Excessively high systemic blood pressure in the early phase of reperfusion exacerbates early-onset paraplegia in rabbit aortic surgery

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Objective: We have demonstrated that therapeutic augmentation of systemic blood pressure during spinal cord ischemia plays an important role in minimizing spinal cord injury in both experimental and clinical aortic surgery. However, there remain concerns that excessively high blood pressure during spinal cord reperfusion may aggravate the reperfusion injury. The purpose of this study is to investigate the effect of high blood pressure during spinal cord reperfusion on postoperative neurologic outcomes after aortic surgery in rabbits.

Methods: Experiments were performed using a rabbit spinal cord ischemia-reperfusion model in 2 randomly divided groups: (1) In the HR group, the mean blood pressure was maintained at a high level (121 ± 1.3 mm Hg) during reperfusion with intravenously administered phenylephrine; and (2) in the CR group, the mean blood pressure was not medically controlled (75 ± 9.1 mm Hg) during reperfusion. Neurologic and histologic assessments and evaluation of early reperfusion injury were performed.

Results: In the HR group, slow and incomplete recovery of transcranial motor-evoked potentials ($P = .02$) and low neurologic scores ($P < .005$) were observed during spinal cord reperfusion compared with the CR group. At 48 hours of reperfusion, there were significantly fewer viable neuron cells, more apoptosis, and more perivascular edema with gray matter vacuolation in the HR group ($P < .001$ for each). At 3 hours, myeloperoxidase activity ($P = .0021$), vascular permeability ($P = .0012$), and superoxide generation ($P < .0001$) were significantly increased in the HR group.

Conclusion: Excessively high blood pressure in the early phase of spinal cord reperfusion increased reperfusion injury in the spinal cord, leading to exacerbation of early-onset paraplegia. Avoidance of spinal cord reperfusion with high blood pressure may be one management strategy in thoracoabdominal aortic surgery. (J Thorac Cardiovasc Surg 2010;140:400-7)

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Neurologic complications such as paraplegia or paraparesis are still major concerns associated with thoracoabdominal aortic repairs. The incidence of neurologic complications has gradually declined with advances in surgical techniques and several managements, including preoperative identification of the Adamkiewicz artery, mild or deep hypothermia, distal aortic perfusion, segmental aortic clamping, reconstruction of the intercostal or lumbar arteries, cerebrospinal fluid drainage, monitoring of motor-evoked potentials, and pharmacologic agents. However, definite strategies to prevent the intractable complications with high mortality and morbidity cannot be established.

Spinal cord ischemia (SCI) is of primary importance for the development of paraplegia or paraparesis after aortic surgery. It is well known that temporary interruption of blood flow to the spinal cord during an operative procedure such as aortic crossclamping induces irreversible neuron damage in the spinal cord. However, the blood supply to the spinal cord depends on a highly variable collateral system from the systemic circulation.[1] We recently demonstrated that augmentation of systemic blood pressure (BP) during SCI protects the spinal cord and prevents paraplegia after aortic surgery in an experimental model.[2]

It is well known that spinal cord motor neurons are sensitive and vulnerable to any degree of ischemic insult. Early spinal cord reperfusion (SCR) with sufficient blood flow is important to reduce ischemic injury, but the SCR itself may cause spinal cord cell damage, known as "reperfusion injury." Some investigators have suggested that controlled blood perfusion after ischemia may reduce reperfusion injury in various other organs.[3-5] Although Shi and colleagues[6] demonstrated that controlled low-pressure perfusion at the beginning of reperfusion attenuates neurologic injury after SCI, the impact of BP augmentation during SCR and SCI on the spinal cord in aortic surgery still remains controversial.

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Abbreviations and Acronyms

BP = blood pressure
MPO = myeloperoxidase
MTS = modified Tarlov scale
OD = optical density
SCI = spinal cord ischemia
SCR = spinal cord reperfusion
tc-MEP = transcranial motor-evoked potential
TUNEL = terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling

The present study aims to elucidate the effect of high BP during SCR on reperfusion injury in aortic surgery. To focus on the SCR injury (not the SCI injury), we used a rabbit spinal cord ischemia-reperfusion model with a high BP during the SCI for a minimal ischemic injury, based on our recent study.[2]

MATERIALS AND METHODS

Animals

Thirty-six Japanese white rabbits weighing 2.5 to 3.0 kg were obtained from Kitayama Labes Co (Nagano, Japan). The handling of laboratory animals and their use in experiments conformed to the *Guidelines for Animal Experiment at Kobe University Graduate School of Medicine* (permission number: P090309) and the *Guide for the Care and Use of Laboratory Animals* (www.nap.edu/catalog/5140.html).

Surgical Procedure

Experiments were performed using a rabbit spinal cord ischemia-reperfusion model, which we previously described.[7] To establish the SCI, the catheter balloon (Swan–Ganz thermodilution catheter, 93-132-5F; Baxter Health Corporation, Santa Ana, Calif) was fully inflated 0.5 to 1.5 cm distal to the left renal artery for 15 minutes. According to the results of our previous study,[2] the mean BP during the SCI was medically kept at approximately 120 mm Hg for a minimal ischemic injury. After 15 minutes of SCI, the catheter balloon was deflated, and the SCR was performed with an indicated BP that was medically controlled for 15 minutes in its early phase, followed by the natural recovery with no medication until each end point. During the operation, the body temperature was monitored with a rectal thermostat and maintained at 37°C to 38°C using a heating pad.

Experimental Groups

Animals were randomly divided into 2 groups according to the BP level during SCR: 1) the high BP group (HR group), for which the mean BP was maintained at approximately 120 mm Hg by intravenously administered phenylephrine (Neo-Synesin Kowa Injection; Kowa Co, Tokyo, Japan); and 2) the control BP group (CR group), for which the BP was not medically controlled and the mean BP recorded was approximately 80 mm Hg. The mean body weight was not significantly different in both groups.

Neurologic Assessment

Serial assessments of motor function of the hind limbs in all animals were performed at 3, 24, and 48 hours of reperfusion using the modified Tarlov scale (MTS; 0 = no movement, 1 = slight movement, 2 = sits with assistance, 3 = sits alone, 4 = weak hop, 5 = normal hop), as described previously.[7] Animals with an MTS score of 4 or more were considered to be nonparaplegic, whereas those with an MTS score of 3 or less were considered to be paraplegic in this study.

Measurement of Transcranial Motor-Evoked Potentials

Transcranial motor-evoked potentials (tc-MEPs) were recorded during 15 minutes of ischemia and a subsequent 30 minutes of reperfusion, and the recovery ratio of tc-MEP amplitude was measured and analyzed according to our previous report.[2] The baseline of tc-MEPs was defined as an average of 3 consecutive amplitudes recorded before aortic occlusion, and the reappearance was defined as devoid of flat waves in 3 consecutive responses: recovery ratio of tc-MEPs amplitude = (amplitude anterior tibial muscles baseline anterior tibial muscles) × (baseline anterior radial muscles amplitude anterior radial muscles) × 100 (%).

Evaluation of Pathologic Outcome

The spinal cord sections between L3 and L4 were harvested at 3, 24, and 48 hours of reperfusion and stained with hematoxylin-eosin for histopathologic observation, such as motor neuronal viability,[2] perivascular edema, and gray matter vacuolation. To detect DNA fragmentation in cell nuclei, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) staining was performed.[2] Morphometric analyses of spinal cord sections were performed using ImageJ version 1.41 software (National Institutes of Health, Bethesda, Md). Viable neuron cells and TUNEL-positive neurons were counted, and the degree of perivascular edema and gray matter vacuolation were judged by 2 blinded investigators using the following scoring system (0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe).

Western Blot Analysis

Immunoblotting assay was performed according to our previous study.[2] The primary antibody used was mouse anti-rabbit caspase 3 antibody (Millipore Corp, Billerica, Mass), and the secondary antibody used was goat anti-mouse immunoglobulin antibody. The signals were quantified by an image analyzer (LAS-3000; FUJI-FILM Corp, Tokyo, Japan). Blots were subsequently probed for β-actin (Bio Vision Research Products, Mountain View, Calif) as an internal control for equivalent protein loading. The optical density (OD) of each band was measured on the same membrane.

Vascular Permeability Assay

Vascular permeability in the spinal cord at 3 hours of reperfusion was assessed by Evan's blue (Sigma-Aldrich, St Louis, Mo) assay, as previously described with some modification.[8,9] After 15 minutes of reperfusion, Evan's blue (50 mg/kg) was injected into the animals intravenously and they were sacrificed at 3 hours. The spinal cord samples were quantified after formamide extraction (55°C for 2 hours) by measuring absorbance at 595 nm. Data were expressed as the OD per gram of wet tissues.

Myeloperoxidase Activity

Myeloperoxidase (MPO) activity in spinal cords at 3 hours of reperfusion was assessed as previously described,[8,10] with some modification. MPO values were expressed as the change in absorbance at 450 nm/min/g of wet tissue.

Superoxide Generation

Superoxide levels during early reperfusion were evaluated on tissue cryosections of the spinal cord between L3 and L4 at 3 hours of reperfusion as previously described.[2] Dihydroethidium (Invitrogen, Carlsbad, Calif) was used as an oxidative fluorescent dye. Semiquantitative analyses of the superoxide generation were performed using ImageJ software. The average fluorescence intensity was expressed as a fluorescence unit per field.

Statistical Analysis

Database management and statistical analysis were performed with Statview version 5.0 (SAS Institute Inc, Cary, NC). All values are expressed as means ± standard error of the mean. Comparisons between the 2 groups were performed with an unpaired Student *t* test.

RESULTS

Intraoperative Blood Pressure Status

In the present experiments, all animals survived until each end point. The intraoperative BP is shown in Figure 1. There were no statistical differences in the mean BP before and during SCI between the HR and CR groups (before, 81.5 ± 6.6 mm Hg vs 82.3 ± 3.6 mm Hg; during 122.4 ± 1.6 mm Hg vs 122.5 ± 2.8 mm Hg). The mean BP in the early phase of SCR was adjusted at 121 ± 1.3 mm Hg in the HR group, whereas it was 75 ± 9.1 mm Hg naturally in the CR group, with a significant difference according to their definition ($P < .0001$).

Transcranial Motor-Evoked Potential Recovery

The tc-MEPs disappeared immediately after aortic occlusion and reappeared after balloon deflation. The tc-MEP recovery time was 17.3 ± 4.2 minutes in the HR group and 10.0 ± 3.1 minutes in the CR group. There was a tendency for a longer recovery time in the HR group than in the CR group, although statistical significance was not reached (Figure 2, *A*). The recovery ratio of tc-MEP amplitude at 30 minutes of reperfusion in the HR group was significantly lower than in the CR group ($P = .008$; Figure 2, *B*).

Neurologic Outcomes

The MTS scores at 3, 24, and 48 hours of reperfusion are shown in Figure 2, *C*. In the HR group, paraplegia was observed in 44% of rabbits at 3 hours, 83% of rabbits at 24 hours, and 100% of rabbits at 48 hours of reperfusion.

