Augmentation of systemic blood pressure during spinal cord ischemia to prevent postoperative paraplegia after aortic surgery in a rabbit model

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Objective: Paraplegia from spinal cord ischemia remains an unresolved complication in thoracoabdominal aortic surgery, with high morbidity and mortality. This study investigated postoperative effects of systemic blood pressure augmentation during ischemia.

Methods: Spinal cord ischemia was induced in rabbits by infrarenal aortic occlusion for 15 minutes with infused phenylephrine (high blood pressure group, n = 8) or nitroprusside (low blood pressure group, n = 8) or without vasoactive agent (control, n = 8). Spinal cord blood flow, transcranial motor evoked potentials, neurologic outcome, and motor neuron cell damage (apoptosis, necrosis, superoxide generation, myeloperoxidase activity) were evaluated.

Results: Mean arterial pressures during ischemia were controlled at 121.9 ± 2.8, 50.8 ± 4.3, and 82.3 ± 10.7 mm Hg in high blood pressure, low blood pressure, and control groups, respectively. In high blood pressure group, high spinal cord blood flow ($P < .01$), fast recovery of transcranial motor evoked potentials ($P < .01$), and high neurologic score ($P < .05$) were observed after ischemia relative to low blood pressure and control groups. At 48 hours after ischemia, there were significantly more viable neurons, fewer terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick-end labeling–positive neurons, and less α-fodrin expression in high blood pressure group than low blood pressure and control groups. Superoxide generation and myeloperoxidase activity at 3 hours after ischemia were suppressed in high blood pressure group relative to low blood pressure group.

Conclusions: Augmentation of systemic blood pressure during spinal cord ischemia can reduce ischemic insult and postoperative neurologic adverse events. (J Thorac Cardiovasc Surg 2010;139:1261-8)

Spinal cord ischemia (SCI) is a major devastating and unpredictable complication in thoracoabdominal aortic surgery. Although SCI is not directly associated with high mortality, it may spoil the quality of life in patients and indirectly influence mortality. Many strategies have been devised to protect the spinal cord, including mild or deep hypothermia, distal aortic perfusion, segmental aortic clamping, reconstruction of intercostal or lumbar arteries, cerebrospinal fluid drainage, monitoring of motor evoked potentials, and pharmacologic agents. The reported incidence of paraplegia, however, still ranges from 2% to 11%.[1-3] The mechanism for the development of paraplegia related to SCI is multifactorial, and this complication still cannot be prevented completely.

Some clinical and experimental reports have suggested that appropriate control of blood pressure (BP) could prevent SCI-related paraplegia after surgery.[4-7] In this study, we hypothesized that intraoperative augmentation of systemic BP (SBP) during SCI could protect ischemic spinal cord injury. We investigated the impact of SBP augmentation on the spinal cord by means of neurophysiologic and histopathologic evaluations.

MATERIALS AND METHODS

Animals

Japanese white rabbits weighing 2.6 to 4.1 kg were obtained from Kitayama (Kitayama Labs Co Ltd, 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"; in addition, all animals received humane care and treatment in accordance with the "Guide for the Care and Use of Laboratory Animals" (www.nap.edu/catalog/5140.html).

Surgical Procedure

Experiments were performed with a rabbit SCI model, which we have previously described.[8] Briefly, rabbits anesthetized with intramuscular ketamine (Ketalar intramuscular, 50 mg/kg; Daiichisankyo Co Ltd, Tokyo, Japan) and intravenous propofol (1% Diprivan Injection, 10 mg/kg; AstraZeneca, Boston, Mass) had a 5F balloon-tipped catheter (Swan-Ganz thermodilution catheter, 93-132-5F; Baxter Health Corporation, Santa Ana,

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Abbreviations and Acronyms

BP = blood pressure
HBP = high blood pressure
LBP = low blood pressure
LLI = lower limb ischemia
MAP = mean arterial pressure
MTS = modified Tarlov scale
SBP = systemic blood pressure
SCBF = spinal cord blood flow
SCI = spinal cord ischemia
SSEP = somatosensory evoked potential
tc-MEP = transcranial motor evoked potential
TUNEL = terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling

Calif) inserted into the abdominal aorta through the right superficial femoral artery. To establish the SCI model, the balloon of the catheter was inflated 0.5 to 1.5 cm distal to the left renal artery with an indicated SBP for 15 minutes and then deflated with the SBP returned to normal level (approximately 80 mm Hg). For a preliminary study, the balloon was inflated at terminal aorta with an indicated SBP for 15 minutes to establish a lower-limb ischemia (LLI) model.

Experimental Groups

According to the SBP level during SCI, rabbits were randomly divided into 3 groups as follows. In the high BP (HBP) group (n = 8), the mean arterial pressure (MAP) was maintained at 120 mm Hg by an intravenous phenylephrine (Neo-Synesin Kowa Injection; Kowa Co Ltd, Tokyo, Japan). In the low BP (LBP) group (n = 8), MAP was maintained at 50 mm Hg by an intravenous nitroprusside (Nitopro continuous intravenous solution; Maruishi Pharmaceutical Co Ltd, Osaka, Japan). Finally, in the control group (n = 8), MAP was approximately 80 mm Hg without any additional medication. After the balloon deflation, we stopped using the vasoactive agents immediately, and the SBP was maintained naturally.

Neurologic Assessment

Serial assessments of motor function in the hind limbs of all animals were performed at 3, 24, and 48 hours after SCI according to a modified Tarlov scale (MTS) as described previously[8]: 0 for no movement, 1 for slight movement, 2 for sitting with assistance, 3 for sitting alone, 4 for weak hop, and 5 for normal hop).

Measurement of Spinal Cord Blood Flow

Spinal cord blood flow (SCBF) was measured as described previously[9] with modifications. A laser probe (LP-N; Unique Medical Co Ltd, Tokyo, Japan) was used, and SCBF was continuously monitored until 30 minutes after the SCI by laser Doppler flowmetry (TBF-LC1; Unique Medical). After the SCBF baseline was recorded at 80 mm Hg, SCBFs at the indicated SBPs were measured in each group. The experimental SCBF was expressed as a percentage of the SCBF baseline.

