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Discussion

Dr John Elefteriades *(New Haven, Conn).* I congratulate the authors on an outstanding paper on hybrid therapy for aortic arch aneurysm. The number of patients is large, the follow-up is quite complete, and the duration of follow-up is long. The mortality and stroke rates are excellent. I do take issue with the underlying theme of the paper, that a direct surgical approach to the aortic arch is to be feared and avoided in favor of extra-anatomic and stent-graft therapy. Direct approaches to the aortic arch are safe, durable, and time tested. Many series, including our own recently presented experience, show stroke and mortality rates with the conventional approach that are very comparable with those in your presentation.

Also, our experience shows that the descending aorta is not commonly problematic, even in the long term, after successful type A repair, raising doubt about whether adjunctive stent therapy in the descending aorta is really necessary.

I have 3 questions. My first question has to do with early mortality. You list your hospital mortality as 3%, but by 6 months 19% of the patients are dead. How did another 16% of the patients die within 6 months of hospital discharge? What was going on clinically and radiographically with their aortas and their brains before death?

My second question has to do with anatomic morphology and selection for operation. It appears that a large proportion of cases in this paper are not really extended arch lesions, as the title indicates, but rather typical type A and type B dissections. I am uncomfortable with the classification of the large number of patients with chronic type B dissection in this series as having "arch" lesions. Descending dissections are nearly always limited to the region distal to the subclavian artery. These lesions are well treated by a relatively straightforward resection via left thoracotomy on left atrial–femoral artery bypass. With a clamp placed between the left carotid and left subclavian arteries, one has excellent exposure for the proximal anastomosis. Why did the authors classify these as arch lesions and perform their complex extra-anatomic repair?

For the third question, let us consider the failures of therapy. How do you explain the persistence or progressive enlargement of the aneurysm in 25% of your patients?

Congratulations on an excellent presentation.

Dr Shimamura. Thank you, Dr Elefteriades, for your kind comments and important questions.

Regarding the first question about mortality, the early mortality included 3 patients with postoperative strokes, and we lost these 3 patients within 1 year. It could be said that we have lowered the quality of life of the patients postoperatively, but the death is not associated directly to the stent graft. Also, there is a patient who had an fatal aortoesophageal fistula, as I showed in my slides. We lost this patient after successful treatment for a ruptured aneurysm however, this endoluminal treatment does not resect the whole aneurysm, so this kind of problem needs more investigation. Most of the late deaths are associated with the relatively high risk of the background of the patients. We introduced stent-graft treatment in clinical use in 1993, and this is the very first in Japan. Many patients with severe comorbidities were sent to our institution, and we have to deal with these high-risk patients. This could explain the relatively poor overall survival in the long term. However, we believe that avoidance of the aortic arch–related deaths is satisfactory.

Your second question concerned the indication for this procedure. Yes, we include type B dissection for this procedure, but the indication is only for the complication-specific treatment for type B dissection. We undertook this procedure for the patient with type B dissection who has a very proximal intimal tear near to the subclavian artery. These tears cannot be treated with endovascular repair. Of course, there are options to do graft replacement with a left thoracotomy, but we think that closure of the intimal tear via a median approach is compatible with this treatment, and the results are satisfactory in our study.

Regarding the third question, the majority of the aneurysms have an extension distally, and it was thought to be difficult to treat that extension with conventional treatment via a median sternotomy. Our series contains about 20% of patients who have a relatively proximal location of the distal end of the aneurysms, and these could be treated with traditional surgical repair. However, this procedure has an advantage even in these aneurysms, because with the stent graft you can alternate your distal anastomosis and manipulate only in the proximal arch. This could be a very easy way to control the bleeding.

Dr Bruce W. Lytle *(Cleveland, Ohio).* Regardless of the specific indications for how often you do a debranching or whether this is just an extension of a conventional arch repair, the concept of putting in a stent graft during an open aortic operation, perhaps to extend it to the descending aorta, makes a lot of sense. We certainly have tried to do this. One of the things I have been really disappointed in is the lack of response of our industrial partners to this issue. We have tried to get a number of the companies interested in making devices specifically for the purpose of being put in at the time of surgery. They just cannot seem to get this.

The way you wrap the string around the graft is very clever, but are you still doing it that way after 14 years? Has there not been some company that has agreed to manufacture that on sort of a prospective basis?

Dr Shimamura. We do not use the sheath to deliver the stent graft, but we have no company that makes this kind of commercially available stent graft. I hear that that kind of device is available in Germany, and I think the production of such a device could expand this technique widely.

Dr Lytle. I invite our colleagues to help our industrial partners to understand that we are interested in this, because regardless of the specific indication, there is no doubt that this concept will have some degree of usefulness.