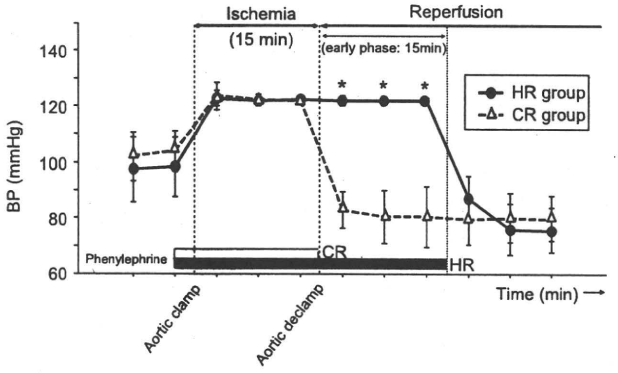

FIGURE 1. Systemic BP during surgery. There were no significant differences in BP during ischemia between the HR and CR groups. In the early phase of reperfusion, BP in the HR group was significantly higher than in the CR group. *$P < .05$. *BP*, Blood pressure; *HR*, high BP group; *CR*, control BP group.

The neurologic score deteriorated with time and were significantly different between the HR and CR groups (3 hours, $P = .0005$; 24 hours, $P = .0032$; 48 hours, $P < .0001$).

Histologic Assessment

At 3 and 48 hours of reperfusion, the number of viable neuron cells in the HR group was significantly less than in the CR group ($P = .0400$ and $P = .0005$, respectively, Figure 3, *A*, *B*), and the degree of perivascular edema and gray matter vacuolation in the HR group was significantly larger than in the CR group (edema, $P = .0100$ and $P < .0001$, respectively, Figure 3, *A*, *C*; vacuoles, $P = .0030$ and $P < .0001$, respectively, Figure 3, *A*, *D*). There were distinct differences between the 2 groups at 48 hours compared with 3 hours of reperfusion.

Spinal Cord Apoptosis

To detect apoptosis in the spinal cord after the SCR, we performed TUNEL staining and Western blot analysis of caspase 3, which is one of the major effectors of neuronal apoptosis.[11] At 48 hours of reperfusion, the number of TUNEL-positive neuron cells in the HR group was significantly more than in the CR group ($P < .0001$; Figure 4, *A*, *B*). Compared with the CR group, the protein expression of caspase 3 was significantly up-regulated in the HR group ($P = .0002$l; Figure 4, *C*, *D*).

Early Reperfusion Injury

The early response of reperfusion injury is generally initiated by increased fluid filtration, calcium influx, and neutrophil accumulation into tissues.[12] We evaluated the level of vascular permeability in the spinal cord by Evan's blue assay and the extent of neutrophil infiltration by MPO assay. At 3 hours of reperfusion, both Evan's blue level and MPO activity in the spinal cord tissues were significantly increased in the HR group compared with the CR group (Evan's blue, 1.97 ± 0.19 OD/g wet tissue vs 0.66 ± 0.12 OD/g wet tissue, $P = .0012$; MPO activity, 0.15 ± 0.26 ΔAbs/min/g wet tissue vs 0.008 ± 0.006 ΔAbs/min/g wet tissue, $P = .0021$; Figure 5, *A*, *B*). To further evaluate the severity of reperfusion injury, we next semiquantified levels of superoxide in the spinal cord by in situ oxidative fluorescent staining. At 3 hours of reperfusion, the intensity of red oxidative fluorescence in the HR group was significantly higher than in the CR group ($P < .0001$; Figure 5, *C*, *D*).

DISCUSSION

Although it is not surprising that early reperfusion is important to reduce reperfusion injury, reperfusion itself could bring irreversible cell damage beyond that caused by the preceding ischemia alone. All organ tissues are susceptible to reperfusion injury, but this susceptibility varies among tissues. Given the delicate nature of arterial supply to the anterior spinal cord, it is well known that motor neuron cells of

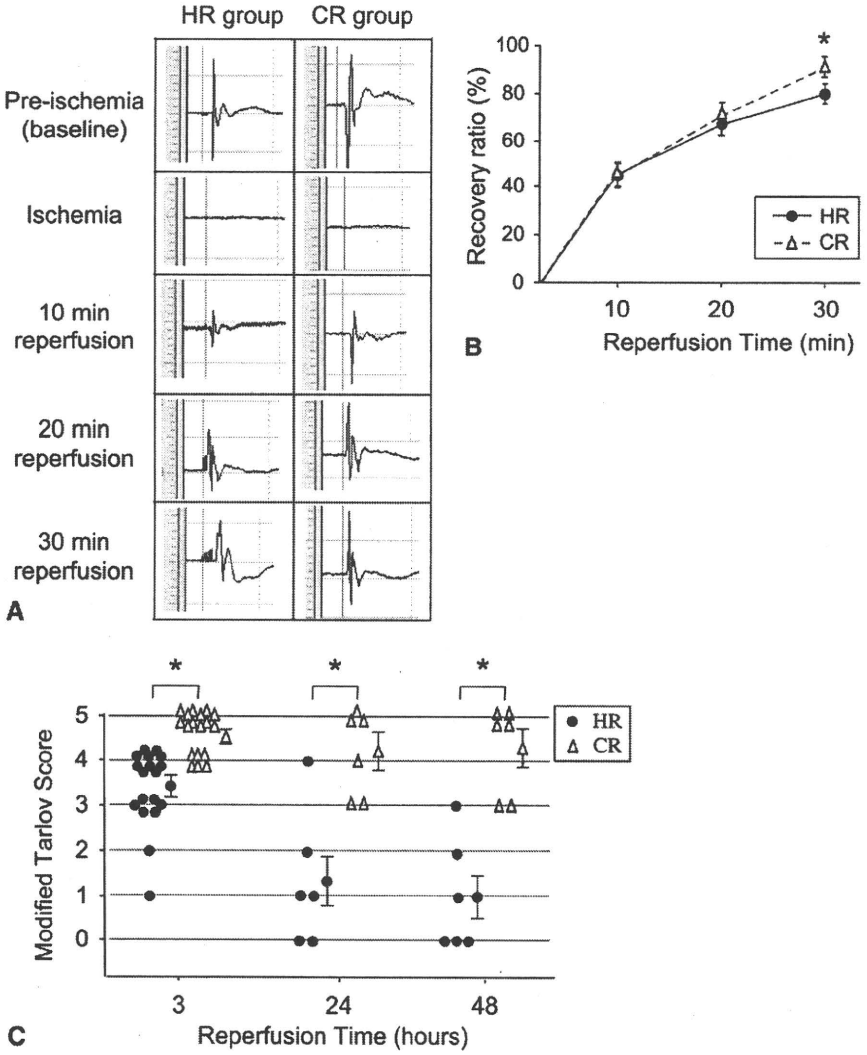

FIGURE 2. Intraoperative and postoperative neurologic assessment. A, Representative tc-MEP complex. B, Recovery ratio of tc-MEP amplitude at 10, 20, and 30 minutes of reperfusion. n = 18 in each group. C, Modified Tarlov score at 3, 24, and 48 hours of reperfusion. n = 18 at 3 hours and n = 6 at 24 and 48 hours of reperfusion in each group. All data are expressed as means ± standard error of the mean (SEM). *$P < .05$. *HR*, High BP group; *CR*, control BP group.

the spinal cord are sensitive and vulnerable to any degree of ischemic insult. In the field of aortic surgery, major intraoperative causes of spinal cord injury are the occurrence of one or more of the following events: (1) the duration and degree of ischemia, (2) the failure to reestablish blood flow to the spinal cord by surgical repair, and (3) the degree of postischemic reperfusion injury.[13] By focusing on the intraoperative management during SCI, we demonstrated that systemic BP augmentation during SCI protected the spinal cord and prevented postoperative paraplegia after aortic surgery in rabbits.[2]

The current study represents a consistent approach to the improvement of strategies to attenuate spinal cord injury in aortic surgery by focusing on the intraoperative management during SCR. Our first concern in the current study was whether subsequent BP augmentation during SCR, as high as during SCI, could have a beneficial effect on the spinal cord in aortic surgery because blood supply to the spinal cord is partially maintained through the collateral circulation. In contrast, some investigators have shown that controlled reperfusion with a low flow or pressure,[4-6] or gradual reinstitution of reperfusion flow,[3] limited reperfusion injury in their setting of experimental ischemia-reperfusion. However, the impact of controlled reperfusion with high pressure on the spinal cord, which has a complex blood supply system during thoracoabdominal aortic surgery, remains unclear. Our recent study[2] showed that rabbits with a BP of 120 mm Hg during the 15-minute SCI had a reduced ischemic insult, resulting in less neuronal damage. By using this model with the same ischemic conditions, we