Measurement of Transcranial Motor Evoked Potentials

Transcranial motor evoked potentials (tc-MEPs) were measured and analyzed with a modification of the method in our previous report.[8] Tc-MEPs were evoked with a multiple transcranial electrical stimulator (NS-101 cortical stimulator; Unique Medical). Data acquisition, processing, analysis, and storage were performed with a personal computer system (UAS-108S; Unique Medical). In this study, the tc-MEPs were measured every minute during the operation. The baseline for tc-MEPs was defined as an average of 3 consecutive amplitudes recorded before aortic occlusion, and the reappearance of tc-MEPs was defined as absence of flat waves in 3 consecutive responses. Recovery ratio of tc-MEPs amplitude was calculated as the amplitude of anterior tibial muscles divided by the baseline of anterior tibial muscles multiplied by the baseline of anterior radial muscles divided by the amplitude of anterior radial muscles and expressed as a percentage.[10]

Evaluation of Pathologic Outcome

Rabbits were killed by deep sodium pentobarbital anesthesia (100 mg/kg, intravenously) after 48 hours of reperfusion. The spinal cord between L3 and L4 was removed and placed in 4% paraformaldehyde/0.1 mol/L phosphate-buffered saline solution at 4 °C for 1 week. Sections were cut transversely at the L3 and L4 levels and embedded in paraffin. The sections were stained with hematoxylin and eosin for histopathologic observation of motor neurons, according to our previous report[8]: viable neurons were indicated by basophilic stripling (containing Nissl substance), whereas nonviable neurons were indicated by pyknotic nuclei, eosinophilic cytoplasm, or absent nuclear hematoxylin staining. The numbers of viable neurons in unilateral Rexed laminae VII, VIII, and IX were counted and expressed as an average.

To detect DNA fragmentation in cell nuclei, the sections were also processed according to the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) method. The number of neurons with nuclei clearly stained by the TUNEL method was counted in the same way as the number of viable neurons.

Western Blot Analysis

Frozen spinal cord samples were homogenized, and the protein concentrations were evaluated with a dye-binding assay with the Bio-Rad reagent (Bio-Rad Laboratories, Hercules, Calif). Equal amounts of protein (10 μg protein per lane) were electrophoresed on a 10% sodium dodecyl sulfate polyacrylamide gel and then transferred onto nitrocellulose membrane. The membrane was incubated with anti–mouse α-fodrin antibody (Millipore Corp, Billerica, Mass) for 1 hour at room temperature and then incubated with goat anti–mouse immunoglobulin antibody for 30 minutes. Enhanced chemiluminescence analysis was performed according to manufacturer instructions (GE Healthcare UK Limited, Buckinghamshire, UK). Blots were subsequently probed for β-actin (Bio Vision Research Products, Mountain View, Calif) as an internal control for equivalent protein loading. The signals were quantified with an image analyzer (LAS-3000; FUJIFILM Corp, Tokyo, Japan). Optical density of each band was measured on the same membrane.

Superoxide Detection

Superoxide generation was evaluated on tissue cryosections of the spinal cord between L3 and L4 at 3 hours after SCI. The sections were quickly removed, embedded in OCT compound (Sakura Finetech, Torrance, Calif), and stored at –80 °C until use. Dihydroethidium (Invitrogen, Carlsbad, Calif) was used as an oxidative fluorescent dye.

Myeloperoxidase Activity

Tissue myeloperoxidase activity was determined by measuring the hydrogen peroxide–dependent oxidation of *o*-dianisidine as previously described,[11] with modifications. In brief, frozen spinal cord samples were homogenized in hexadecyltrimethyl ammonium bromide (Sigma-Aldrich, St Louis, Mo) and phosphate-buffered saline solution at pH 6.0. The supernatants were reacted with *o*-dianisidine dihydrochloride (Sigma-Aldrich) and hydrogen peroxide. The change in absorbance was measured spectrophotometrically at 450 nm. The activity was expressed as a percentage of that in the control group.

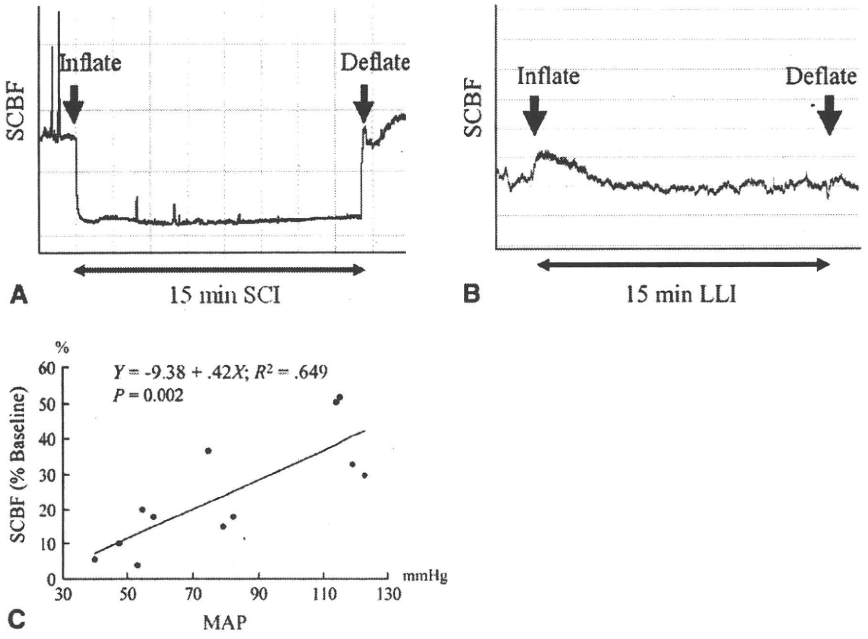

FIGURE 1. A, Spinal cord blood flow *(SCBF)* recordings in spinal cord ischemia *(SCI)* model. B, Spinal cord blood flow recordings in lower limb ischemia *(LLI)* model. C, Relationship between mean arterial pressure *(MAP)* and spinal cord blood flow during aortic occlusion in spinal cord ischemia model. Raw data shown as *points*.

Statistical Analysis

Data were processed with Stat View J-5.0 software (SAS Institute, Cary, NC). All values are expressed as mean±SD. Comparisons among groups were performed with Kruskal–Wallis test, Scheffé multiple comparison test, or repeated measures analysis of variance as appropriate.

RESULTS

Rabbit SCI model

To confirm our SCI model, experiments with a LLI model were performed in a preliminary study. The SCBF in the LLI model did not decrease during 15 minutes of the aortic occlusion, whereas that in the SCI model decreased dramatically and stayed low during the 15 minutes of aortic occlusion (Figure 1, *A* and *B*). No animal in the LLI group had neurologic and histologic damage at 48 hours after reperfusion. On the basis of this result, we performed the following experiments with the rabbit SCI model.