臨床

胸腹部大動脈瘤に対する分枝再建を併用したステントグラフト治療

倉谷　徹

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SUMMARY

胸腹部大動脈瘤に対する手術成績は，未だ満足し得るものではない．特に術後脊髄麻痺は極めて重篤な合併症である．そこでステントグラフト手術に脊髄麻痺が発生しにくい点に着目し，腹部主要分枝に対してバイパス術（分枝再建）を行った上で，ステントグラフトを内挿するハイブリットステントグラフト治療を考案した．その結果，十分に満足できる手術成績を得ることができ，特に術後脊髄麻痺を認めていないことは特筆されることである．現在，Fenestrated deviceやBranched deviceを用いた胸腹部大動脈瘤に対するステントグラフト手術が行われつつあるが，まだDevice自体に未熟な点も多く良好な手術成績を得られていない．今後さらなるDeviceならびに術式の開発が期待される．

はじめに

大動脈瘤に対するステントグラフト治療（Endovascular aortic repair; EVAR）は，1986年にAlexander Balkoがnitinol製Z stentをポリウレタンで被覆した人工血管を羊の大動脈に挿入したのが最初であり[1]，1991年にJuan C. Padoriらが腹部大動脈瘤に対するEVARの臨床報告を行っている[2]．このように，この術式は導入されてから20年も経っていない新しい術式であるが，根治性と革新的を併せ持った低侵襲術式である．しかしその技術面，Device面ともまだまだ未熟な点も多い．特に分枝血管が動脈瘤に巻き込まれている症例においては，現状のステントグラフトでは治療不可能であると言わざるを得ない．なぜなら現状では，ステントグラフト形状は1本の筒でありステントグラフトを留置した部位の分枝血管はすべて犠牲になる．そこで現状のステントグラフトを用いてそのような部位を治療するために考えられたのが，Debranched EVARといわれるハイブリッドステントグラフト治療である．この手術が必要となるのは，弓部と胸腹部大動脈瘤であるが，弓部大動脈瘤に対しては，多くの施設で頸部分枝同士のバイパス術（Debranching）を行った後TEVARを行う術式が行われている．

そこで今回，我々が1997年より行ってきた胸腹部大動脈瘤に対するハイブリットステントグラフト治療を解説するとともに，その現状と未来について報告する．

胸腹部大動脈瘤に対するステントグラフト治療

1．分枝再建を行ったハイブリッドステントグラフト治療

胸腹部大動脈瘤は，瘤の部位のため最も治療の困難な大動脈瘤の1つである．すなわち，弓部大動脈瘤と同様に腹部主要分枝血管が瘤から分岐するため，それらの血管を慎重に再建する必要がある．さらに胸腹部大動脈瘤の場合，脊髄への栄養血管である肋間動脈が大動脈より分岐しており，特にAdamkiewicz動脈を必ず同定して再建する必要があると考えられてきた．腹部分枝および肋間動脈再建の上，大動脈人工血管置換術が通常の手術として行われてきたが，術後脊髄麻痺は20%程度のリスクがあると言われてきた．それに対して種々の脊髄保護手段が併用され

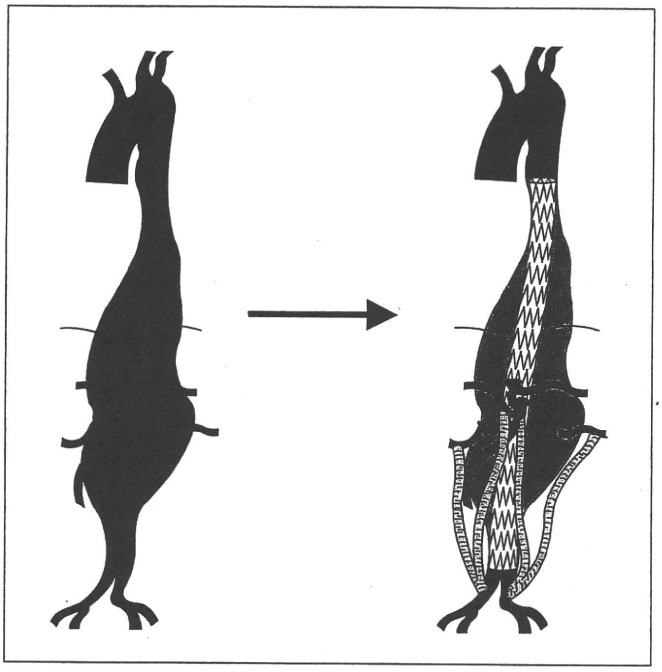

図1　腹部分枝再建を併用したハイブリットステントグラフト手術

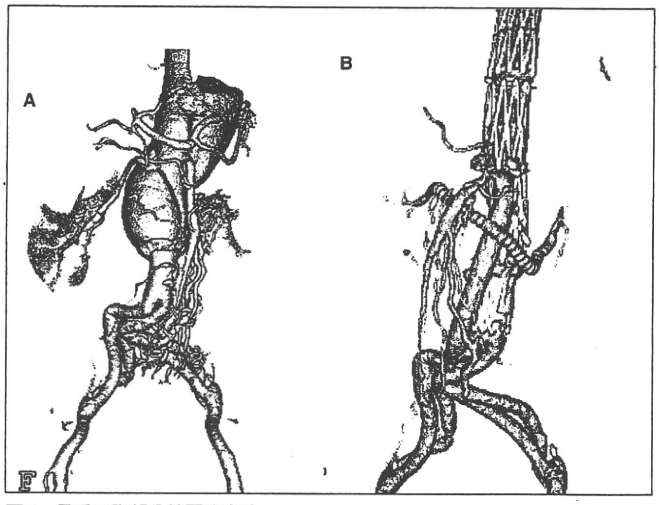

図2　最近の腹部分枝再建方法
A：術前3D-CT
B：術後3D-CT
右総腸骨動脈―上腸間膜動脈バイパス(10mm Hemashield)
10mm Hemashield―両側腎動脈(6mm Ringed Gore-Tex)
腹腔動脈は結紮

