmed to be correctly positioned by transthoracic echocardiography (ProSound SSD-5500SV; Aloka Co., Mitaka, Tokyo). A Stony incision was used as the surgical approach to the aneurysm. The entire aneurysm was exposed, with tapes applied for multisegmental aortic clamping at intervals of approximately every three vertebral lengths. A full dose of heparin (300 U/kg) was administered. Adjuncts for aortic clamping consisted of normothermic partial femoral vein-femoral artery bypass. The cardiopulmonary bypass circuit was an open system and included a reservoir, oxygenator, and heat exchanger. During the stage of cardiopulmonary bypass for distal perfusion, left ventricular cavity size and function were monitored by transesophageal echocardiography to allow adequacy of preload and optimal fluid resuscitation for maintenance of both upper and lower body perfusion.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>BW, kg</th>
<th>Duration of Surgery, min</th>
<th>Duration of Anesthesia, min</th>
<th>Level of Aortic Clamp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>M</td>
<td>51</td>
<td>498</td>
<td>720</td>
<td>T9</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>F</td>
<td>44</td>
<td>300</td>
<td>450</td>
<td>T6</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>58</td>
<td>300</td>
<td>348</td>
<td>T6</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>M</td>
<td>85</td>
<td>420</td>
<td>630</td>
<td>T6</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>M</td>
<td>68</td>
<td>255</td>
<td>420</td>
<td>T6</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>M</td>
<td>61</td>
<td>270</td>
<td>405</td>
<td>T7</td>
</tr>
<tr>
<td>7</td>
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<td>M</td>
<td>64</td>
<td>355</td>
<td>480</td>
<td>T10</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>M</td>
<td>48</td>
<td>420</td>
<td>535</td>
<td>T8</td>
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<tr>
<td>9</td>
<td>40</td>
<td>M</td>
<td>58</td>
<td>440</td>
<td>660</td>
<td>T9</td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>M</td>
<td>51</td>
<td>930</td>
<td>1,110</td>
<td>T10</td>
</tr>
</tbody>
</table>

BW = body weight.

was maintained between 50 and 60. The rate of ketamine infusion was consistently 1 mg · kg\(^{-1}\) · h\(^{-1}\) until cross clamping of the aorta and was decreased to 0.5 mg · kg\(^{-1}\) · h\(^{-1}\) thereafter. Fentanyl, 2-3 µg/kg, was administered whenever inadequate analgesia was assessed throughout the surgery.

Blood samples for measuring the plasma propofol concentration were drawn from arterial lines (right radial artery and left femoral artery) before clamping; at 15, 30, and 45 min during clamping; and 15 min after declamping of the DTA. All samples were retained for high-performance liquid chromatography (MC Medical, Inc., Osaka, Japan) analysis.

### Statistical Analysis

Data were analyzed with SPSS software 8.0.1 for Windows (SPSS Institute, Chicago, IL) and are presented as mean ± SD. Propofol infusion rate, BIS values, and plasma propofol concentrations of radial arterial blood were analyzed by means of repeated-measures analysis of variance. When significant, an appropriate multiple comparison method (Dunnett t test) was applied to assess differences between before and during cross clamping of the DTA or after declamping. To compare differences in plasma propofol concentrations between radial and femoral arterial blood at the same time, the unpaired t test was performed. Statistical significance was defined as \(P < 0.05\).

### Results

Data evaluation was performed in 10 patients (table 1). Mean aortic cross clamping time was 98.9 ± 36.5 min. The average maximal perfusion flow rate was 3.0 ± 0.6 l/min at the start of partial cardiopulmonary bypass, and the mean pressure of the distal aorta monitored from femoral arterial pressure was maintained between 50 and 110 mmHg.

An example of typical changes in BIS values and infusion rate of propofol over time is presented in figure 1. Before aortic cross clamping, the mean infusion rate of propofol was 6.2 ± 1.1 mg · kg\(^{-1}\) · h\(^{-1}\), and BIS values
varied between 52 and 64 (fig. 2). In this period, there was no difference in the propofol concentration between radial and femoral arterial blood. Approximately 15 min after initiating aortic cross clamping, BIS values in all cases started to decrease abruptly (fig. 2). Although the infusion rate of propofol was reduced according to our protocol, BIS values kept decreasing, and the minimum BIS values varied between 6 and 38 (figs. 2 and 3 and table 2). Propofol concentrations of samples taken from the radial artery (proximal to aortic cross clamp) after cross clamping of the aorta were significantly increased compared with pre–cross clamping values, and the mean concentrations at 15, 30, and 45 min after aortic cross clamping was 3.4 ± 0.4, 5.3 ± 1.5, and 3.0 ± 0.9 μg/ml, respectively (fig. 4 and table 2). In addition, there were significant differences in plasma propofol concentrations between radial and femoral arterial blood samples throughout aortic cross clamping. Propofol concentrations in samples from the radial artery were approximately two to seven times higher than those from the femoral artery (table 2).