Intraoperative Physiologic Status

In the SCI model, all animals survived for 48 hours after the balloon deflation. The intraoperative data are shown in Table 1. There were no statistical differences in intraoperative hemoglobin, arterial Pao_2, and pH among the 3 groups. The MAP in the control group was 82.3 ± 10.7 mm Hg. The average MAP during SCI was significantly different among the groups according to their definition ($P < .001$). During SCI, the SCBF in HBP group was significantly higher than that in LBP or control group ($P < .001$, $P = .009$, respectively), whereas no significant difference was found between the LBP and control groups. A clear correlation between MAP and SCBF was observed during SCI (relation coefficient=0.81, P=.002; Figure 1, *C*).

Intraoperative and Postoperative Neurologic Evaluation

The tc-MEPs disappeared immediately after aortic occlusion and reappeared after balloon deflation. The recovery of tc-MEPs is shown in Figure 2 (*A* and *B*). The tc-MEPs in the HBP group reappeared only 3.8 ± 5.6 minutes after SCI, whereas the reappearance times for the LBP and control groups were 22.2 ± 5.2 minutes and 21.0 ± 6.7 minutes, respectively. The reappearance time of tc-MEPs in the HBP group was significantly faster than that in either the LBP group or the control group ($P = .005$, $P = .008$, respectively). The recovery ratio of tc-MEP amplitude through 30 minutes after SCI was also significantly larger in the

TABLE 1. Intraoperative physiologic status by group

	High blood pressure	Low blood pressure	Control
pH	7.34 ± 0.04	7.37 ± 0.01	7.38 ± 0.05
Arterial Pao_2 (mm Hg)	94.0 ± 16.0	90.0 ± 15.8	99.7 ± 17.0
Hemoglobin (g/dL)	12.6 ± 0.3	12.3 ± 1.1	11.5 ± 0.9
Mean arterial pressure (mm Hg)	121.9 ± 2.8*	50.8 ± 4.3*	82.3 ± 10.7
Spinal cord blood flow (%)	45.2 ± 7.2†‡	11.7 ± 6.7	23.8 ± 8.4

All values are mean ± SD. *$P < .001$ versus control. †$P < .01$ versus control. ‡$P < .001$ versus low blood pressure.

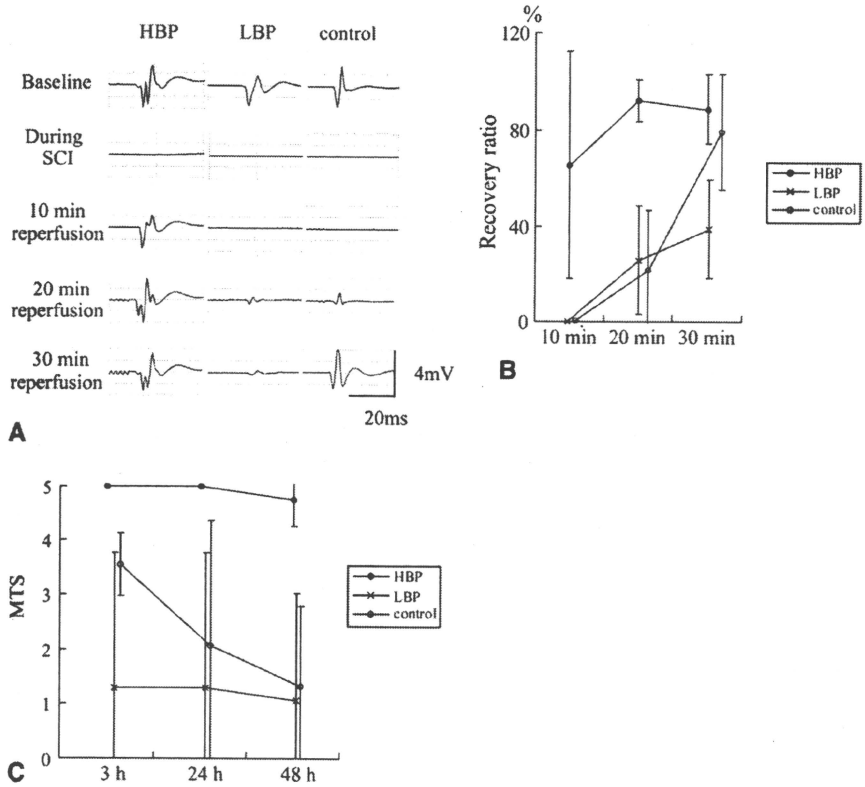

FIGURE 2. Intraoperative and postoperative neurologic assessments. A, Representative transcranial motor evoked potential *(tc-MEP)* complex. B, Recovery ratios of transcranial motor evoked potential amplitude at 10, 20, and 30 minutes after spinal cord ischemia *(SCI)*. C, Neurologic scores with modified Tarlov scale *(MTS)* at 3, 24, and 48 hours after spinal cord ischemia. *HBP*, High blood pressure; *LBP*, low blood pressure.

HBP group than in either the LBP group or the control group ($P = .004$ and $P = .01$ by analysis of variance, respectively). MTS scores for each group are shown in Figure 2 *(C)*. No rabbits in the HBP group were neurologically damaged at 3, 24, and 48 hours after the MTS, although 48 hours after the SCI in HBP group was significantly higher than that in LBP or control group ($P = .01$, $P = .01$, by analysis of variance, respectively). There were no significant differences in intraoperative and postoperative neurologic evaluations between the LBP and control groups.

Histologic Assessment

At 48 hours after SCI, the number of viable motor neurons in the HBP group was significantly more than those in the LBP and control groups (23.3 ± 5.5, 8.5 ± 5.0, and 6.2 ± 3.8 per unilateral section, respectively, HBP vs LBP $P < .001$, HBP vs control $P < .001$; Figure 3, *A* and *C*). On the other hand, there were no significant differences between LBP and control group. The numbers of TUNEL-positive neurons per unilateral section in HBP, LBP, and control groups at 48 hours after SCI were 0.8 ± 0.9, 4.0 ± 4.4, and 12.8 ± 5.8, respectively (Figure 3, *B* and *D*). The number of TUNEL-positive neurons in HBP group was significantly less than that in control group ($P = .01$), whereas there were no significant difference between HBP and LBP groups. The number of TUNEL-positive neurons in the control group was significantly larger than that in the LBP group ($P = .04$).