ていたが，肋間動脈再建や補助術式を用いても10-15%程度の症例に脊髄麻痺を認めている．

我々は，1993年にB型解離性大動脈瘤に自作ステントグラフトを用いて，世界に先駆けて手術を行った．以来，胸部大動脈瘤を中心にステントグラフト治療を進めてきた．その結果，胸部下行大動脈瘤に対するステントグラフト治療において，術後脊髄麻痺の発生率が極めて低いことに着目して，1997年より腹部主要血管に対するバイパス術の後TEVARを行う術式を考案した(**図1**)．

この術式は開腹の上，総腸骨動脈か大動脈分岐部分より腹部4分枝(腹腔動脈，上腸間膜動脈，両側腎動脈)にバイパスを行う．バイパス経路は，大動脈前や後腹膜経由で行い，バイパス方法としては，以前は各分枝血管に1本ずつバイパスを置く方法を行ってきたが，バイパス術が非常に煩雑になり，かつグラフトがそれぞれ長くなることがあった．そのため腎動脈に行ったバイパス1本に閉塞を認めたため，2004年よりCT画像の術式に変更した(**図2A，B**)．つまり上腸間膜動脈に10-12mmの人工血管でバイパスを行い，その人工血管にCross shapeになるよう6mm PTFE graftを側々吻合し，そのグラフトを用いて両側腎動脈と端々吻合を行う．腹腔動脈にバイパスを行う場合は，上腸間膜動脈への人工血管から大伏在静脈を用いて，胃の後面を通して腹腔動脈に端側吻合を行う．術前に上腸間膜動脈から腹腔動脈へ副側血行が良好な症例では，腹腔動脈を閉鎖することもある．このようなバイパス術(Debranching)を行ってから，それぞれの分枝血管の大動脈分岐部にて結紮を行う．続いて胸腹部大動脈瘤を完全にカバーするようにステントグラフトを挿入するが，通常2-3本のDeviceを必要とすることが多い．現在TAG®は2本までが保険適応内であるため，時としてHome-made deviceを1本使用せざるを得ない場合もある．

1997年より72名にこの術式を行ったが，全例に手術成功し，通常手術へのConversionは認めていない．1名が人工血管感染により死亡し，腎動脈へのバイパスの閉塞を1例に認めている．また急性腎不全を3例に認めたが，透析を導入した症例は認めていない．この72例において1例もparaplegia, parapresisを認めておらず，全症例とも独歩退院している．

この術式は開腹せざるを得ず，決して低侵襲であるとは言えない．しかし術後脊髄麻痺が防げることは，患者本人にとってのQOLから考えると，極めて有用な術式と考えられる．またAdamkiewicz動脈を再建せず，さらに1本の肋間

動脈も再建しないこの術式で脊髄麻痺が発症しないということは，脊髄麻痺の発症機序自体を再考する必要があると考えられるのではないか．この領域に関しては今後さらなる検討が必要であろう．

2. Fenestrated DeviceとBranched Device

この胸腹部大動脈瘤に対するステントグラフト治療において，次に導入されるのはFenestrated deviceさらにはBranched deviceであろう．ただこれらのDeviceは1990年代にすでに導入されている．Fenestrated deviceを用いて1996年にParkらが初めて手術を行い[3]，1997年に井上らが世界に先駆けてBranched type deviceを用いて手術を行っている[4]．その後企業製造のCustom made deviceを中心に手術が行われてきたが（**図3**），その成績はあまり満足し得るものではなく，10%弱に術後腎不全を認め，通常の腹部大動脈瘤に対するEVARと比べて高値である．最近の傍腎動脈型腹部大動脈瘤を含んだ胸腹部大動脈瘤に対するFenestrated typeとBranched type deviceを用いた手術成績を6施設で集計した[5-10]．336例において死亡率は2.1%，腹部分枝血管の閉塞率は7.7%，腎不全は17.7%に及んでいる．確かに死亡率は低いが，分枝血管の閉塞，腎不全を中心にまだまだ解決すべき問題は多い．また胸腹部大動脈瘤に対するBranched TEVARのみの報告では[11]，23症例にこの術式を行う予定とし，11例に施行することができた．8例がまだDevice製造のため待機であるが，2例はthin slice CTにて不可能と診断され，1例は待機中に大動脈破裂で死亡し，1例は破裂のため通常手術が行われた．手術を施行した11例すべてが成功したが，3例が術後早期に死亡し，2例の腎動脈へのステントグラフトが閉塞，1例にparaplegia，1例にparaparesisを認めた．この成績から推測するに，やはりDeviceの製造に長期間を要するために，待機期間中に破裂などの問題が生じる．さらに現状では，死亡率も高く，分枝血管の閉塞率も高い．脊髄麻痺などの合併症に関しては，術中の補助手段（Cerebrospinal drainageなど），または術後管理に問題がある可能性がある．まだまだDeviceおよび術式は未熟であり，実用化までにはまだ時間を要すると判断せざるを得ない．