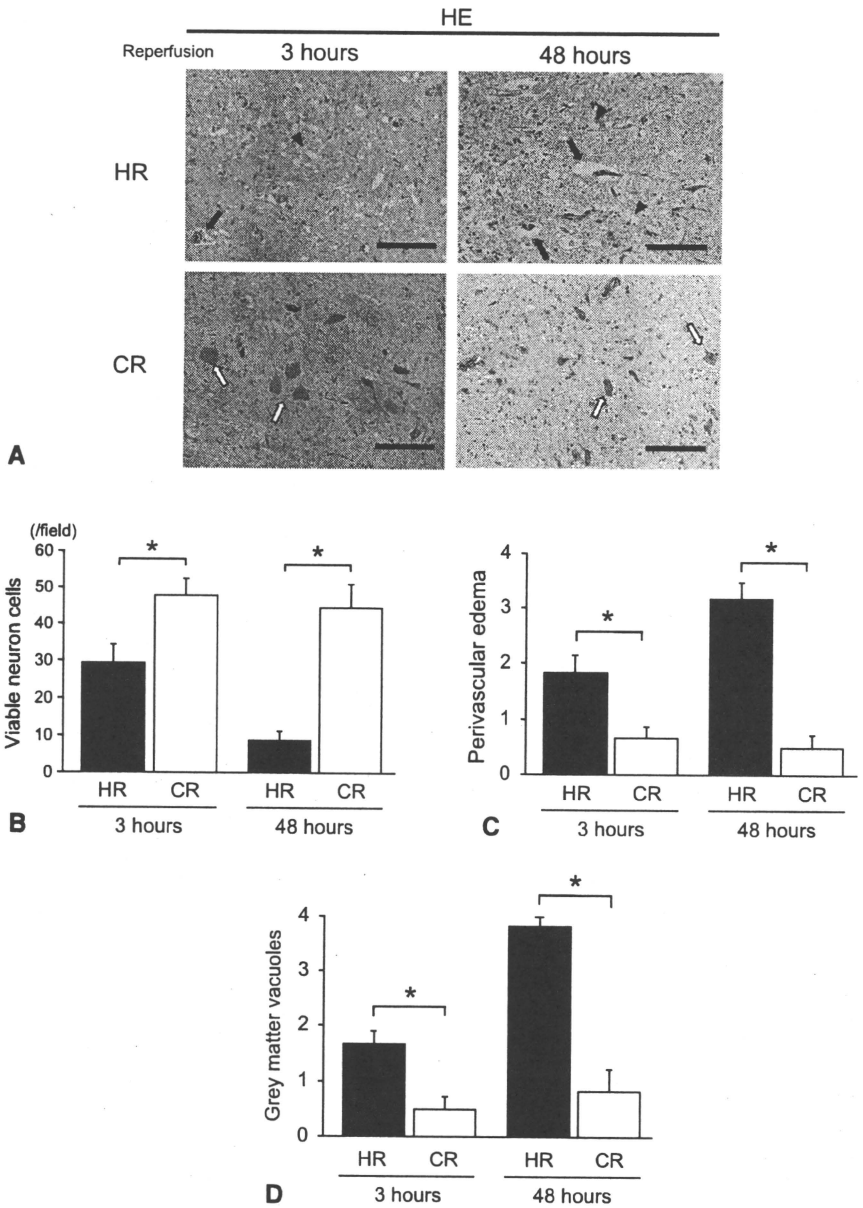

FIGURE 3. Postoperative histologic assessment. A, Hematoxylin–eosin staining in the ventral gray matter of spinal cord at 3 and 48 hours of reperfusion. Photomicrographs of sections show viable neuron cells (*white arrows*), perivascular edema (*black arrows*), and gray matter vacuoles (*black arrowheads*). Bar = 200 μm. Quantitative analyses of viable neuron cells (B), perivascular edema (C), and gray matter vacuoles (D). *$P < .05$. All data are expressed as means ± SEM for n = 6 rabbits. *$P < .05$. *HE*, Hematoxylin-eosin; *HR*, high BP group; *CR*, control BP group.

evaluated the effect of a similarly high BP (120 mm Hg) during SCR on simple reperfusion injury under minimal ischemic insult.

This study demonstrated that a high mean BP of 120 mm Hg (~>1.5 times the normal) in the early phase of reperfusion has disadvantageous effects on the spinal cord, in contrast with beneficial effects of a high BP during SCI in our previous study.[2] Because the normal mean BP in conscious rabbits ranged from 64.4 to 66.0 mm Hg in our previous model,[2] the 120-mm Hg BP in rabbits might correspond to excessively high BP in humans. In neurologic assessment, the high BP in the early phase of SCR caused a slow and incomplete Tc-MEP recovery followed by a decreased modified Tarlov score at 3 hours of reperfusion. Neurologic events after aortic surgery are well known as 2 chronologically distinct entities: early- or delayed-onset neurologic deficit. An early-onset deficit is recognized immediately after operation, whereas a delayed deficit

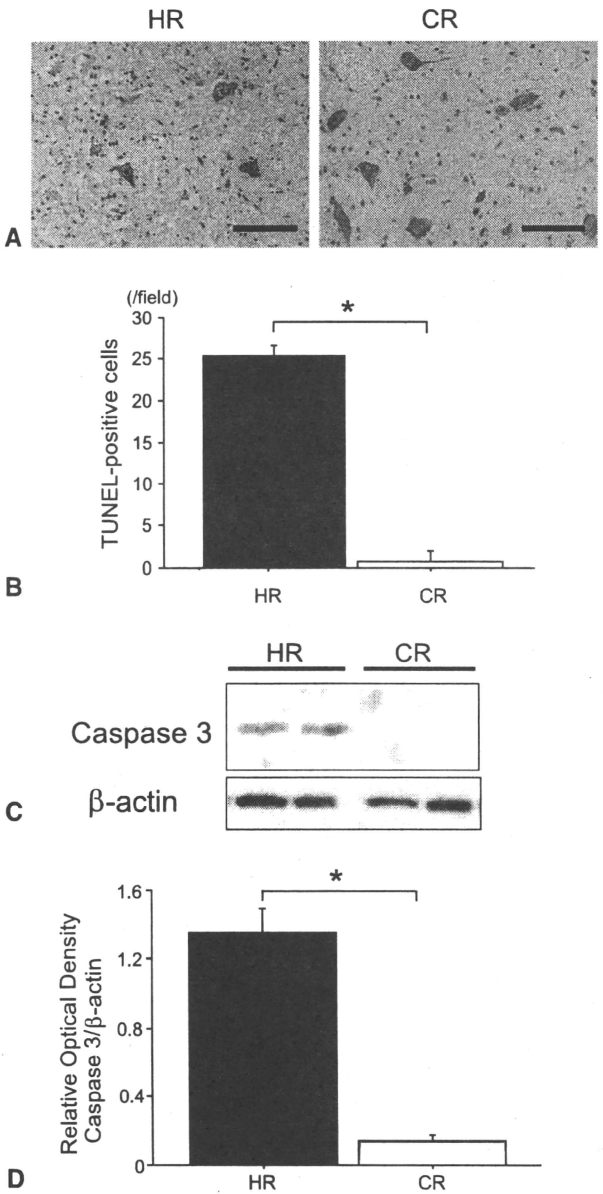

FIGURE 4. Postoperative evaluation of spinal cord apoptosis. A, TUNEL staining of the ventral gray matter of spinal cord at 48 hours of reperfusion. Photomicrographs of sections show TUNEL-positive cells (*brown*). Bar = 200 μm. B, Quantitative analysis of TUNEL-positive neuron cells at 48 hours of reperfusion. C, Western blot analysis of caspase 3. D, Relative OD of caspase 3 in each group. All data are expressed as means ± SEM for n = 6 rabbits. *$P < .05$. *TUNEL*, Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling; *HR*, high BP group; *CR*, control BP group.

develops anytime after 1 day postoperatively.[14] Our results suggest that the high BP in the early phase of SCR may be related to the exacerbation of early-onset paraplegia.

Tc-MEPs reflect the functional integrity of motor neuron pathways and promptly respond to ischemia in the spinal cord. Tc-MEPs disappear soon after SCI and recover to a certain level during SCR. Our previous study demonstrated that the recovery ratio of tc-MEP amplitude is positively correlated to the MTS and the number of viable neuron cells in the anterior horn of the spinal cord.[7] In this study, the recovery ratio of tc-MEPs in the HR group was significantly lower than in the CR group. This precise profile of tc-MEPs is one of the strong pieces of evidence that high BP in the early phase of SCR may be associated with the incidence of postoperative paraplegia. Notably, tremor of the hind limbs was observed in the early phase of reperfusion in almost all cases in the HR group, and the degradation of tc-MEP was observed after its maximal recovery in some cases in the HR group. These findings in the early phase of reperfusion may be important. However, further studies of tc-MEPs are needed throughout the SCR period.

In histologic assessment, there were fewer viable neuron cells and more TUNEL-positive cells in the anterior horn of the spinal cord in the HR group compared with the CR group. To further evaluate spinal cord apoptosis, we performed Western blotting of caspase 3. Ischemia by itself can trigger apoptosis and reperfusion accelerates the process,[15] and apoptosis has been shown to be an important mode of earlier neuronal damage in the spinal cord after ischemic insults.[16] This study shows that the neurologic score at 48 hours was worse than at 3 hours and that apoptosis was significantly more severe at 48 hours, suggesting that the acceleration of spinal cord injury may have been mainly caused by apoptosis.

Microscopic neuron cell damage by BP augmentation has also been shown as perivascular edema and gray matter vacuolation in this study. Because reperfusion in a form of hyperperfusion induces secretion of more inflammatory and vasodilatory substances, such as bradykinin, arachidonate, and superoxides,[17] those findings might be the result of reperfusion hyperemia and free radical generation. Early reperfusion injury triggers an endothelial barrier dysfunction, characterized by neutrophil infiltration and increased vascular permeability caused by oxidative stress.[12] The present study showed that the high BP in the early phase of SCR promoted an oxidative inflammatory cascade involving the enhancement of vascular permeability, MPO activity, and superoxide generation. These findings suggest that increased oxidative stress by the BP augmentation in the early phase of SCR may contribute to the mechanism of early-onset paraplegia.

It is generally believed that systemic hypotension has adverse effects on delayed paraplegia after aortic surgery, whereas systemic[18-21] hypertension has an effective role. Our previous clinical research also demonstrated that the duration of hypotension after weaning from bypass was an independent risk factor for paraplegia in patients undergoing thoracoabdominal aortic repair.[22] However, Shi and colleagues[6] reported that low-pressure perfusion for 10 minutes at the beginning of reperfusion attenuated neurologic deficits

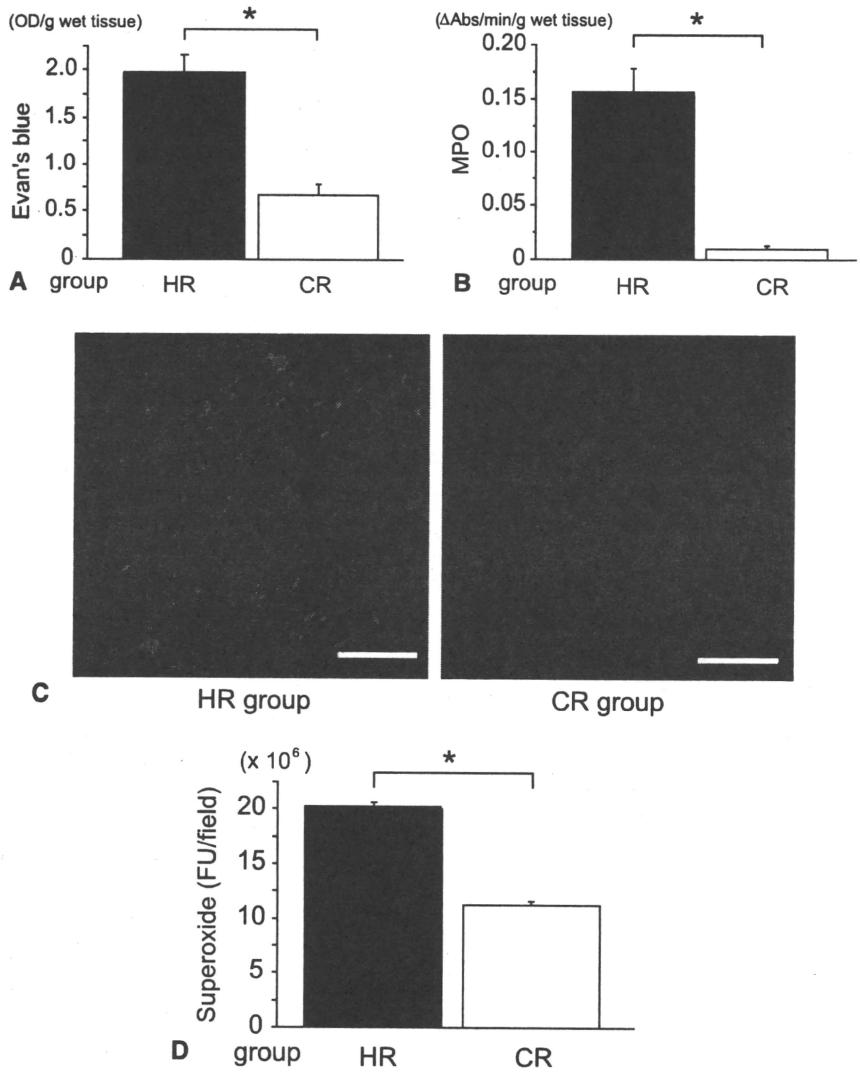

FIGURE 5. Early reperfusion injury in the spinal cord at 3 hours of reperfusion. A, Vascular permeability. B, MPO activity. *ΔAbs* indicates a change in absorbance. C, In situ detection of superoxide generation (*red fluorescence*). Bar = 200 μm. D, Semiquantitative analysis of the superoxide generation. All data are expressed as means ± SEM for n = 6 rabbits. *$P < .05$. *OD*, Optical density; *MPO*, myeloperoxidase; *FU*, fluorescence unit; *HR*, high BP group; *CR*, control BP group.