Expression of α-Fodrin Fragments

To quantify neuronal damage after SCI, we evaluated the protein expression of α-fodrin in the spinal cord at 48 hours after SCI by Western blot analysis (Figure 4). The 120-, 145- and 150-kDa fragments of α-fodrin are generated in accordance with proteolysis of a membrane cytoskeletal protein by neuronal damage of brain or spine.[12-14] The total α-fodrin level in the HBP group was significantly lower than those in both the LBP and control groups ($P < .001$, $P < .001$, respectively). There was also a significant difference between the LBP and control groups ($P = .004$).

Oxidative Stress

For better understanding of the protective effect of HBP during SCI, we evaluated the superoxide generation and myeloperoxidase activity in the spinal cord at 3 hours after SCI. The intensity of red oxidative fluorescence in the HBP group was apparently lower than in either the LBP or

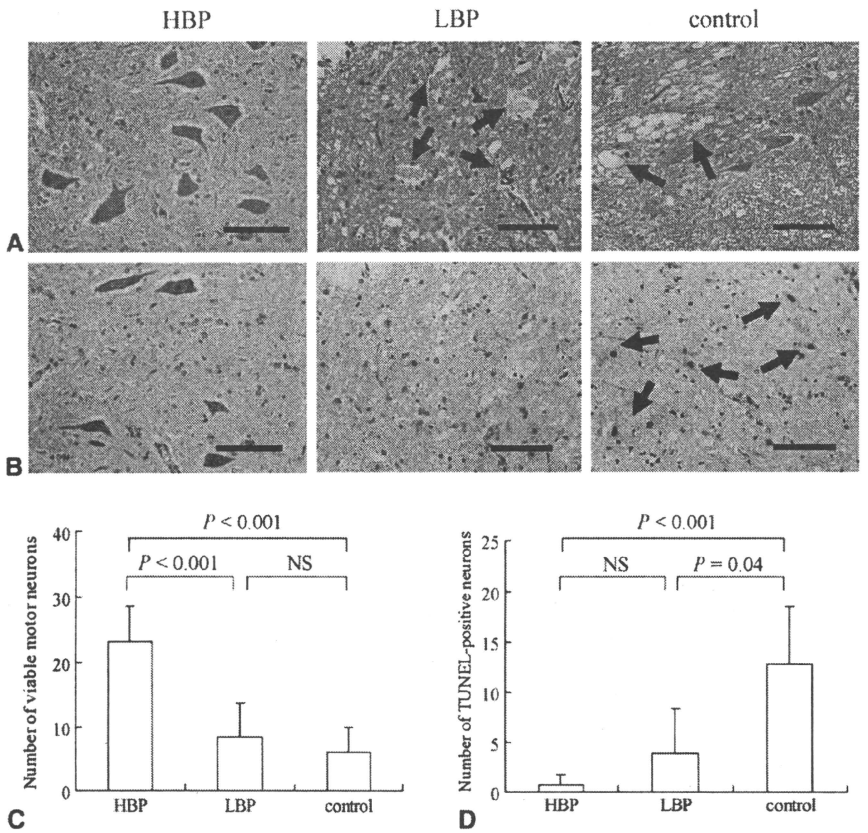

FIGURE 3. Photomicrographs of histologic sections in rabbit spinal cord at 48hours after spinal cord ischemia. A, Hematoxylin and eosin staining of ventral gray matter. Spinal cords in low blood pressure *(LBP)* and control groups show necrotic change *(arrows)*. B, Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling *(TUNEL)* staining of ventral gray matter. There were many positively staining neurons in control group *(arrows)*. C, Numbers of viable motor neurons in each group at 48hours after spinal cord ischemia. D, Numbers of terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling–positive neurons in each group at 48hours after spinal cord ischemia. *NS*, Not significant. *Scale bar* represents 100μm.

control group (Figure 5, *A*). Myeloperoxidase activities in the HBP and LBP groups were 86.4% ± 34.2% and 181.4% ± 68.6% of those in the control group, respectively. The myeloperoxidase activity in the LBP group was significantly higher than those in the HBP and control groups ($P = .007$, $P = .03$, respectively), whereas there was no significant difference between the HBP and control groups (Figure 5, *B*).

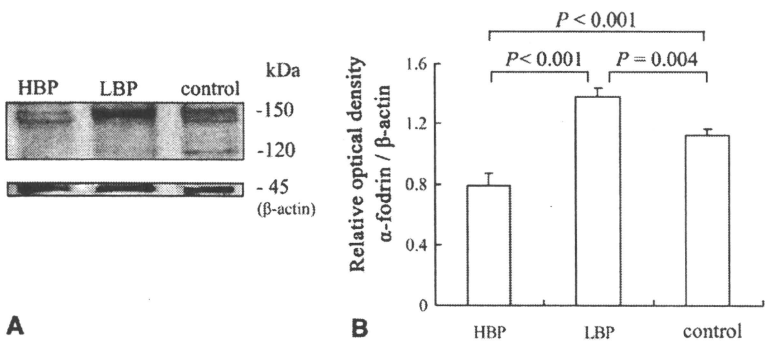

FIGURE 4. A, Western blot analysis of α-fodrin fragments at 48 hours after spinal cord ischemia. B, Relative optical densities of total α-fodrin fragments in each group at 48 hours after spinal cord ischemia. *HBP*, High blood pressure; *LBP*, low blood pressure.