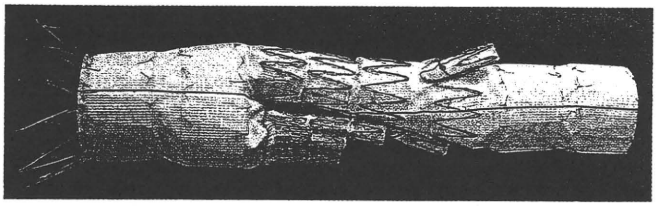

図3　Bracnched device for thoraco-abdominal aortic aneurysm

まとめ

胸腹部大動脈瘤に対するステントグラフト治療における現状を述べた．ステントグラフトを用いた大動脈治療は，ステントグラフトの形状を改善させ，あらゆる大動脈領域にも使用できるように，それぞれの企業が競い合っているのが現状である．しかし現状ではBranched deviceによるステントグラフト治療を胸腹部大動脈瘤に導入するのは，時期尚早ではないか思われる．さらなるDeviceの改良とBranch挿入時での血栓のProtection方法などを早急に進める必要があると考える．現時点では，胸腹部大動脈瘤に対しハイブリットステントグラフト治療が十分満足できる成績を得る術式ではないかと推察される．さらに今後の方向性として，グラフト及びステント自体の改良，さらには開発が必要であると思う．我々もステントグラフト自体の開発，特に次世代グラフトの開発によりステントグラフトの永遠のテーマであるEndoleak, Migrationの根絶を目指している．

これからの10年に大動脈疾患に対する治療方法がいかに変化するか強い期待を持って，さらなる挑戦を続けていきたいと思う．

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Extended replacement of aortic arch aneurysms through left posterolateral thoracotomy

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Abstract

Objective: To present our experience of total aortic arch replacement through a left posterolateral thoracotomy. **Methods:** Sixteen patients (13 males; mean age 62.1 ± 11.3 years) with extended thoracic aortic aneurysms, including those in the thoracoabdominal aorta, underwent replacement through a left posterolateral thoracotomy. The pathology of the diseased aorta was non-dissecting aneurysm due to aortitis in 1 patient and aortic dissection in 15 patients (acute type A: 1, chronic type A: 12, chronic type B: 2). In a prior operation, the patient with aortitis had undergone the Bentall procedure with endovascular stenting of the brachiocephalic artery, and among the other 15 patients, one previously had endovascular stenting for the aortic arch and 12 had hemi-arch replacement for acute type A dissection. Extension of arch replacement was the aortic arch and descending aorta in eight patients, the ascending arch and descending aorta in five patients and the descending arch, and thoracoabdominal aorta in three patients. Additional retroperitoneal dissection was required for the repair of a thoracoabdominal aortic aneurysm. **Results:** One patient died of traumatic cerebral hemorrhage on day 145 (hospital mortality 6.3%). Average duration of ventilation support was 19.4 ± 17.0 h and length of ICU stay was 3.6 ± 1.6 days. Actuarial survival at 2 years after the operations was 67.7%. However, no aortic-related mortality was observed during follow-up. **Conclusions:** Early results of extended aortic arch replacement through a left posterolateral thoracotomy were satisfactory in selected patients.

Keywords: Extended thoracic aneurysm; Left side thoracotomy

1. Introduction

Repair of an extended thoracic aneurysm is challenging. A staged operation is often preferred with safety as the priority [1,2]; however, this strategy may result in greater than expected mortality when considering the combined mortality from the first and second procedures as well as death in the interval between procedures [3].

A one-stage operation is highly effective in terms of both long-term survival and quality of life. However, careful patient selection based on preoperative comorbidity is of vital importance. Simple incision and good aortic exposure is mandatory in the one-stage treatment for extensive thoracic aneurysms. Brain protection during the arch replacement is another important issue in obtaining a satisfactory outcome [4].

Median sternotomy is the gold standard to access the aortic arch, however, exposure of the distal descending aorta is limited even if additional left anterolateral thoracotomy is applied. Residual dissection from the aortic arch down to the descending or thoracoabdominal aorta after ascending aortic replacement for acute type A dissection is often encountered, which requires an extended replacement of the aortic arch. Kouchoukos et al. reported excellent results of a one-stage operation for extended thoracic aneurysms through a clam-shell incision using the arch-first technique [5]. Left posterolateral thoracotomy is another beneficial option to access the ascending, arch and entire descending aorta, which allows for performance of even a thoracoabdominal procedure by entering the retroperitoneal space.

This report describes the surgical experience in repair of thoracic aneurysms through the left posterolateral thoracotomy.

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Table 1
Patient profile.

Case	Age	Sex	Extent	Dissection	Previous operation	Preoperative comorbidity
1	52	M	As, A, Ds	No	Bentall	Aortitis
2	80	M	As, A, Ds	Chronic-B	Nil	DIC
3	73	M	As, A, Ds	Chronic-B	TEVAR	CRF
4	44	M	As, A, Ds	Acute-A	Nil	Leg malperfusion
5	80	M	STJ, As, A, Ds	Chronic-A	Hemi-arch	s/p AAA repair
6	70	M	A, Ds	Chronic-A	Hemi-arch	Nil
7	55	M	A, Ds	Chronic-A	Hemi-arch	Nil
8	69	M	A, Ds	Chronic-A	Hemi-arch	Epidural hematoma
9	48	M	A, Ds	Chronic-A	Hemi-arch	IgA nephropathy
10	58	M	A, Ds	Chronic-A	Hemi-arch	Nil
11	68	F	A, Ds	Chronic-A	Hemi-arch	Nil
12	77	F	A, Ds	Chronic-A	Hemi-arch	Tracheostomy, malignant
13	60	M	A, Ds	Chronic-A	Hemi-arch, TEVAR	Stroke, DIC
14	62	M	A, Ds, TA	Chronic-A	Hemi-arch	OMI, stroke, CRF
15	64	F	A, Ds, TA	Chronic-A	Hemi-arch	Nil
16	49	M	A, Ds, TA	Chronic-A	Hemi-arch	Nil

As: ascending aorta, A: aortic arch, Ds: descending aorta, STJ: sino-tubular junction, TA: thoracoabdominal aortic aneurysm, TEVAR: endovascular thoracic aortic repair, DIC: disseminated intravascular coagulation, OMI: old myocardial infarction, CRF: chronic renal failure, AAA: abdominal aortic aneurysm.