In the postoperative period, none of these patients showed any neurologic deficits, including cerebral infarction, or paraplegia resulting from spinal cord ischemia. Postanesthesia interviews 48 and 72 h after surgery revealed that none of these 10 patients could recall anything in the operating room.

**Discussion**

The current data showed a decrease in BIS values after aortic cross clamping despite reduction of the infusion rate of propofol according to our protocol. Despite the decreases in propofol infusion rate according to our protocol, plasma concentration of propofol in samples from the radial artery (area proximal to the aortic cross clamping) increased to the level of 1.8–4.3 times higher than those before the cross clamping of aorta. Also, plasma propofol concentrations in samples from the radial artery became approximately 2–7 times higher than those from the femoral artery (area distal to the aortic cross clamping) after cross clamping of the DTA. The current study showed data that were consistent with those from our case report, in which BIS values decreased corresponding to the plasma propofol concentration proximal to aortic cross clamping.

The BIS is an empirically derived multifactorial electroencephalographic measurement. The BIS is a dimensionless number between 0 and 100 that correlates with hypnosis. In awake patients, the BIS is between 90 and 100, whereas complete suppression of cortical electrical activity results in a BIS of 0. The BIS is calculated by a proprietary algorithm that combines several features of the electroencephalogram, based on spectral and bispectral electroencephalographic analysis, burst suppression ratio, and a “QUAZI suppression” component into a single numerical value. Therefore, it has been used clinically to guide anesthetic drug administration and to quantify the pharmacokinetic and pharmacodynamic action of anesthetic drugs in the laboratory setting. However, it is well known that BIS values can be affected by factors other than the anesthetic level, including body temperature, cerebral hypoperfusion, and electromyographic activity as a source of interference for BIS monitoring. As for body temperature, although Mathew et al. reported that hypothermia by itself can decrease...
troencephalographic (0.5–30 Hz) and electromyographic (30–300 Hz) signals, causing an increase in the BIS value.14

In general, however, electromyographic signals are considered to increase BIS values because of the overlap of electromyographic and electroencephalographic parameter may be a clinical monitor for detection of severe cerebral ischemia.9–13 In all patients of this study, because pulsation of bilateral carotid arteries was clearly palpable during the cross clamping of the DTA and postoperative neurologic function was normal, it cannot be believed that hypoperfusion in the brain may be associated with this decrease in the BIS value after aortic cross clamping.

Because the electroencephalographic changes with cerebral ischemia are well known, the BIS as a processed electroencephalographic parameter may be a clinical monitor for detection of severe cerebral ischemia.9–13 In all patients of this study, because pulsation of bilateral carotid arteries was clearly palpable during the cross clamping of the DTA and postoperative neurologic function was normal, it cannot be believed that hypoperfusion in the brain may be associated with this decrease in the BIS value.

At our institution, myogenic transcranial motor-evoked potentials (tc-MEPs) were used to monitor the functional integrity of the descending motor pathways during thoracic or thoracoabdominal aneurysm surgery. With this monitoring, muscle relaxation should be controlled to record compound muscle action potentials throughout surgery. Therefore, electromyographic activity might have resulted in a false interpretation of the BIS value in this series. In general, however, electromyographic signals are considered to increase BIS values because of the overlap of electroencephalographic (0.5–30 Hz) and electromyographic (30–300 Hz) signals, causing an increase in the BIS value.14

In addition, a decrease in BIS value recovered corresponding to a reducing the rate of propofol infusion. Therefore, we do not believe that an artifact induced by electromyographic signals was associated with the low BIS value during descending aortic cross clamping.

As discussed previously,7 there are two explanations for the decrease in the BIS value corresponding to an increase in the plasma propofol concentration in the area proximal to cross clamping of the thoracic aorta. After cross clamping of the DTA, blood flow from the heart should be only for perfusion of the area proximal to the cross clamp, e.g., the head, neck, and upper limbs. Considering that blood flow through the DTA was approximately 65–70% of the cardiac output in human subjects,16 it is presumed that cross clamping of the thoracic aorta would change circulatory conditions and reduce circulatory volume to only 30–35% of total circulatory blood volume from the heart in the area proximal to the aortic cross clamp. This change would greatly reduce the distribution volume of propofol infused via the upper limb and result in much higher plasma propofol concentrations in the body proximal to the aortic cross clamp when the infusion rate was set on the basis of body weight.

Another possible explanation for the increase in the plasma propofol concentration in the area proximal to the aortic cross clamp is the reduction of hepatic clearance of propofol. It has been shown that total plasma clearance of propofol in the anhepatic phase was significantly lower than that in the postanhepatic phase during liver transplantation in animal17 and human studies.18 Because cross clamping of the descending aorta ultimately eliminated hepatic blood flow from the heart (area proximal to aortic cross clamp), propofol infused via an upper limb had not reached to the liver. It is thought that this stage of cross clamping of the DTA induces a condition for propofol metabolism, almost the same as the anhepatic phase in orthotopic liver transplantation.