after ischemia. Furthermore, we showed that high-pressure perfusion for 15 minutes in the early phase of reperfusion exacerbated neurologic deficits in the present study. These discrepancies in the effects of controlled BP during SCR on spinal cord injury seem to be associated with the timing and duration of the controlled BP. We believe that both avoidance of reperfusion injury and maintenance of optimal blood flow to the spinal cord during reperfusion are crucial factors to prevent postischemic paraplegia. Therefore, excessively high BP should be avoided in the early phase of reperfusion, but sufficient BP for spinal cord blood flow may be required during reperfusion. Further investigation is necessary to elucidate the relationship between the BP management during reperfusion and the spinal cord injury in aortic surgery.

We have reported that the proximal mean arterial pressure was clinically maintained between 60 and 100 mm Hg and that the distal perfusion pressure was kept at more than 70 mm Hg during aortic crossclamping.[2,22] By taking the idea from this study and relating it to the clinical setting, excessive BP augmentation immediately after aortic unclamping, particularly when reconstructing the intercostal or lumbar pivotal arteries (which has the potential to provide excessive blood flow), might worsen the early reperfusion injury in aortic surgery. Our previous study indicated that BP augmentation by distal aortic perfusion using left-sided heart bypass or partial cardiopulmonary bypass during SCI caused by aortic crossclamping may decrease the incidence of spinal cord injury after paraplegia.[22] Because the increased

collateral blood flow solely maintains a sufficient blood supply to the spinal cord during aortic clamping, BP augmentation during SCI should be important in protecting the spinal cord. BP augmentation during SCR might not only increase direct blood flow through the reconstructed intercostal arteries but also increase collateral flow to the spinal cord, boosting the reperfusion injury. Subsequently, avoidance of SCR with high BP immediately after aortic unclamping might create a more sophisticated protection of the spinal cord in aortic surgery.

Study Limitations

The rabbit SCI model had less ischemic injury with a high BP during the SCI, according to our previous study.[2] This model enabled the discovery of a potential management strategy to better protect the spinal cord in aortic surgery. The conditions of this model, including the duration and level of BP during the SCI or SCR, were determined according to the previous study. Therefore, the optimal duration or level of BP during the SCR was not evaluated in the present study. There are some differences in vascular anatomy and clinical response to the SCI and SCR between rabbits and humans. In rabbits, there are some collaterals from pial anastomoses via the posterior spinal artery to the lumbar cord, but the caudal blood flow is mainly from the segmental arteries.[23] On the other hand, there are many collaterals from the lumbar and internal iliac arteries via the anterior spinal artery to the caudal spinal cord in humans.[23,24] We did not completely assess the delayed-onset neurologic deficit in the present study. Although there seems to be a main concern that pharmacologic intervention with phenylephrine may have produced severe vasoconstriction that leads to SCI by constricting the arteries supplying the spinal cord, our previous study[2] demonstrated that the mean BP of 120 mm Hg induced by phenylephrine did not alter the spinal cord blood flow compared with preintervention. In addition, Lindsberg and colleagues[25] reported that pharmacologic infusion of phenylephrine does not constrict spinal arteries severely enough to produce SCI.

CONCLUSIONS

High BP in the early phase of SCR deteriorated early reperfusion injury in the spinal cord, leading to exacerbation of early-onset paraplegia in rabbits. The present study suggests that it may be important to avoid excessive BP augmentation immediately after aortic unclamping for spinal cord protection and that totally coordinated BP management during both SCI and SCR may reduce postoperative neurologic complications in thoracoabdominal aortic surgery.

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Minimizing Cerebral Embolism in Resection of Distal Aortic Arch Aneurysm Through a Left Thoracotomy

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Background. In order to reduce the risk of cerebral embolism during aortic replacement through a left thoracotomy, we performed ascending or arch aortic cannulation (AAC) as well as early extracorporeal perfusion (EEP) under deep hypothermic circulatory arrest (DHCA). In this study we examined the effectiveness of these modifications in preventing cerebral embolism after distal arch replacement.

Methods. Between January 2006 and March 2010, 40 patients underwent distal arch replacement through a left thoracotomy, using 2 pieces of an artificial graft. In all patients, AAC, EEP, and the open technique for aortic anastomosis were performed under DHCA. The AAC resulted in the proximal aortic perfusion from the proximal site of the diseased aorta. The EEP was induced by aortic distal perfusion from the side branch of a distal graft. After completion of the proximal anastomosis under EEP and DHCA, anastomosis between the proximal and distal grafts was made during rewarming. Neurologic deficit in the brain and spinal cord, as well as early surgical results, were clinically evaluated.

Results. There was no permanent neurologic deficit after the surgery in the operative survivors. No patient had a stroke (0%). Temporary paraplegia and paraparesis occurred in 1 and 2 patients, respectively (7.7%); all 3 patients were able to walk prior to their discharge from hospital. Mortality in this series was 5.0% (2 of 40 patients); the cause of death was rupture of an esophageal ulcer and cardiogenic shock possibly due to myocardial infarction.

Conclusions. The AAC and EEP, in addition to deep hypothermia and DHCA, minimized the risk of cerebral embolism after distal arch aortic replacement by the left lateral approach.

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Aortic replacement with an artificial graft through a left thoracotomy is the gold standard for the radical treatment of distal arch and descending aortic aneurysms [1–4]. Despite advances in surgical technique and the development of new devices, postoperative cerebral and spinal cord disorders are still a major problem. Recent publications report a stroke rate of 4.0% to 5.0% after thoracic aortic replacement by the left lateral approach utilizing deep hypothermic circulatory arrest (DHCA) [2, 5]. These outcomes compare unfavorably with the excellent results after ascending or arch replacement using the median sternotomy approach, and therefore much more effort has to be made to reduce the cerebral complications after distal arch replacement.

Deep hypothermia and DHCA is widely used in aortic surgery because of its organ protective effects, as well as because it allows the use of an open technique for aortic anastomosis without cross-clamping. We have previously reported two modifications to prevent cerebral complications, but we have not yet evaluated their effectiveness [6, 7]. One of the modifications is to perform ascending or arch aortic cannulation (AAC), which makes it possible to maintain antegrade aortic perfusion from the proximal site of an aneurysm or entry site of dissection as well as to flush the embolic materials beyond the distal arch at the time of reperfusion. The other modification is to induce the backward flow from the aortic arch branches by early extracorporeal perfusion (EEP) from the side branch of the aortic distal graft. The backward flow from the aortic arch branches, which would be similar with retrograde cerebral perfusion, leads to the prevention of a cerebral embolism due to atheromatous debris and (or) thrombus.

In this study we examined the effectiveness of these two modifications, in addition to deep hypothermia and DHCA, in reducing the risk of cerebral embolism after distal arch replacement through the left lateral approach. In addition, we investigated the adverse outcome after this surgery including the incidence of spinal cord disorders, renal failure, and mortality.

Material and Methods

Patients

Between January 2006 and March 2010, adult patients who underwent aortic replacement from the distal arch to the

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descending or thoracoabdominal aorta through a left thoracotomy approach were eligible for enrollment in this study. Retrospective review of this database and patient consent were approved by the Institutional Ethics Committee at Osaka Medical College Hospital. Cardiopulmonary bypass (CPB), open proximal, and distal aortic anastomosis under DHCA, AAC, and EEP during the open proximal anastomosis, were performed in all patients.

The severity of the patients' aortic wall characteristics were also reported according to the following definitions. (1) "Severe"; a notched aortic wall surrounded by hard and soft atheromatous plaque and large amount of thrombus. (2) "Mild"; atheromatous formation and thrombosis adhesion was observed in the aortic wall, but the aortic wall was relatively smooth. (3) "Moderate"; findings of the aortic wall were between mild and severe.

Establishment of CPB

A double-lumen endotracheal tube was used to allow collapse of the left lung. Patients were placed on the operating table in the right lateral position. A left thoracotomy was then performed through the fourth intercostal space. If necessary, the sternum was transected. The left internal thoracic artery was harvested and divided. The fifth rib was routinely excised to increase exposure. The extended left thoracotomy provided access to the entire thoracic aorta, including the ascending aorta.

Arterial return was first established with the Sarns high-flow aortic cannula (Termo; Hatagaya, Tokyo, Japan) or DLP aortic cannula (Medtronic, Higashi-Shinbashi, Tokyo, Japan) in the proximal site of the aneurysm and intimal tear in the ascending or arch of aorta. The cannulation sites were chosen to avoid potential embolic materials, where the manual palpation of the aorta was performed for calcification. Venous drainage to the pump oxygenator was performed with a long straight femoral venous cannula (24 or 28 Fr) (Edwards Lifesciences, Irvine, CA) into the right atrium through the left femoral vein. A venting tube was inserted into the right ventricle through the main pulmonary artery. When the long straight cannula could not reach the right atrium through the left femoral vein, a right-angled DLP venous cannula (40 Fr) (Medtronic) was inserted into the right ventricle through the pulmonary artery. The CPB was established, maintaining a flow of 2.4 $L \cdot min^{-1} \cdot m^{-2}$, and cooling was started to reach a rectal temperature of 18°C. Meanwhile, the left phrenic and left recurrent laryngeal nerves were identified, mobilized from the aneurysm, and protected.