2. Methods and patients profile

From 2002 to 2007, 16 patients underwent one-stage repair of extended thoracic aneurysms (all including the aortic arch and descending aorta of varying lengths) through a left posterolateral thoracotomy. Profiles of the patients were retrospectively reviewed and are shown in Table 1. The average age was 62.1 ± 11.3 years (range: 44–80) and 13 of the 16 patients were male. Chronic type A dissection (n = 12) was the major aortic pathology among these patients and all 12 patients (cases 5–16) underwent ascending aortic replacement and had progressive enlargement of residual dissection of the aortic arch and the descending aorta. One patient (case 1), who had undergone a Bentall operation and stenting in the brachiocephalic artery aneurysm due to aortitis, had a non-dissected aneurysm from the ascending, aortic arch to the descending aorta. Another patient (case 2) had dilated chronic type B 3-channel dissection associated with the arch aneurysm. Two patients (cases 2 and 3) had chronic type B dissection. Cases 3 and 13 had undergone endovascular thoracic aortic repair (TEVAR) from the aortic arch to the descending aorta, followed by progressive aortic dilatation due to type I endoleak. One patient (case 4) had acute type A aortic dissection complicated by rupture of the descending aorta and right leg malperfusion [6]. Three patients (cases 14, 15 and 16) had extensive dilation further down to the thoracoabdominal aorta (Crawford type II, I, I) (Table 1).

3. Preoperative risk evaluation (Table 1)

With regard to preoperative brain complications, one patient (case 8) had an epidural hematoma, which required the external decompression of the brain before the aortic repair and another (case 13) had experienced a stroke after the previous TEVAR. Case 14 had stenosis of the right middle cerebral artery accompanied by an old cerebral infarction. Three patients had preoperative chronic renal failure (cases 3, 9 and 14). Case 5 had an abdominal aortic aneurysm (AAA) and previously had undergone the replacement of an AAA. Two patients (cases 2 and 13) were diagnosed to have DIC with a decreased platelet count and increased FDP level. The average standard EuroSCORE was 9.7 ± 2.5, ranging from 6 to 15. Case 4, who had acute type A aortic dissection with left leg malperfusion and a rupture in the left pleural cavity, underwent surgery on emergency basis (Table 2).

4. Surgical procedure

With the patient in the right recumbent position, the entire thoracic aorta was exposed through the 4th intercostal spaces with or without left rib-cross thoracotomy [7]. The 5th rib was transected anteriorly or posteriorly, which provided sufficient aortic exposure (Fig. 1A). The 6th rib was

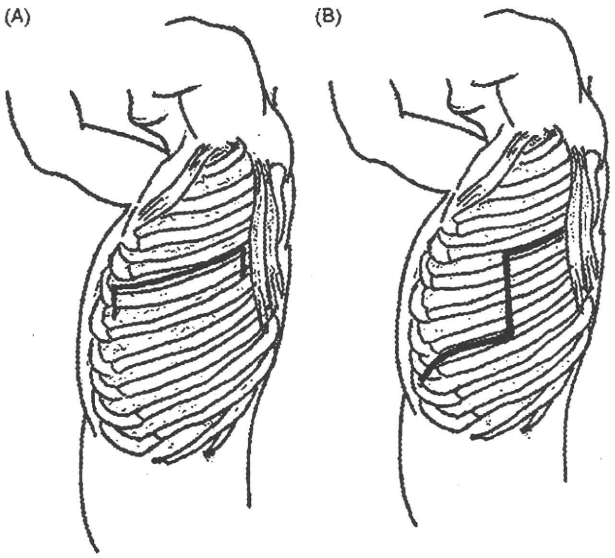

Fig. 1. Schema of thoracotomy. (A) Left side thoracotomy through the left 4th intercostal space. The 5th rib was transected anteriorly or posteriorly. (B) Left side rib-cross thoracotomy. The 4th and 7th intercostal spaces were opened. The 5th, 6th, and 7th ribs were transected at the midaxillar line, afterward the 8th costal cartilage was transected.

Table 2
Operative procedure and outcome.