This study has limitations. Because of our protocol approved by our department, the infusion rate of propofol should be reduced gradually according to change of the BIS value. As a result, it is unclear how much the plasma propofol concentration should increase during the de-

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**Table 2. Changes in Propofol Infusion Rates, Bispectral Index Values, and Plasma Propofol Concentrations before, during, and after Cross Clamping of the Descending Thoracic Aorta**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>C15</th>
<th>C30</th>
<th>C45</th>
<th>DC15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol infusion rate, μg · kg⁻¹ · min⁻¹</td>
<td>620 (113.5)</td>
<td>600 (149.0)</td>
<td>130† (58.7)</td>
<td>300† (74.5)</td>
<td>315† (53.0)</td>
</tr>
<tr>
<td>Bispectral Index value</td>
<td>58.5 (3.9)</td>
<td>38.0* (5.7)</td>
<td>22.7† (12.1)</td>
<td>42.4* (3.8)</td>
<td>52.2 (9.7)</td>
</tr>
<tr>
<td>Propofol concentration, μg/ml</td>
<td>Radial arterial blood 1.8 (0.4)</td>
<td>3.4† (0.4)</td>
<td>5.3† (1.5)</td>
<td>3.0† (0.9)</td>
<td>2.3 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Femoral arterial blood 1.8 (0.4)</td>
<td>1.4‡ (0.4)</td>
<td>1.5‡ (0.4)</td>
<td>1.6‡ (0.3)</td>
<td>2.1 (0.6)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

* P < 0.05, † P < 0.01, significant differences in comparison with before. ‡ P < 0.01, significant differences in comparison with plasma propofol concentration of the radial arterial blood.

Before = right before cross clamping; C15 = 15 min after cross clamping; C30 = 30 min after cross clamping; C45 = 45 min after cross clamping; DC15 = 15 min after declamping.
scending aortic cross clamp. In all cases, however, the current data consistently revealed a decrease in BIS value and an increase in plasma propofol concentration in the area proximal to the aortic cross clamp. It is easy to imagine that the plasma propofol concentration in the area proximal to the aortic cross clamp might increase enough to reduce the BIS value to zero without a decrease in infusion rate of propofol after the aortic cross clamp. We speculated that the almost “split circulation” produced by the thoracic aortic cross clamp may be associated, in part, with an increase in the plasma propofol concentration in the upper body. However, there is no evidence in the current study to elucidate whether a “split circulation” should occur during the stage of thoracic aortic cross clamp and cardiopulmonary bypass for distal perfusion. Clarifying this matter would be a new field of research worthy of investigation in the future.

It is known that spinal cord ischemic injury remains the most devastating complication after descending thoracic or thoracoabdominal aneurysm repair. Because tc-MEPs monitor the descending motor system located in the anterior and lateral corticospinal tracts and the anterior horn motor neuronal system, it is a highly sensitive technique to assess spinal cord integrity, identifying insufficient blood flow to the spinal cord through excluded segmental arteries that make a critical contribution to spinal cord perfusion. Recently, tc-MEP monitoring became essential monitoring for spinal cord ischemia during descending thoracic or thoracoabdominal aneurysm repair surgery. Although propofol-based anesthesia is currently considered to be the standard anesthetic regimen for intraoperative monitoring of tc-MEP, its amplitudes were suppressed by propofol in a dose-dependent manner, regardless of the stimulation paradigm. Therefore, we should pay careful attentions to keep an adequate range of propofol concentration during tc-MEP monitoring. According to the current results, if anesthesiologists do not control the rate of propofol infusion after cross clamping of the DTA, the plasma propofol concentration proximal to aortic cross clamping should increase to a level of the isoelectric electroencephalogram and result in abolishing tc-MEPs. In this point, we would like to emphasize that anesthesiologists should control the infusion rate of propofol according to BIS values during descending thoracic or thoracoabdominal aneurysm repair surgery to avoid “false-positive results” in tc-MEP monitoring.

In clinical situations, it is also very likely that the pharmacokinetics of other drugs administered into the upper limb veins would be changed during cross clamping of the DTA. Hence, if anesthesiologists infuse any intravenous drugs (e.g., intravenous anesthetics, muscle relaxants, catecholamine) via the area proximal to cross clamping of the aorta, their plasma concentration would be increased and, as a result, would have an overdosing effect on the organs proximal to the cross clamp. Also, when using a target-controlled infusion system for intravenous anesthetics, it can be expected that there would be a great difference between the effect site concentration and its plasma concentration during cross clamping of the DTA. The current data suggest that BIS monitoring provides an appropriate pharmacodynamic measure to adjust propofol infusion rate during thoracoabdominal aortic aneurysm surgery. Therefore, we emphasize that all anesthesiologists should control the infusion rate carefully, taking into consideration the abrupt changes in pharmacokinetics, especially during cross clamping of the DTA.

References

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