Deep Hypothermic Circulatory Arrest With Early Extracorporeal Perfusion

The schema for the operating procedure is shown in Figure 1. With a rectal temperature of 18°C, the descending aorta was clamped at a position furthest from the distal arch and the aneurysm, and CPB flow was decreased to 1.0 to 1.5 $L \cdot min^{-1} \cdot m^{-2}$ to maintain the cerebral and myocardial flow. Under DHCA, after re-

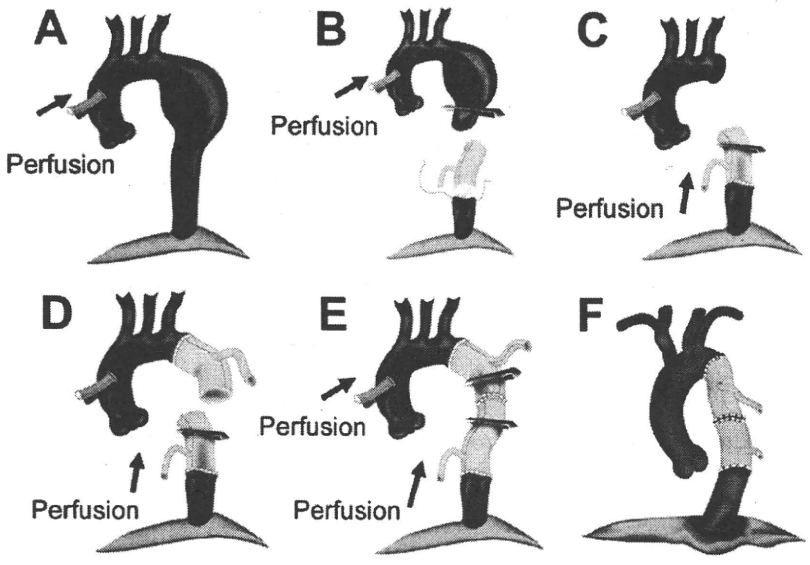

Fig 1. Schematic diagrams of the operative procedure. (A) Ascending or arch aortic cannulation (AAC) was performed to maintain antegrade flow. After establishment of cardiopulmonary bypass, cooling was begun to achieve a rectal temperature of 18°C. (B) After aortic cross-clamping of the descending aorta, an open distal anastomosis was made using a vascular graft with a single side branch. Cerebral and myocardial perfusion was maintained. (C) After clamping of the vascular graft, the aortic perfusion was switched to the single side branch of the graft. Early extracorporeal perfusion (EEP) from the side branch of the distal graft (1.5 to 2.0 L/minute) was started to induce backward flow from the arch branches as well as to maintain the flow in the lower torso. (D) After establishment of EEP, an open proximal anastomosis was made under deep hypothermic circulatory arrest (DHCA). (E) The anastomosis between the proximal and the distal vascular graft was made after reperfusion from the AAC. Aortic replacement was achieved, and rewarming of the body temperature was started. (F) Completion of the aortic replacement.

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moval of embolic materials, the descending or abdominal aorta was trimmed for the distal anastomosis. In case of communicating dissection, aortic fenestration was performed to maintain communication between the true and false lumens.

The open distal anastomosis was made using a gelatin-sealed vascular graft with a single side branch, (Gelweave; Vascutek, Vascutek Termo, Renfrewshire, Scotland) (Fig 1B). The Sarns flexible arterial cannula (Termo, Hatagaya) was connected to the single side branch of the vascular graft for aortic distal perfusion. After removing air from the distal anastomosis site, aortic distal perfusion was restarted toward the lower torso at a speed of 1.5 to 2.0 L/minute. The aortic distal perfusion was performed in order to maintain distal circulation including to the kidneys, abdominal organs, and lower extremities, as well as to induce backward flow from arch branches. We named this distal perfusion "early extracorporeal perfusion" (EEP). After the arterial perfusion from AAC was stopped, the aneurysm was opened longitudinally. At this time, the continuous backward blood flow due to EEP could be observed from the aortic arch branches and the distal arch of the aorta was trimmed. During EEP, central venous pressure (CVP) was maintained between 3 and 7 mm Hg by controlling venous drainage (Fig 1C). The proximal anastomosis was made using the other vascular graft with a single side branch in the same manner as for the distal anastomosis. After completion of the anastomosis, arterial perfusion from AAC was restarted in order to flush out potential embolic materials (Fig 1D). While aortic perfusion from both AAC and the single side branch of the distal graft was started with 2.4 $L \cdot min^{-1} \cdot m^{-2}$ of CPB flow, the anastomosis between the proximal and distal vascular graft was carried out (Fig 1E, F). When reconstruction of the left subclavian artery was necessary, the single side branch of the proximal vascular graft was used. After completion of the aortic reconstruction, rewarming was initiated up to a rectal temperature of 35°C and the patient was weaned off CPB. During these procedures, cardioplegic solution was not used (deep hypothermic ventricular fibrillation). Intercostal arteries were ligated and not reconstructed in all patients. During the surgery we used INVOS cerebral oximeter (Somanetics Corporation, Troy, MI) as a monitor for cerebral ischemia. Motor evoked potentials and somatosensory evoked potentials were not measured as monitors for spinal cord ischemia. We did not perform cerebrospinal fluid drainage; however, cooling to a rectal temperature of 18°C and EEP were both performed to ensure spinal protection. Neurologic deficit in the brain and spinal cord, as well as early surgical results, were clinically evaluated by reviewing the medical records. Data are presented as means ± standard deviation.

Results

Patient Characteristics

During the time period of our study, thoracic aortic replacement by a left lateral approach was carried out in 77 patients; however, of these 77 patients, 37 were excluded from the study cohort for the following reasons: descending aortic replacement far from the distal arch (n = 30); proximal anastomosis at distal arch replacement without open technique (n = 4); and high-risk patients who underwent stent graft replacement into the elephant trunk after total arch replacement (n = 3). Thus, ultimately, our study population comprised a cohort of 40 patients. Preoperative patient characteristics are shown in Table 1.

Table 1. Preoperative Patient Characteristics

Characteristics	Patients, n (%) (n = 40)
Age (years)	65.0 ± 13.3
Gender (male)	29 (72.5%)
Hypertension	22 (55.0%)
Smoking history	23 (57.5%)
Chronic obstructive pulmonary disease	2 (5.0%)
Marfan syndrome	4 (10.0%)
Prior aortic surgery	8 (20.0%)
Modified Bentall operation	1 (2.5%)
Ascending aortic replacement	2 (5.0%)
Abdominal aortic replacement	4 (10.0%)
Prior cardiac surgery	2 (5.0%)
Coronary artery bypass grafting	1 (2.5%)
Aortic valve replacement	1 (2.5%)
Stroke history	2 (5.0%)
Prior dialysis-dependent renal insufficiency	0

Surgical Results

With regard to etiology and mode of presentation, 24 cases (60.0%) were aneurysms and 16 (40.0%) were chronic dissections. There was 1 (2.5%) emergency case; this concerned a case of rupture in a patient who was taken to the operating theatre as an emergency.

Arterial cannulation site, extent of the aortic disease, and the range of graft replacement are shown in Figure 2. The AAC from the proximal site of the diseased aorta was achieved in all patients. The choice of cannulation site was made by intraoperative manual palpation and based on the findings of a preoperative computed tomography.

The mean total CPB time was 294.7 ± 57.8 minutes, the mean deep hypothermic ventricular fibrillation time was 204.4 ± 52.7 minutes, and the mean EEP time was 38.7 ± 9.5 minutes. This all corresponded to DHCA time of the upper torso; the mean DHCA time of the lower torso was 34.7 ± 12.5 minutes.

All 40 patients underwent aortic replacement from the distal arch to the descending or thoracoabdominal aorta. Four patients underwent reconstruction of the left subclavian artery. One patient underwent reconstruction of the left subclavian and cervical arteries. Two patients underwent extended aortic replacement, including the abdominal aorta, through the diaphragm. Fenestration of the intimal flap was made in the descending aorta in 3 patients who had communicating aortic dissections.

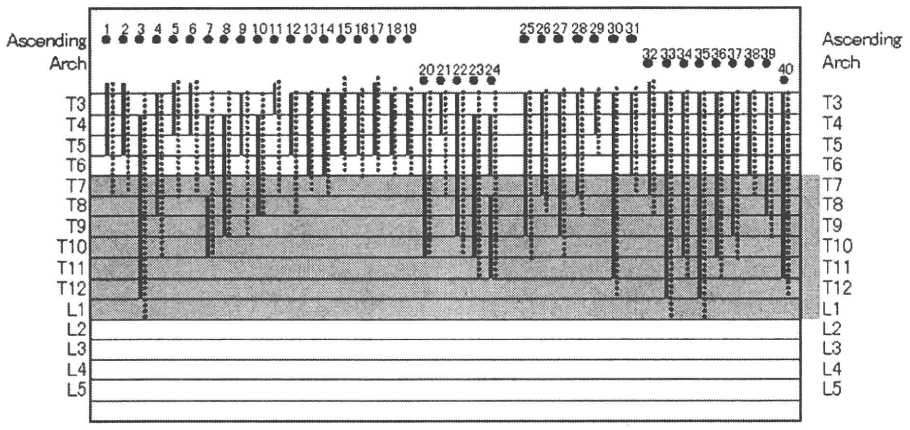

Fig 2. Aortic cannulation site, distribution of aortic disease, and range of aortic replacement. Ascending or arch aortic cannulation (AAC) was performed from the proximal site of the aortic disease. The patients from No. 1 to No. 24 had a nondissecting aneurysm; the patients from 25 to 40 had chronic dissection. The range between T7 and L1, in which the Adamkiewitz artery is considered to exist, is shown in gray. All intercostal arteries were sacrificed in all patients under deep hypothermia. (Black dot = arterial cannulation site; black line = extent of aortic disease; dotted line = range of the aortic replacement.)

The severity of aortic wall characteristics around the arch and distal arch is known to be associated with the incidence of postoperative cerebral embolism. We evaluated the severity of aortic wall characteristics in our patient series by reviewing the operative records of all patients and dividing them into 3 groups depending on the severity of the aortic wall characteristics. The numbers of patients within each classification are presented in Table 2 for the aneurysm and dissection groups, respectively.

Postoperative Outcome

No patient had permanent focal neurologic deficit after surgery. The range of aortic replacement is shown in Figure 2. Intercostal arteries existing within the range of aortic replacement were sacrificed in all patients. The range between seventh thoracic vertebra (T7) and first lumber vertebra (L1) levels are shown in gray in Figure 2. Thirty-four patients (85.0%) were included in this area and distal aortic replacement beyond T10 was observed in 13 patients (33.3%). No patient had permanent spinal cord complications. However, temporary paraplegia and paraparesis occurred in 1 and 2 patients, respectively (patient Nos. 25, 30, and 37). The cause of the temporary spinal cord complication in the 2 patients (Nos. 25 and 30) was considered to be clinical and caused by ischemia of the Adamkiewitz artery during the aortic replacement, possibly due to steal phenomena and severe aortic regurgitation, respectively.