Case	Urgency	Repair	Brain protection	Reconstruction of arch vessels	SCP/DHCA time (min)	Myocardial ischemic time (min)
1	Elective	As, A, Ds	DHCA, RCA	Island, arch-first	40	66
2	Elective	As, A, Ds	DHCA, RCA	Island, arch-first	30	60
3	Elective	As, A, Ds	DHCA, RCA	Island, arch-first	43	60
4	Emergent	As, A, Ds	SCP	Three branched	102	172
5	Elective	As, A, Ds	SCP	Three branched	162	91
6	Elective	A, Ds	SCP	Island	79	113
7	Elective	A, Ds	SCP	Island	84	97
8	Elective	A, Ds	SCP	Island	97	107
9	Elective	A, Ds	SCP	Island	56	68
10	Elective	A, Ds	SCP	Island	64	54
11	Elective	A, Ds	SCP	Island	55	65
12	Elective	A, Ds	SCP	Island	83	92
13	Elective	A, Ds[a]	SCP	Island	90	70
14	Elective	A, Ds, TA	SCP	Island	53	62
15	Elective	A, Ds, TA	SCP	Island	108	81
16	Elective	A, Ds, TA	SCP	Island	64	68

As: ascending aorta, A: aortic arch, Ds: descending aorta, FA: femoral artery, FV: femoral vein; mPA: main pulmonary artery, RA: right atrium, DHCA: deep hypothermic circulatory arrest, RCA: retrograde cerebral perfusion, SCP: selective cerebral perfusion.
[a] 8th intercostal artery reattachment.

transected particularly for thoracoabdominal procedure. With regard to the rib-cross thoracotomy (case 4), a skin incision was made from the midpoint between the spinal process and the scapula, around the lower end point of the scapula, down to the left subchondral lesion. The 4th and 7th intercostal spaces were opened, after which the 5th, 6th, and 7th ribs were transected at the midaxillar line. The 8th costal cartilage was transected along the incision through the 7th intercostal space (Fig. 1B). The sternum was not transected and the left internal thoracic artery was preserved in all cases. Cardiopulmonary bypass was established using the femoral artery for arterial return and the left femoral vein ($n = 7$), the pulmonary artery ($n = 8$) or both ($n = 1$) for venous drainage. Patients were cooled down to at 22.8 ± 3.8 °C (range: 16–28 °C) as measured by a tympanic thermometer. An aortic cross-clamp was placed on the mid-part of the descending aorta, maintaining lower body perfusion. The aorta was opened from the proximal descending aorta to the ascending aorta mainly up to the previous prosthetic graft for the ascending aortic replacement. Cardioplegic solution was given from inside the ascending aorta with a balloon-tipped catheter, and selective cerebral perfusion was established using balloon-tipped catheters from inside the aortic arch. A Dacron graft was anastomosed to the previous graft or the ascending aorta first in the majority of cases (Fig. 2). Afterward, arch vessels were reconstructed as an island cuff in 14 cases. Brain protection was provided by antegrade selective cerebral perfusion under deep hypothermia in 13 patients or deep hypothermic circulatory arrest with complementary retrograde cerebral perfusion in 3 patients (Table 2). Systemic rewarming was initiated after the reconstruction of the arch vessels. Perfusion of the heart and brain was re-established through the side branch of the prosthetic graft. The distal descending aorta was transected at a normal caliber, and the graft was anastomosed to both the true and false lumen to maintain patency distally and to prevent malperfusion of the visceral vital organs or legs. Three patients (cases 14, 15 and 16) with a dilated thoracoabdominal aorta underwent additional replacement down to the previous abdominal Y graft or the terminal aortic bifurcation under the selective perfusion of visceral organs (Fig. 3). Five intercostal arteries were reattached in each case.

5. Extent of the repair

The extent of the thoracic aortic replacement is shown in Table 2, which was from the ascending aorta, arch to the mid-descending aorta in five patients (cases 1–5), aortic arch to the mid-descending aorta in eight patients (cases 6–13) and from the arch down to the thoracoabdominal aorta in three patients (cases 14–16), respectively.

5.1. Statistical analysis

Data were expressed as mean ± SD. Actuarial survival was assessed by the Kaplan–Meier method using the SPSS package for Windows (SPSS Inc., Chicago, IL).

6. Results

6.1. Early results

One patient (case 2), who had the comorbidity of DIC, died during hospitalization from traumatic brain bleeding on day 145 (hospital mortality 6.3%). Cardiopulmonary bypass time was 209.1 ± 58.8 min, myocardial ischemic time was 82.9 ± 29.8 min, SCP time was 84.4 ± 29.7 min and CA with RCP time was 37.7 ± 6.8 min (Table 2). Postoperative ICU stay was 3.6 ± 1.6 days. The postoperative profiles of the patient group are shown in Table 3. A reversible ischemic neurological deficit manifested by right forearm paralysis was observed in case 11, but no other brain complications were noted. Case 14, who underwent extended replacement down to the thoracoabdominal aorta, had temporary paraparesis and ischemic colitis, but had recovered com-