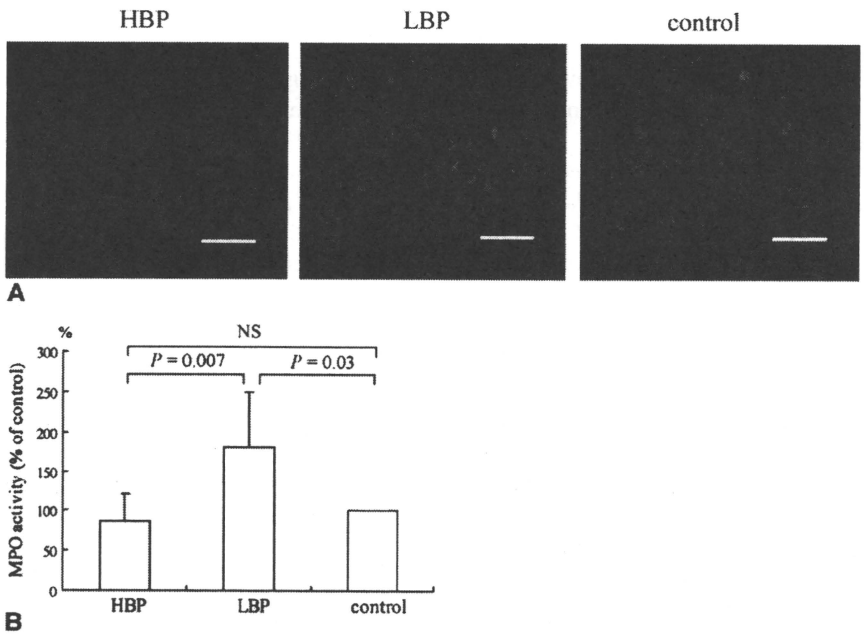

FIGURE 5. A, Fluorescence micrographs of histologic sections in rabbit spinal cord at 3 hours after spinal cord ischemia. Dihydroethidium staining (red fluorescence when oxidized to ethidium bromide by superoxide) of ventral horn. B, Myeloperoxidase *(MPO)* activities in each group at 3 hours after spinal cord ischemia. *HBP*, High blood pressure; *LBP*, low blood pressure; *NS*, not significant. *Scale bar* represents 200 μm.

ET/BS

DISCUSSION

The rabbit model involving infrarenal aortic clamping for 15 minutes is well established as a model of late paraplegia after SCI.[13,15] The rabbit spinal cord is large even in the lumbar segment and extends up to sacral canal, so simple infrarenal aortic occlusion easily leads to paraplegia.[16] Before starting this study, we preliminarily confirmed the appropriateness of our rabbit SCI model by comparing it with a rabbit LLI model.

Lu and colleagues[5] and Taira and associates[6] reported that in rat models aortic occlusion with hypovolemic hypotension caused more profound spinal cord hypoperfusion, resulting in severe ischemic injury of the spinal cord relative to normal arterial pressure. Although intraoperative hypotension as a result of blood loss is a common pathway to postoperative paraplegia, the decrease in perfusion pressure, hemoglobin, and circulatory volume associated with the blood loss are confounding factors in accurately evaluating the effect on the spinal cord of BP during aortic crossclamping. The effects on SCI of hypovolemia and anemia induced by exsanguination were not excluded in previous models. Recently, Toung and colleagues[7] reported that hypertension during aortic clamping improved neurologic outcome in a rat model. Although postoperative neurologic and histologic assessments were performed in that study, they did not show any actual data of SCI demonstrated by SCBF and tc-MEPs in their rat experimental model. The utility of their rat model thus remains unclear.

In this study, SBP during SCI had a positive effect on SCBF in a rabbit model. Increased collateral flow possibly contributed to maintain sufficient SCBF during SCI in the HBP group. Although there are some collaterals from pial anastomoses through the posterior spinal artery to the lumbar cord, the caudal SCBF is mainly supplied from the segmental arteries in rabbits.[16] On the other hand, there are many collaterals from the lumbar and internal iliac arteries through the anterior spinal artery to the caudal spinal cord in human beings.[17,18] Although the effect of collateral supply in rabbits is believed to be smaller than in human beings, the increased collateral flow may have protected motor neurons and prevented paraplegia in this study.

Spinal cord integrity can be monitored with somatosensory evoked potentials (SSEPs), and myogenic motor evoked responses with tc-MEPs. Because SSEPs provide false-negative results and slow responses, tc-MEPs tend to be used as the SCI monitor during thoracoabdominal aortic aneurysm surgery.[19,20] We recently used tc-MEPs to analyze SCI experimentally and clinically.[8,10] In this study, the time for tc-MEPs reappearance in the HBP group was faster, and the recovery ratio of tc-MEP amplitude through 30 minutes after reperfusion was larger than in the LBP and control groups. At 48 hours after SCI in this study, all rabbits in the HBP group did not demonstrate paraplegia, whereas most of the rabbits in the LBP and control groups demonstrated paraplegia. These findings suggest that slow recovery of tc-MEPs after SCI predicts poor neurologic outcome, as

previous reports have suggested.[8,10,21,22] Although half of the rabbits in the control group recovered to the baseline level at 30 minutes after reperfusion, they showed delayed paraplegia. The irreversible change in motor neurons thus may occur after the monitoring of tc-MEPs.

Histologic analysis in this study demonstrated that histologic damage was attenuated in HBP group, whereas significant damage was observed in both the LBP and control groups. There were also many TUNEL-positive neurons in the control group. In addition, the result of Western blot analysis suggested that neuronal death was most suppressed in the HBP group, whereas neuronal death was most facilitated in the LBP group among the 3 groups. The 120-kDa fragment of α-fodrin, which is a specific marker for apoptosis,[14] appeared in the LBP and control groups. Sakurai and coworkers[15] reported that apoptosis plays an important role in delayed paraplegia in the rabbit SCI model. In this study, the histologic and biochemical analyses suggest that delayed paraplegia may have been associated with apoptosis. On the other hand, rabbits in the LBP group both tended to show early paraplegia and had few TUNEL-positive neurons. Although we were unable to quantify the accurate number of necrotic neurons because of severe destruction and vacuolization of the gray matter, the spinal cord section in the LBP group tended to show characteristics of necrotic tissue. Further study is needed to elucidate a relationship between apoptosis or necrosis of motor neurons and paraplegia induced by SCI.

One of the factors involved in the development of ischemia-induced spinal cord injury is thought to be oxidative stress. Ege and colleagues[23] reported that a free-radical scavenger attenuated oxidative stress, and neurologic outcomes were improved in their rabbit SCI models. In this study, superoxide generation and myeloperoxidase activity were facilitated in the LBP group at 3 hours after SCI. Hypoperfusion during SCI may facilitate oxidative stress and subsequent neuronal damage and thus may cause early paraplegia. Meanwhile, superoxide generation and myeloperoxidase activity were suppressed in the HBP group at 3 hours after SCI relative to the LBP group. Sufficient blood flow during SCI may suppress oxidative stress, which could contribute to spinal cord protection.