Table 2. Aortic Wall Characteristics at Distal Arch

	Patients, n (%) (N = 40)	
Severity	Aneurysm Group	Dissection Group
Severe	14 (35.0%)	5 (12.5%)
Moderate	4 (10.0%)	2 (5.0%)
Mild	6 (15.0%)	9 (22.5%)
Total	24 (60.0%)	16 (40.0%)

Repetitive ventricular tachycardia at the time of weaning from CPB was seen in 1 patient (2.5%). Three patients required temporary continuous hemodiafiltration after surgery due to a decrease in urine output (7.5%). No patient needed permanent hemodialysis. Two patients (5.0%) required tracheostomy due to prolonged mechanical ventilation. Mean duration of mechanical ventilation was 2.6 ± 1.7 days and mean length of intensive care unit stay was 5.0 ± 2.3 days. Mortality in this study was 5.0% (2 of 40 patients). The cause of death in these 2 patients was frequent ventricular tachycardia at the time of CPB weaning possibly due to myocardial infarction, and perforation of a huge esophageal ulcer with rupture of a methicillin-resistant Staphylococcus aureus infectious pseudoaneurysm.

Comment

Deep hypothermic circulatory arrest provides organ-protective effects by reducing the metabolic rate in organs and allows us to perform an "open technique" for aortic anastomoses without cross-clamping. In addition, we have routinely introduced AAC as well as EEP in patients requiring distal arch replacement through the left lateral approach. Arch aortic cannulation results antegrade aortic perfusion from the proximal site of the diseased aorta and the flushing of embolic materials after completion of the proximal anastomosis at the distal arch. EEP also results in the prevention of cerebral embolism in the arch branches. In this series, although temporary spinal cord disorders were observed in 3 patients (7.7%), no patient experienced a permanent neurologic deficit. This was due to fact that the surgical procedures were able to shorten ischemic time of the lower torso and spinal cord compared with standard

DHCA (cerebral circulatory arrest) on its own. Thus our two modifications, used alongside DHCA, minimized the risk of cerebral embolism and allowed for complete aortic resection, including the aortic cross-clamp site after thoracic aortic replacement through a left lateral approach. This method will be applicable particularly to patients at high risk of ischemic and embolic complications, such as those with severely athermanous aortas and complex aortic pathology prohibiting proximal cross-clamping.

The importance of antegrade aortic perfusion and the aortic cannulation site has been underestimated during thoracic and thoracoabdominal aortic surgery through the left lateral approach. Cerebral complications occur in 9% of patients after thoracic and thoracoabdominal aortic replacement using DHCA [1]. Although the femoral artery is generally chosen as an aortic cannulation site, aortic perfusion from the femoral artery results in retrograde aortic perfusion, which carries a risk of emboli entering into the arch branches and malperfusion of the dissected aorta. However, little is known about differences in cerebral complications in relation to the aortic cannulation site used in the left lateral approach. We have previously shown that antegrade aortic perfusion by AAC decreases the incidence of neurologic deficit to 7% compared with 28% using retrograde aortic perfusion by femoral artery cannulation [8]. Based on this evidence, we advocate using AAC in the left lateral approach.

In addition to AAC, under DHCA, we also established EEP during the open proximal anastomosis at the distal arch. Although, in part, EEP is similar to the original retrograde cerebral perfusion (RCP) reported by Ueda and colleagues [9] and Takamoto and colleagues [10], the method and degree of increase in CVP, and the purpose, all differ. Thus, in order to increase cerebral perfusion and prevent embolism, RCP is performed by elevating CVP over 15 mm Hg and this high level has been associated with postoperative cerebral edema leading to neurologic dysfunction. In contrast, the EEP used in this series was induced by aortic distal perfusion toward the lower torso from the single side branch of the distal graft. The aortic distal perfusion was also able to maintain antegrade aortic perfusion resulting in backward flow from the arch branches. The CVP levels were maintained between 3 and 7 mm Hg by controlling venous drainage and thus were relatively low compared with RCP. We would emphasize that this technique was used not to increase the cerebral blood flow during DHCA but to prevent emboli entering the arch branches. Importantly, there was no neurologic deficit in the brain postsurgery in our series. Although the degree of cerebral edema and neurologic dysfunction after EEP are still under investigation, this technique could be a safe, simple, and feasible method to prevent embolic stroke after aortic distal arch replacement.

In our surgical procedures we used two cannulation sites for aortic return: AAC and the side branch of the distal graft. The aortic distal perfusion toward the lower torso caused backward flow from the intercostal arteries as well as EEP. The backward flow comes through the cervicothoracic and thoracolumbar arterial networks [11, 12]. Thus, the aortic perfusion using these two cannulation sites alternately allowed us to maintain spinal cord perfusion without interruption of networks. Furthermore, based on the collateral network to the spinal cord, we were able to sacrifice all intercostal arteries without reimplantation. The region between T7 and L1, in which the Adamkiewicz artery is considered to exist, was included in 85% of patients. Etz and colleagues [13] reported postoperative paraplegia in 2 of 100 consecutive patients undergoing sacrifice of intercostal and lumbar arteries during thoracic and thoracoabdominal repair using various CPB techniques. Our results were similar to those in recent reports. In this study, although temporary neurologic deficit in the spinal cord occurred in 3 patients (7.7%), no patient had permanent neurologic deficit. Thus, alternate aortic perfusion from these two cannulation sites was effective in reducing the risk of permanent neurologic deficit in the spinal cord.

Crystalloid potassium and blood cardioplegic solutions are generally used for myocardial protection during ascending and aortic root surgery through a median sternotomy approach. However, little is known about myocardial protection during aortic surgery through the left lateral approach. Takamoto and colleagues [10] infused crystalloid potassium cardioplegic solution using an occlusion balloon in the left lateral approach. However, in our series we maintained hypothermic ventricular fibrillation during surgery without using cardioplegic solution. Cosseli and colleagues [1] have recently reported a method similar to ours. In their report, cardiac complications occurred at 2% and 24% in elective and emergent cases, respectively. In this study, 97.5% of the procedures were performed in elective settings and one patient (2.5%) had frequent ventricular tachycardia at the time of weaning from CPB. This accumulated evidence suggests that deep hypothermic ventricular fibrillation is an acceptable means of myocardial protection during thoracic aortic surgery through the left lateral approach. Further postoperative investigations, such as changes in biochemical markers and the analysis of arrhythmic events will be required to address the feasibility of hypothermic ventricular fibrillation myocardial protection.

Although ischemia-reperfusion injury is inevitable after surgery using DHCA, careful respiratory management should be taken throughout the postoperative period. Tracheotomy is required between 2% and 11% of cases [1, 5, 14] and was needed in two cases (5.0 %) in this study. On average, it took 2.6 ± 1.7 days to achieve tracheal extubation; the length of time that the patients required mechanical ventilation was thus relatively longer than in other recent reports [14]. Several factors, such as prolonged CPB time, neurocognitive dysfunction, and chronic obstructive pulmonary disease, are considered as risk factors for prolonged mechanical ventilation after aortic surgery using DHCA [14, 15]. The CPB time in this study was also longer than in previous reports, although RCP time and DHCA time of the lower torso were less than 40 minutes. The size of the venous cannula through the femoral vein was usually 24 Fr, and this small

size may require much more time for cooling and rewarming of body temperature. The prolonged CPB time may thus be associated with the prolonged mechanical ventilation. On the other hand, permanent hemodialysis is required in 1.0% to 1.2% of elective patients who were not on chronic dialysis before surgery [1, 5]. In our series, no patients needed permanent hemodialysis.

The small number of patients was a limitation in this study. Furthermore, compared with previous reports the characteristics of our patients were relatively mild (eg, number on hemodialysis and those requiring emergency surgery) [1, 5]. These factors may be associated with the superior clinical results of this series. Accumulated clinical experience, as well as long-term follow-up, will be required to estimate the effect of minimizing the risk of cerebral and spinal cord embolism using this technique.

Combined with deep hypothermia and DHCA, AAC and EEP minimized the risk of cerebral embolism in aortic distal arch replacement through the left lateral approach.

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Transcranial motor-evoked potentials following intra-aortic cold blood infusion facilitates detection of critical supplying artery of spinal cord☆

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Abstract

Objective: In order to determine whether critical intercostal artery is present in the aneurysm during descending thoracic or thoracoabdominal aortic surgery, changes of transcranial motor-evoked potentials (Tc-MEPs) were monitored following infusion of cold blood into the aorta as an adjunct 'on-site assessment'. Accuracy of this method was evaluated. **Methods:** Fourteen patients were examined for Tc-MEPs changes following infusion of cold blood (4 °C, 300–450 ml) into the aneurysm. The intercostal arteries in the aneurysm were reconstructed when the Tc-MEPs amplitude decreased to below 50% of the baseline within 3 min after cold blood infusion. When the amplitude did not decrease, every intercostal artery in the aneurysm was ligated. **Results:** The Tc-MEPs amplitude did not decrease in eight cases (57%), while it decreased in six cases (43%). In the former, no case presented with paraplegia despite every intercostal artery being ligated. In the latter, the amplitude recovered after reconstruction in four patients, who had no paraplegia postoperatively. In the remaining two cases, however, the amplitude did not recover: one died of multiple organ failure with postoperative assessment unfeasible; the other developed paraplegia following surgery. Except one case with operative death, both sensitivity and specificity of our criteria with cold blood infusion was 100% in this series. **Conclusions:** Cold blood infusion into the clamped segment of aorta accelerates Tc-MEPs changes and can possibly reduce ischemic insults of spinal cord during diagnostic process, while it accurately detects presence of critical intercostal artery in the segment. This method appears to be promising adjunct on-site assessment.

Keywords: Cold blood infusion; Motor-evoked potentials; Spinal cord ischemia; Aortic surgery

1. Introduction

To prevent spinal cord injury following descending thoracic or thoracoabdominal aortic surgery, various methods have been used, including distal aortic perfusion, reimplantation of intercostal or lumbar arteries, systemic hypothermia, cerebrospinal fluid (CSF) drainage, and pharmacologic agents [1–4]. In addition, intraoperative monitoring of spinal cord potentials, such as motor-evoked potentials (MEPs), evoked spinal cord potentials (ESCPs), and somatosensory evoked potentials (SSEPs) have been used to assess spinal cord function during surgery [5–10]. However, when spinal cord potentials are monitored, the incidence of paraplegia following thoracic and thoracoabdominal aortic surgery ranges from 4.2% to 11.3% [5,7,8].

Reconstruction of critical arteries with minimal duration of spinal cord ischemia is considered to be advantageous to protect the spinal cord [11]. Preoperative assessment with computed tomography angiography (CTA) [12] or magnetic resonance angiography (MRA) [13] is used for detecting the critical artery that supplies the spinal cord. However, it is difficult to determine which intercostal artery is to be reconstructed when these modalities indicate multiple or no intercostal or lumbar arteries that perfuse the spinal cord. We previously reported prompt changes in transcranial motor-evoked potentials (Tc-MEPs) immediately following cold blood infusion into the clamped segment of aorta [14]. The Tc-MEPs amplitude decreased significantly within 3 min after cold blood infusion when the critical intercostal arteries were present in the thoracoabdominal aorta. In that report, MEPs were elicited by transcranial electrical stimulation and recorded from the spinal epidural space (D-wave).