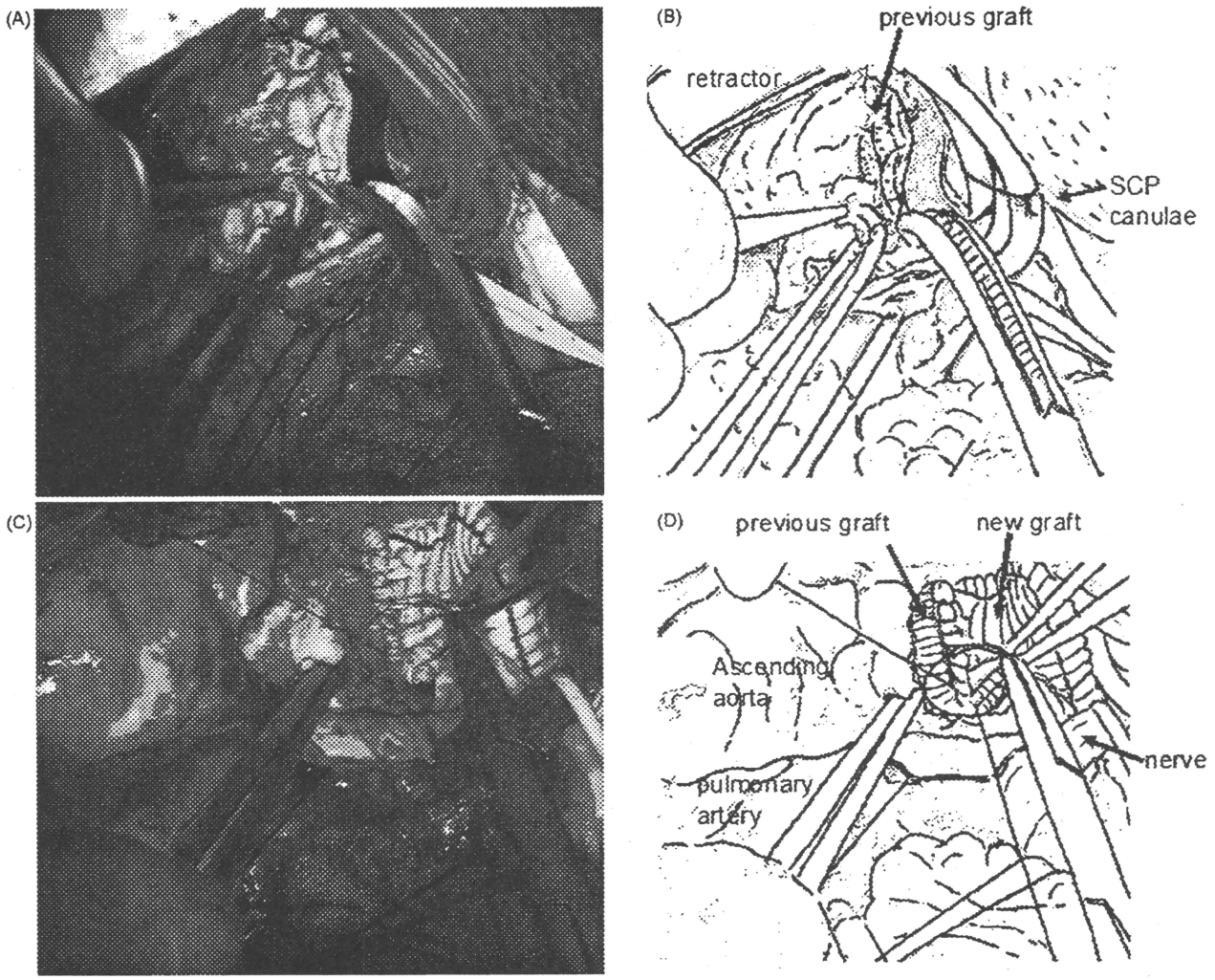

Fig. 2. Exposure of the ascending aorta and aortic arch through left side thoracotomy (case 11). (A) Surgeon's view through the left side thoracotomy through the left 4th intercostal space. Aortic arch aneurysm was opened, through which antegrade selective cerebral perfusion (SCP) cannulae was inserted into neck vessels. Previous graft was grasped by Kelly clamp. (B) Schema of (A). (C) New graft was anastomosed to the previous graft. Ascending aorta was accessible through this thoracotomy. (D) Schema of (C).

Table 3
Postoperative patent profile.

Number	Respiratory support (h)	ICU stay (days)	Complications	Outcome
1	15	4	Nil	Alive
2	19	3	Traumatic intracranial bleeding, GI bleeding	Dead
3	17	3	Hoarseness, pleural effusion	Alive
4	56	6	Phrenic nerve palsy, prolonged respiratory assistance	Alive
5	16	4	Mediastinal bleeding	Alive
6	14	3	Af	Alive
7	33	3	Pleural effusion, prolonged respiratory support	Alive
8	14	5	Nil	Alive
9	7	2	Nil	Alive
10	4	2	Nil	Alive
11	5	3	RIND	Alive
12	7	3	Pneumothorax	Alive
13	10	2	Pleural effusion	Alive
14	19	3	Paraparesis, ischemic colitis	Alive
15	13	8	Hoarseness	Alive
16	62	4	Pleural effusion, prolonged respiratory support	Alive

As: ascending aorta, A: aortic arch, Ds: descending aorta, FA: femoral artery, FV: femoral vein mPA: main pulmonary artery, RA: right atrium, DHCA: deep hypothermic circulatory arrest, RCA: retrograde cerebral perfusion, SCP: selective cerebral perfusion, GI: gastrointestinal, RIND: reversible ischemic neurological deficit.