Although this experiment supports the hypothesis that perfusion pressure in the upper spinal arteries should be increased by the infrarenal aortic occlusion, it also proves that increasing perfusion pressure only by aortic occlusion without phenylephrine (control group) is insufficient to prevent postoperative paraplegia. Pharmacologic intervention to increase perfusion pressure during aortic occlusion (HBP group) significantly prevented postoperative paraplegia in this experiment. Clinically, this study indicates that the maintenance of collateral flow could be effective in spinal cord protection, corresponding with the concept of the distal aortic perfusion. Distal aortic perfusion with left heart bypass or partial cardiopulmonary bypass has been clinically applied to maintain sufficient collateral flow to the spinal cord during aortic crossclamping, leading to decreased incidence of paraplegia.[1,2] We and others[2,4] have reported proximal MAP to be clinically maintained between 60 and 100 mm Hg and distal perfusion pressure kept above 70 mm Hg during aortic crossclamping.

One of the study limitations is that the normal BP in rabbits is different from that in human beings. The MAP ranged from 64.4 to 66.0 mm Hg in a study on BP in conscious rabbits.[24] Surgical procedure and aortic occlusion may influence BP, thus making the MAP in the control group relatively high in our study. Another limitation is that spinal cord vasculature in rabbits may be different from that in human beings. Another study limitation is that the SCBF may not have exactly reflected the blood flow of the anterior spinal artery because the SCBF was measured at the posterior side of the spinal cord. A final limitation is that this study could not simulate the situation in which the patient has coagulopathy and must be kept relatively hypotensive for a time to control the bleeding in clinical settings. To evaluate the effect of BP during aortic crossclamping on the spinal cord accurately, we eliminated the potential effects of hypovolemia, anemia, or reperfusion pressure in our study.

In conclusion, SBP augmentation during SCI in a rabbit model maintained sufficient SCBF so that ischemic insult to spinal cord and postoperative neurologic damage were reduced. This study suggests that it is important to maintain adequate BP for spinal cord protection during thoracoabdominal aortic surgery.

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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)

ETVBS

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.

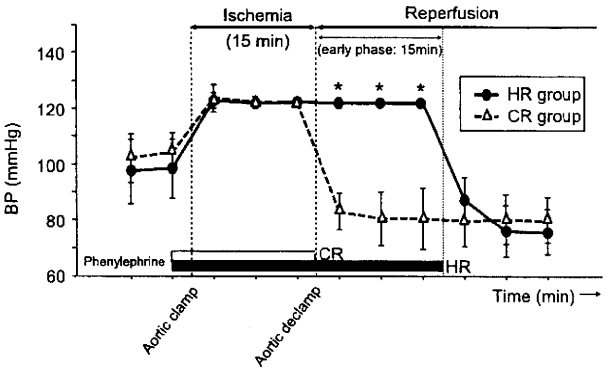

FIGURE 1. Systemic BP during surgery. There were no significant differences in BP during ischemia between the HR and CR groups. In the early phase of reperfusion, BP in the HR group was significantly higher than in the CR group. *$P < .05$. *BP*, Blood pressure; *HR*, high BP group; *CR*, control BP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

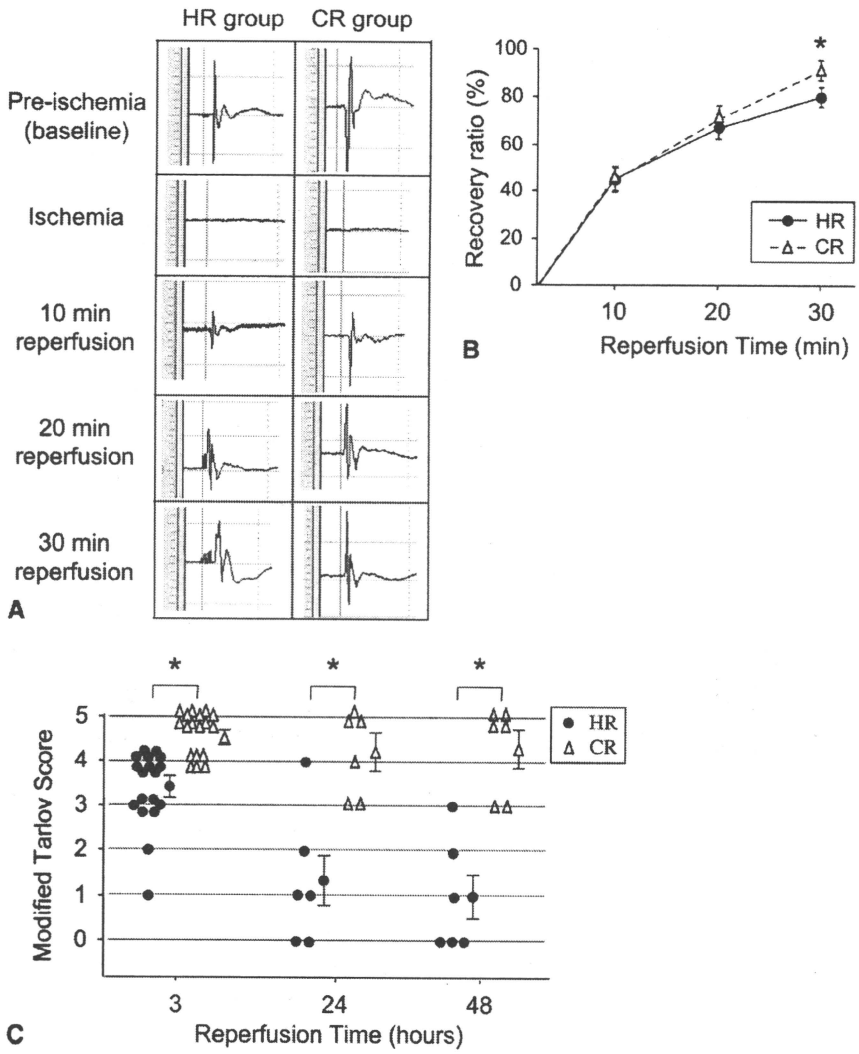

FIGURE 2. Intraoperative and postoperative neurologic assessment. A, Representative tc-MEP complex. B, Recovery ratio of tc-MEP amplitude at 10, 20, and 30 minutes of reperfusion. n = 18 in each group. C, Modified Tarlov score at 3, 24, and 48 hours of reperfusion. n = 18 at 3 hours and n = 6 at 24 and 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