Based on this result, Tc-MEPs were monitored following cold blood infusion into the clamped segment of aorta as an adjunct 'on-site assessment' to determine whether intercostal or lumbar arteries in the aneurysm should be

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reconstructed. The purpose of this study was to examine the sensitivity and specificity of our Tc-MEP criterion for the presence of a critical artery supplying the spinal cord within the clamped aortic segment.

2. Materials and methods

2.1. Patients

We examined 14 cases that underwent repair of descending thoracic or thoracoabdominal aortic aneurysm, in which intraoperative Tc-MEPs monitoring was feasible throughout the operations and Tc-MEPs changes following cold blood infusion were examined. The profiles of the patients and their surgical procedures are summarized in Table 1. They included nine men and five women ranging in age from 55 to 86 years old (71.1 ± 9.2 years). The pathology of the aorta included descending thoracic aortic aneurysm in six patients and thoracoabdominal aortic aneurysm classified as Crawford type I, II, III, and IV in 4, 1, 3, and 0, respectively.

2.2. Measurements of evoked potentials

An epidural catheter with five unipolar electrodes (UKG-100-5PM, Unique Medical, Tokyo, Japan) was placed at the level of the lumbar enlargement (T12-L1) through a 17-gauge Tuohy needle for recording Tc-MEPs and descending ESCPs. Another epidural catheter was introduced into the dorsal epidural space of the cervical spinal cord (C5–C6) for electrical stimulation to record the descending ESCPs. A CSF drainage catheter was inserted at a low lumbar location (L3–L4). Every catheter was inserted on the day before surgery.

After induction of anesthesia, two spiral needle electrodes (001-220, CS-F Electrodes, Agram Co., USA) were placed on the scalp above the bilateral cerebral motor cortices. Direct single-pulse transcranial electrical stimulation (duration, 0.5–1 ms; intensity, 400 V; rate, 7.3 Hz) of the cerebral motor cortices was applied, and Tc-MEPs were recorded at the lumbar enlargement (D-wave) (Fig. 1). The descending ESCPs were also recorded at the lumbar enlargement after single-pulse stimulation (duration, 0.2 ms; intensity, 10 mA; rate, 7.3 Hz) of the cervical spinal cord in parallel (Fig. 1). Each spinal cord potential recording was obtained by averaging a total of 20–50 responses.

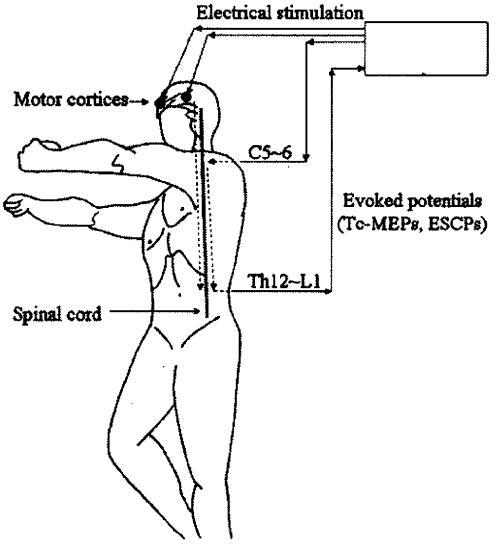

Fig. 1. Monitoring of spinal cord evoked potentials. Direct transcranial electrical stimulation of the cerebral motor cortices was applied, and the transcranial motor-evoked potentials (Tc-MEPs) were recorded at the lumbar enlargement. The descending evoked spinal cord potentials (ESCPs) were also recorded at the lumbar enlargement after stimulation of the cervical spinal cord (C = cervical; Th = thoracic; L = lumbar).

Stimulation and recording were performed using a Nicolet Viking select (Nicolet Biomedical, Inc., USA). All action potentials were recorded by one of five electrodes at the lumbar enlargement, which recorded the largest amplitude along the trunk. The amplitude of each spinal cord potential was expressed as a percent change from the corresponding control value recorded prior to the injection of cold blood into the clamped aortic segment.

2.3. Anesthesia

Anesthesia was induced with 10 μg/kg fentanyl and 5 mg/kg propofol and was maintained with 2–4 μg/kg fentanyl per

Table 1
Profiles of patients and surgical procedures

Case no.	Age (years)	Sex (M/F)	Aneurysm type	History of operation	Operative time (min)	F–F bypass (min)	AOC (min)
1	86	M	I	–	360	169	145
2	80	F	I	–	332	84	66
3	67	M	III	AAA	1020	224	186
4	67	F	DTAA	–	260	80	71
5	83	F	DTAA	–	350	70	61
6	69	M	III	–	590	159	154
7	65	M	I	–	270	77	68
8	84	M	III	AAA	430	97	82
9	70	F	DTAA	–	230	54	38
10	66	M	DTAA	–	465	174	152
11	55	M	II	TARA, DTAA	835	253	244
12	72	M	I	TAAA, AAA	865	390	258
13	71	M	DTAA	–	390	118	93
14	60	F	DTAA	TAAA	522	101	69

AAA: abdominal aortic aneurysm; DTAA: descending thoracic aortic aneurysm; F: female; M: male; TAAA: thoracoabdominal aortic aneurysm; TARA: total arch aneurysm; I: Crawford classification type I; II: Crawford classification type II; III: Crawford classification type III.

h and 2 mg/kg propofol per h. Muscle relaxation was induced with pancuronium at 0.1 mg/kg and maintained with 0.02–0.04 mg/kg h. Intubation was performed with a double-lumen endotracheal tube under fiberoptic bronchoscopy. Controlled ventilation and isolated lung ventilation were adequately performed.

2.4. Surgical technique

On the right lateral decubitus position, left thoracotomy or thoracoabdominal incisions were adequately performed. A femorofemoral partial cardiopulmonary bypass was established, and the rectal temperature was maintained at 34 °C. While the aorta was cross-clamped, systemic blood pressure was mainly controlled by adjusting the bypass flow. Mean radial arterial pressure was maintained at 60–100 mmHg, while distal aortic pressure was >60 mmHg.

The aorta was clamped at sites proximal and distal to the aneurysm. If the aneurysm extended longer than several vertebrae, the aneurysm was segmentally clamped [15]. Cold blood (4 °C) was infused into the clamped segment of aorta through a 14-gauge needle at a rate of 100–200 ml/min, to a total amount of 200–450 ml. The amount of infused cold blood was determined according to the size of the clamped aortic segment: 300–450 ml for a large segment and 200–300 ml for a small segment. We then observed changes of the Tc-MEPs and ESCPs amplitudes during and after cold blood infusion, and after aneurysmectomy.

2.5. Tc-MEPs criterion following cold blood infusion

When the Tc-MEPs amplitude did not decrease to a level below 50% of baseline during and after cold blood infusion, we concluded that no critical supplying artery was present in the aneurysm, and ligated all intercostal or lumbar arteries in the aneurysm. Then, the proximal and distal parts of the aorta were anastomosed using a 20–30 mm woven double velour vascular graft, and the visceral arteries were reconstructed with the branched graft under visceral arterial perfusion (150 ml/min for each visceral artery) if necessary.

When the Tc-MEPs amplitude decreased to below 50% of baseline within 3 min after cold blood infusion, we determined that the critical supplying artery was present in the clamped segment of aorta, and then the intercostal or lumbar arteries with significant back bleeding were reconstructed. Other intercostal or lumbar arteries were ligated immediately to minimize the steal of collateral flow away from the anterior spinal artery during anastomosis. The intercostal or lumbar arteries were reconstructed using 8 or 10 mm woven double velour vascular grafts. The intercostal artery was reperfused immediately through the attached vascular graft with warm blood at a flow rate of 40–50 ml/min and a perfusion pressure of 100 mmHg for each intercostal artery pair [16]. If the recovery of the Tc-MEPs amplitude was not satisfactory, other intercostal or lumbar arteries were additionally reconstructed. After completing the prosthetic replacement of the aneurysm, each attached vascular graft of the intercostal arteries was anastomosed to the main tube graft and perfused segmentally.

2.6. Statistical analysis

Data were processed using StatView J-5.0 (SAS Institute, Cary, NC) software. All values are expressed as the mean ± standard deviation. Statistical analysis was performed with the Mann–Whitney U test to compare the incidence of spinal cord injury between patients with and without a decrease in Tc-MEPs amplitude to below 50% of baseline, as well as between patients with and without reimplantation of visceral arteries. Differences were considered statistically significant when the p value was <0.05. Confidence intervals for sensitivity and specificity were defined as 95%.

3. Results

3.1. Changes in evoked potentials after cold blood infusion

Changes in spinal cord potentials (Tc-MEPs and ESCPs) and neurologic outcomes are summarized in Table 2. The changes

Table 2
Changes in spinal cord potentials and neurologic outcomes

Case no.	Tc-MEPs, ESCPs (minimum amplitude after cold blood infusion)	Tc-MEPs, ESCPs (amplitude after reperfusion)	Reconstructed artery	Neurologic outcome
2	100%, 100%	70%, 100%	–	No deficit
3	100%, 100%	100%, 100%	CEA, SMA, RA	No deficit
4	100%, 100%	100%, 100%	–	No deficit
5	100%, 100%	100%, 100%	–	No deficit
7	100%, 100%	100%, 100%	–	No deficit
8	100%, 100%	100%, 100%	CEA	No deficit
9	100%, 100%	100%, 100%	–	No deficit
14	100%, 100%	100%, 100%	–	No deficit
1	40%, NR	85%, NR	Th11, Th12	No deficit
6	50%, 60%	0%, 0%	Th12, CEA, SMA, RA	Paraplegia
10	20%, 80%	85%, 75%	Th9, Th10	No deficit
11	50%, 100%	60%, 90%	L1, CEA, SMA, RA	No deficit
12	50%, 70%	0%, 0%	Th9	Dead
13	45%, 100%	95%, 100%	Th10	No deficit

The cases that Tc-MEPs amplitude did not decrease were serialized from top to the eighth line. The cases that Tc-MEPs amplitude decreased were serialized from the ninth line to bottom. CEA: celiac artery; ESCPs: evoked spinal cord potentials; NR: not recorded; RA: bilateral renal artery; reconstructed artery (Th: thoracic; L: lumbar); SMA: superior mesenteric artery; Tc-MEPs: transcranial motor-evoked potentials.