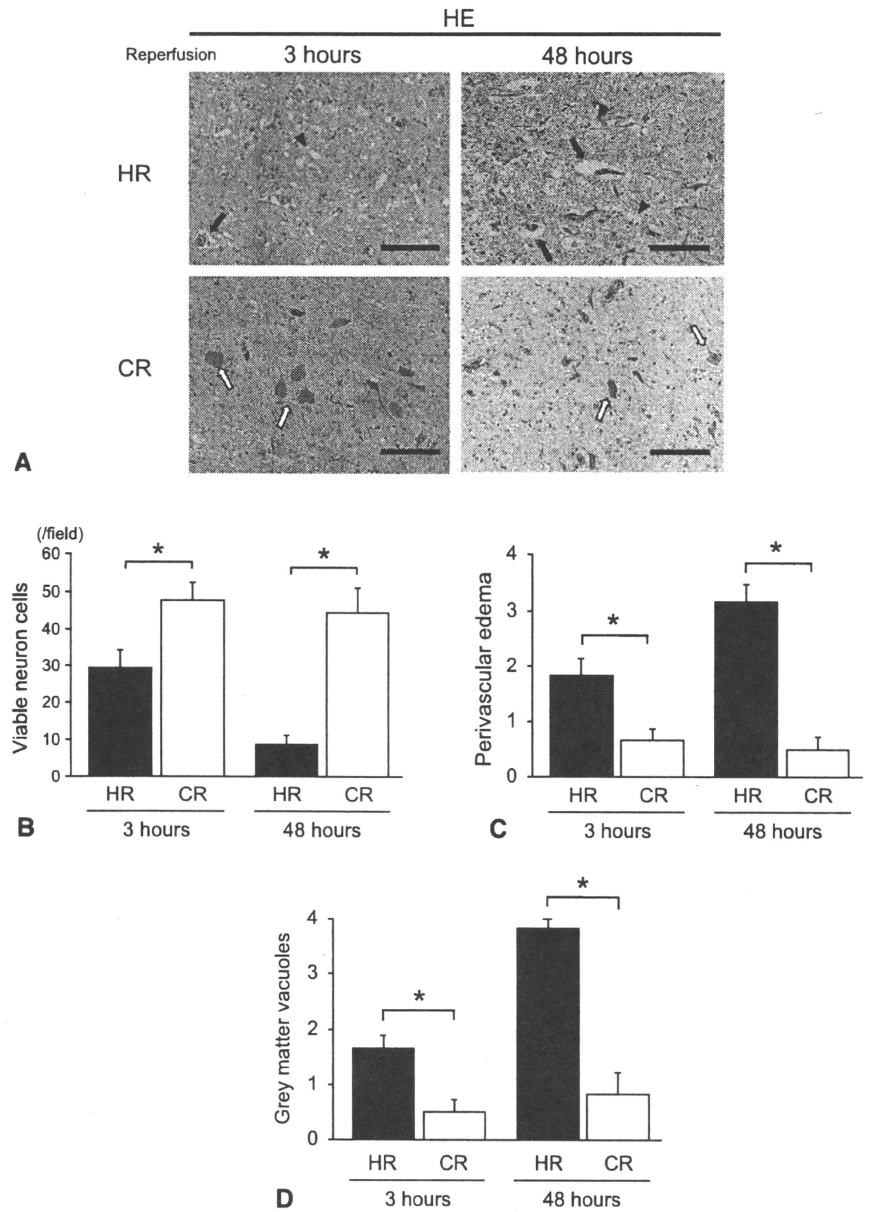

FIGURE 3. Postoperative histologic assessment. A, Hematoxylin–eosin staining in the ventral gray matter of spinal cord at 3 and 48 hours of reperfusion. Photomicrographs of sections show viable neuron cells (*white arrows*), perivascular edema (*black arrows*), and gray matter vacuoles (*black arrowheads*). 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

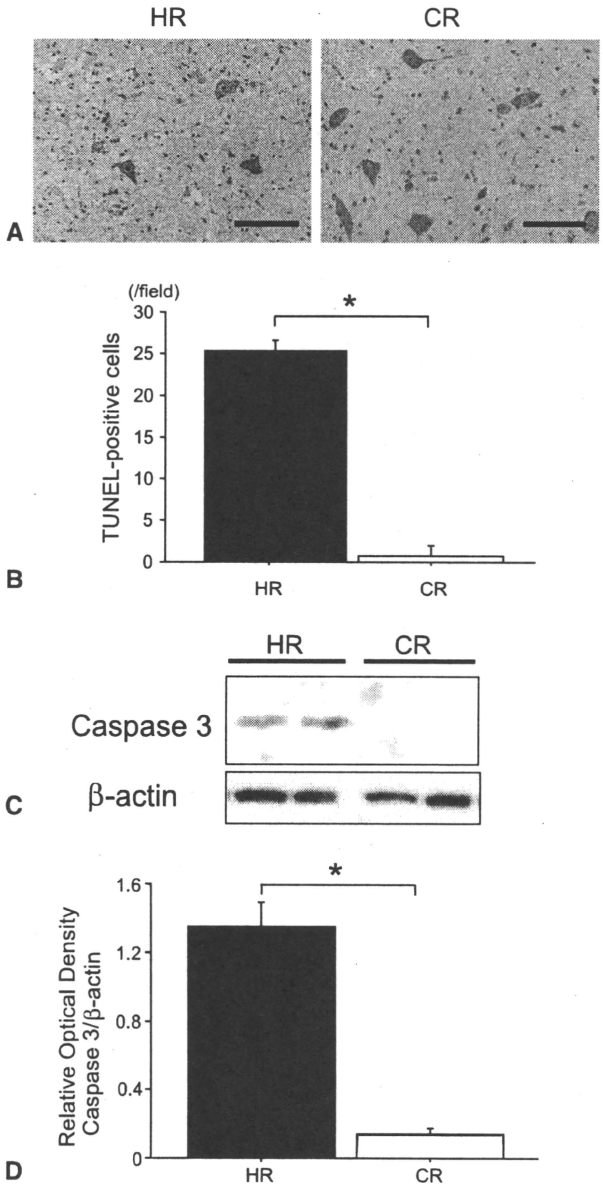

FIGURE 4. Postoperative evaluation of spinal cord apoptosis. A, TUNEL staining of the ventral gray matter of spinal cord at 48 hours of reperfusion. Photomicrographs of sections show TUNEL-positive cells (*brown*). Bar = 200 μm. B, Quantitative analysis of TUNEL-positive neuron cells at 48 hours of reperfusion. 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

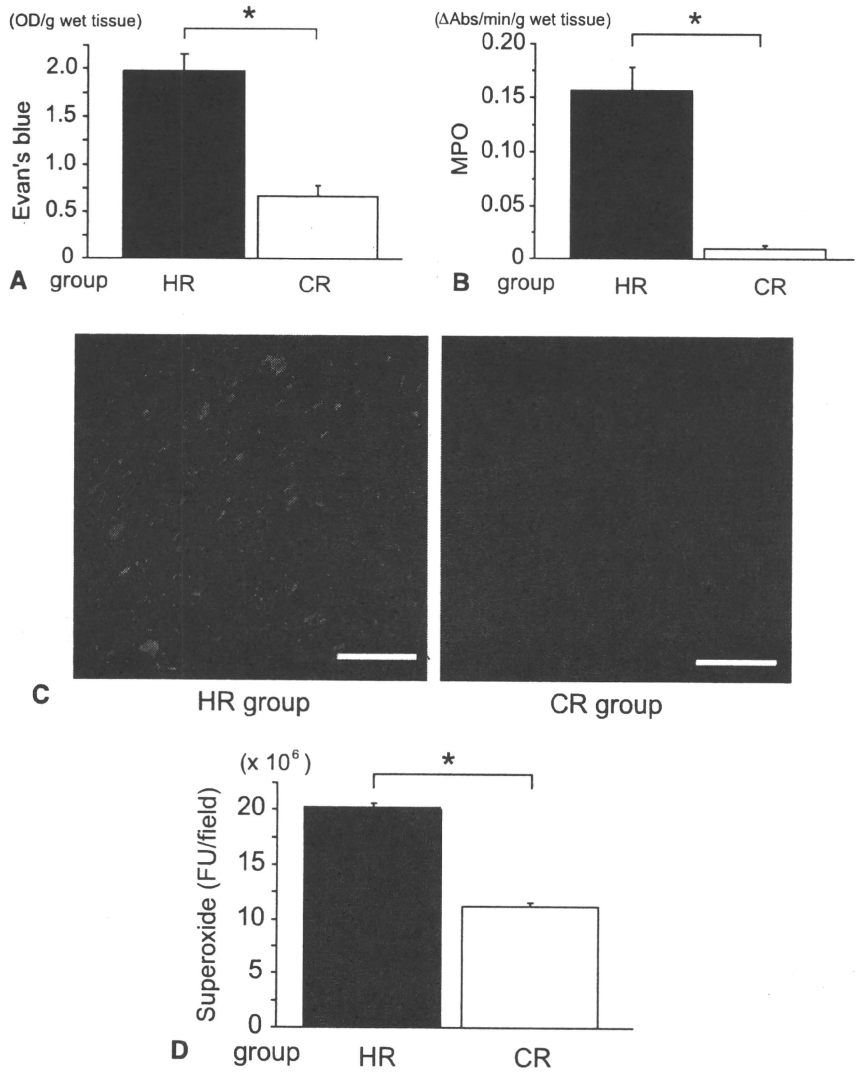

FIGURE 5. Early reperfusion injury in the spinal cord at 3 hours of reperfusion. A, Vascular permeability. B, MPO activity. *ΔAbs* indicates a change in absorbance. C, In situ detection of superoxide generation (*red fluorescence*). Bar = 200 μm. D, Semiquantitative analysis of the superoxide generation. 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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ADULT CARDIAC

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-

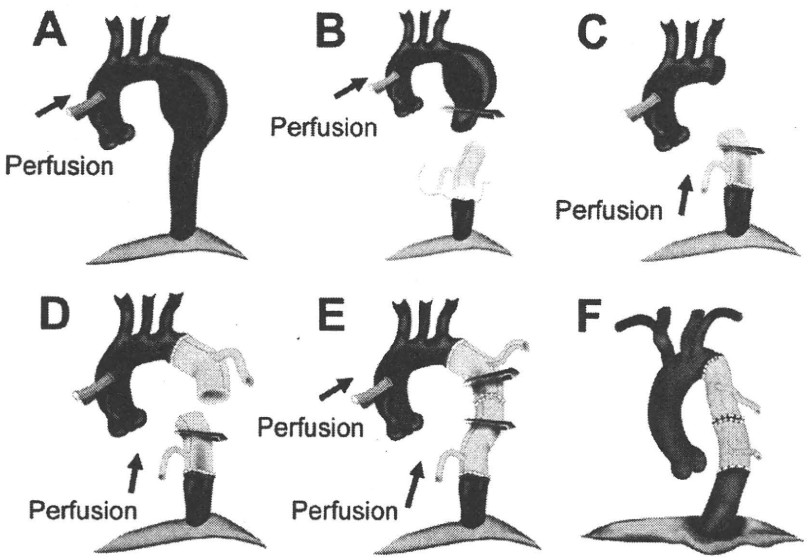

Fig 1. Schematic diagrams of the operative procedure. (A) Ascending or arch aortic cannulation (AAC) was performed to maintain antegrade flow. After establishment of cardiopulmonary bypass, cooling was begun to achieve a rectal temperature of 18°C. (B) After aortic cross-clamping of the descending aorta, 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 · min^{-1} · 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.

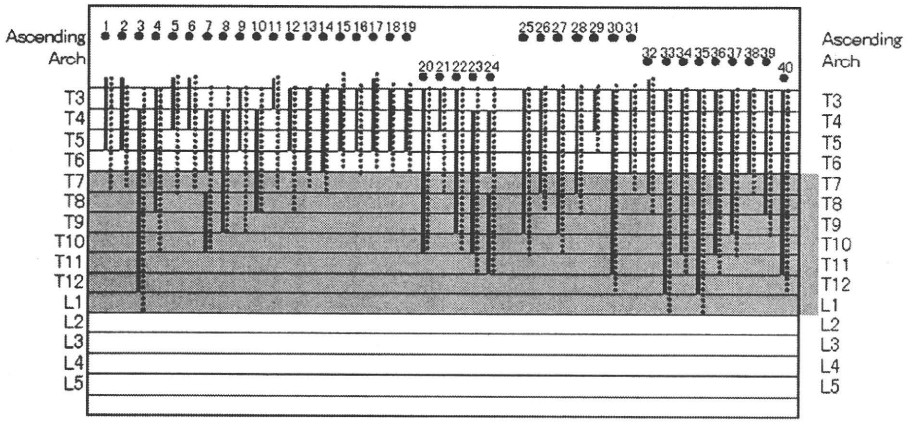

Fig 2. Aortic cannulation site, distribution of aortic disease, and range of aortic replacement. Ascending or arch aortic cannulation (AAC) was performed from the proximal site of the aortic disease. The patients from No. 1 to No. 24 had a nondissecting aneurysm; the patients from 25 to 40 had chronic 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