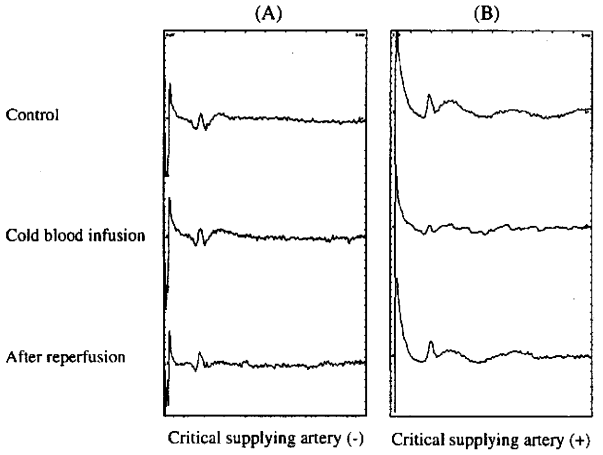

Fig. 2. Changes in transcranial motor-evoked potentials (Tc-MEPs) following cold blood infusion. (A) Tc-MEPs without decrease to <50% of baseline during and after cold blood infusion. (B) Tc-MEPs with a decrease to <50% of baseline within 3 min after cold blood infusion.

of Tc-MEPs amplitude after cold blood infusion were examined in all 14 patients during the operation.

The Tc-MEPs amplitude did not decrease to below 50% of baseline in eight patients (57%) during and after cold blood infusion into the clamped segment of aorta (Fig. 2). There was no change in Tc-MEPs amplitude in these eight patients and the Tc-MEPs amplitude within 3 min after cold blood infusion was 100% ± 0% of the baseline value. The ESCPs amplitude also did not change during and after cold blood infusion in these eight cases. Although every intercostal or lumbar artery was ligated, none of these patients presented with paraplegia after surgery.

The Tc-MEPs amplitude decreased to below 50% of baseline in six patients (43%) within 3 min after cold blood infusion (Fig. 2). The minimal Tc-MEPs amplitude within 3 min after cold blood infusion was 43% ± 12%. However, in these six patients, the amplitude of the ESCPs did not change in two, decreased in three, and was not recorded in one. We determined that the critical supplying artery was present in these cases, and therefore, the intercostal or lumbar arteries with significant back bleeding were reconstructed. The number of intercostal arteries reconstructed was one or two pairs in each case. The amplitude of the Tc-MEPs significantly recovered to >50% of baseline after reconstruction in four patients, and these patients had no postoperative paraplegia. In the remaining two cases, however, the amplitude of the Tc-MEPs did not recover, even though we reconstructed as many intercostal and lumbar arteries as possible, and they were perfused immediately with warm blood through the attached vascular graft. One patient died of multiple organ failure and did not have any postoperative assessment. The other patient developed paraplegia following surgery. In the latter case, the amplitude of the Tc-MEPs decreased within 3 min after cold blood infusion and further dropped following aortotomy. The twelfth intercostal artery with significant back bleeding was reconstructed. The amplitude of Tc-MEPs did not recover despite selective perfusion of this artery. The first and second lumbar arteries were not reconstructed because they were already occluded. There was no significant difference in the incidence of spinal cord injury between six patients with a decrease in Tc-MEPs amplitude and eight patients without a decrease in Tc-MEPs amplitude ($p = 0.21$). In 13 cases in which postoperative neurological assessment was feasible, a critical artery supplying the spinal cord was detected in 5 patients, and was not detected in 8 patients. Both the sensitivity and specificity of our criterion for detection of a critical artery was 100%.

3.2. Classification by the extent of aortic replacement

The 13 patients except for 1 patient with operative death were divided into two groups: a thoracic group (descending thoracic aortic aneurysm and Crawford type I aneurysm) and a thoracoabdominal group (Crawford type II and III aneurysm). The incidence of spinal cord injury was examined in each group. In the thoracic group, three of nine patients (33%) presented with a Tc-MEPs decrease (below 50% of baseline) but none had spinal cord dysfunction (0%). In the thoracoabdominal group, two of four patients (50%) had a decrease of Tc-MEPs and one had postoperative paraplegia (25%). There was no significant difference in the incidence of spinal cord injury between the two groups ($p = 0.13$).

4. Discussion

This study showed that changes in Tc-MEPs amplitude within 3 min after cold blood infusion indicate the presence or absence of a critical artery that supplies the spinal cord. The Tc-MEPs monitoring with cold blood infusion may potentially serve as an adjunct on-site method in thoracoabdominal aortic surgery.

Although Tc-MEPs monitoring is widely used for assessment of spinal cord function during surgery [5,8–10], it often takes longer than 10 min to detect amplitude changes and the diagnostic process is associated with ischemic injury of the spinal cord. We previously reported that a rapid decrease in amplitude of Tc-MEPs following cold blood infusion indicated the presence of a critical spinal cord artery in the aneurysm [14] and have used Tc-MEP monitoring with cold blood infusion. The mechanisms of amplitude decrease may be related to local hypothermia by cold blood (4 °C). In an experimental study, intra-aortic infusion of cold lactated Ringer's solution (3 °C) cooled the spinal cord by 6–7 °C [17]. Hypothermia induces a depression of the electrophysiologic response of both cerebral and peripheral neurologic activity [18,19]. This topical cooling of spinal cord might induce the rapid decrease of Tc-MEP amplitude [17–19].

Van Dongen and colleagues reported that when the amplitude of Tc-MEPs was ≤50% of baseline during cross-clamping and closure of the skin, the relative risks of paraplegia after thoracic and thoracoabdominal aortic aneurysm repair were respectively 3.4-fold and 31-fold compared with Tc-MEPs >50% of baseline [8]. Based on this data, we assigned the cut-off point of the Tc-MEP amplitude as 50% of baseline. A duration of 3 min was used for detecting Tc-MEP changes, because the Tc-MEP amplitude decreased within 3 min in our previous experience [14].

Paraplegia did not occur in cases without a significant decrease in Tc-MEP amplitude, although the intercostal or lumbar arteries were ligated. This on-site assessment may

reduce the operative time by shorting the assessment time (3 min) and reducing the time for unnecessary reconstruction.

In a case of postoperative paraplegia, the spinal cord might have been injured, or another intercostal artery was the critical artery. Regretfully it is not feasible to specifically identify one intercostal artery. Nevertheless, the presence/absence of a critical supplying artery can be determined within 3 min with a sensitivity and specificity of 100%. Accelerated Tc-MEP changes with topical cooling can possibly reduce the ischemic insult of the spinal cord during the diagnostic process.

The extent of aortic replacement can affect outcomes as well. In this series, the incidence of paraplegia was 0% in the thoracic group and 25% in the thoracoabdominal group. There was no statistical difference between the two groups because of the small number of cases. We admit that the incidence of postoperative paraplegia (7.7%) is not lower than that in other excellent centers, because of the limited number of cases in this series. Further study with a larger number of cases is needed to evaluate our criterion.

Changes in Tc-MEP amplitude were more rapid than in ESCP amplitude. This difference may be due to temperature sensitivity of each evoked potential or due to ischemia [18,19]. The Tc-MEPs appeared to be more accurate than ESCPs in the assessment of spinal cord ischemia during aortic surgery.

In this series, changes in Tc-MEPs were discrete; either there was no change or a decrease to below 50%. Although it is uncertain as to whether a 50% decrease is an appropriate cut-off value, this criterion was adequate in this series. A 100% sensitivity and specificity can be obtained with a cut-off value between 50% and 90% of baseline as well. If the cut-off value is increased to limit false-negative results (for example, ligation of a critical supplying artery), then the number of arteries that need reconstruction will increase.

A limitation of cold blood infusion should be noted. It is hard to carry out in cases of dissecting aneurysm or highly atheromatous aneurysm, because of possible inappropriate infusion into the false lumen in the former and because of embolism in the latter.

In conclusion, Tc-MEP monitoring following cold blood infusion into the clamped segment of aorta is a rapid and accurate method for detecting the presence of critical supplying arteries in the clamped segment of aorta. This method may be helpful for minimizing the duration of spinal cord ischemia and unnecessary reconstruction of intercostal arteries. It appears to be a promising adjunct for on-site assessment during descending thoracic or thoracoabdominal aortic surgery.

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Appendix A. Conference discussion

Dr F. Beyersdorf (Freiburg, Germany): With your method of intra-aortic cold blood infusion, you have some sort of protection (hypothermia only) for a certain period of time. However, there is, of course, also some rewarming after a certain period of time. And I saw in one of your slides the duration of the operations which were in some cases rather long. Did you relate the outcome also to the duration of the operation in order to see if this is a time-dependent factor?

Dr Hamaishi: Cold blood was infused at a rate of 100–200 ml to a total amount of 200–450 ml within 3 min.

ELSEVIER

Low-Dose Edaravone Injection into the Clamped Aorta Prevents Ischemic Spinal Cord Injury

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Previous studies have indicated that high-dose intravenous edaravone (3-10 mg/kg) protects against ischemic spinal cord injury. This study examined whether direct injection of low-dose edaravone into the clamped segment of the aorta prevents ischemic spinal cord injury. Spinal cord ischemia was induced in rabbits by aortic clamping below the renal artery and above the aortic bifurcation for 15 min at normothermia. In groups A and B, 3 and 1 mg/kg of edaravone, respectively, was injected into the clamped segment of the aorta immediately following aortic clamping. In group C, saline was injected. Neurological function was assessed at 8, 24, and 48 hr and 7 days after reperfusion with Tarlov criteria. The spinal cord was histologically examined at 7 days with hematoxylin-eosin staining and in situ terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) staining. The Tarlov score remained grade 4 throughout the period in groups A and B, whereas it dropped to grade 0 or 1 at 7 days in group C, significantly higher in the former two groups. The number of intact motor neurons was significantly greater in groups A and B with less necrotic motor neurons than in group C. There was no significant difference in terms of spinal cord protection between groups A and B. There was no TUNEL-positive neuron in any group, indicating the absence of apoptosis. Low-dose intra-aortic edaravone injection prevents immediate neuronal injury by reducing neuronal cell damage in the early stage as well as delayed neuronal injury at 7 days.

INTRODUCTION

Spinal cord injury after surgery on the thoracic and thoracoabdominal aorta is a disastrous complication. Various methods have been used for preventing ischemic spinal cord injury, such as distal aortic perfusion, systemic hypothermia, cerebrospinal fluid drainage, and pharmacological agents.[1-3] The incidence of paraplegia following operations of the thoracic and thoracoabdominal aorta ranges 4.5-11.4%.[4-7] In addition, patients undergoing thoracic and thoracoabdominal aneurysm repair sometimes suffer from the delayed onset of paraplegia.[8]

We reported that the use of cold spinoplegia and transvertebral cooling-pad application effectively reduced ischemic injury of the spinal cord. Cold saline infusion into the clamped segment of the aorta also exerted a protective effect on the spinal cord.[9] These results suggested that drugs injected into the cross-clamped segment of the spinal cord might suppress neuronal injury if the critical intercostal artery was in the clamped aorta.

Edavarone (Mitsubishi Pharma, Tokyo, Japan), a commercially available free radical scavenger, has been used as an antioxidative agent in acute ischemic brain disorders.[10] The protective effect of intravenous edaravone against ischemic spinal cord injury has been reported in rabbit models.[11-14] However, more than 3 mg/kg of edaravone administered intravenously was necessary to effectively reduce

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