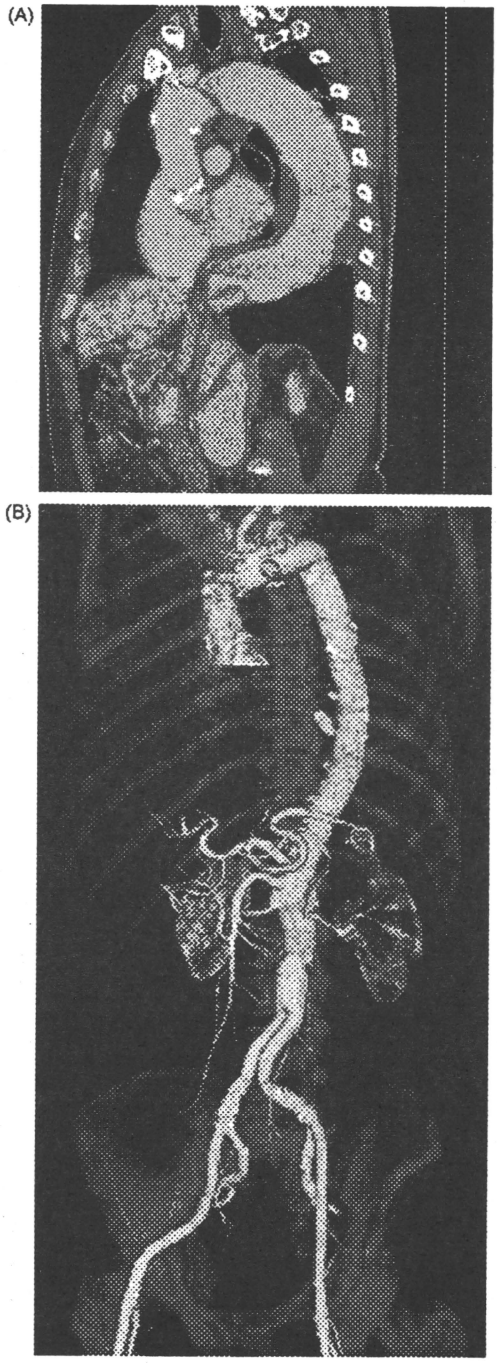

Fig. 3. Pre- and postoperative CT scan (case 10). (A) Preoperative CT scan demonstrated chronic type A dissection from the arch to thoracoabdominal aorta after hemi-arch replacement. (B) Postoperative CT scan showed entire thoracic and thoracoabdominal aortic aneurysm replacement.

pletely by discharge. Respiratory failure, defined as the necessity of more than 48 h support by mechanical ventilation, was observed in three patients (cases 4, 7 and 16). Average duration of respiratory support was 19.4 ± 17.0 h (range: 4–62 h). Intractable pulmonary bleeding was not observed.

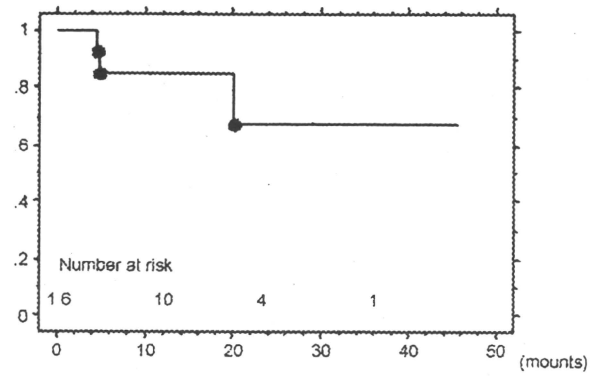

Fig. 4. Actuarial survival after the operation.

6.2. Mid-term results

Follow-up was 100% completed. Average follow-up was 16.4 ± 12.6 months (range: 1.4–45.5 months). During follow-up, cases 1 and 7 died due to pneumonia and the rupture of a pre-existing middle cerebral artery aneurysm, respectively. Actuarial survival at 2 years after surgery was 67.7% (95% CI: 0.13–1.23) (Fig. 4). However, no aortic-related mortality was observed.

7. Discussions

Patients who underwent ascending aorta or hemi-arch replacement for acute type A dissection sometimes had extensive thoracic aortic aneurysms due to residual flow in the distal false lumen [8]. When patients are carefully selected based on the evaluation of preoperative comorbidity, a single stage operation can be expected to be highly effective in terms of long-term survival and quality of life. Svensson et al. [9], Massimo et al. [10] and Hu et al. [11] had reported the superior outcome of one-stage surgery for extended thoracic aortic aneurysms.

Wide exposure with a simple incision is mandatory and of primary importance in one-stage treatment for extensive thoracic aneurysms. Median sternotomy is the gold standard to access the aortic arch; however, exposure to the distal descending aorta is limited even if additional left anterolateral thoracotomy is applied. Kouchoukos et al. [5] reported the clam-shell approach as an excellent procedure for one-stage extended aortic arch replacement. We entirely agree that the clam-shell approach is highly useful if aortic root replacement is required.

In the current series, we could approach the ascending aorta, aortic arch and entire descending aorta through a left posterolateral thoracotomy alone. In case 5, who had undergone hemi-arch replacement, there was an unexpected disruption of the proximal anastomosis of the previous hemi-arch graft at the sino-tubular junction (STJ) level during the operation that required access to that level and that resulted in successful repair. A sternum transverse division might be an additional option to obtain better working space for the aortic root. However, we believe that avoiding division of the sternum while preserving the internal thoracic artery is important in terms of wound healing and possible future

coronary artery bypass grafting. A left posterolateral thoracotomy without sternum division eventually provided working space for the extended replacement of the aortic arch up to the STJ.

Massimo et al. [10] and Hu et al. [11] reported the efficacy of multiple independent incisions for the exposure of thoracic and thoracoabdominal aneurysms. In addition, a left posterolateral thoracotomy through the 4th intercostal space with a single skin incision is a beneficial and flexible alternative for access to the ascending, aortic arch and entire descending aorta, which enables reconstruction of the intercostal artery (case 13) and repair of even the thoracoabdominal aorta with the intercostal artery reconstruction (cases 14, 15 and 16) through the retroperitoneal space approached by the extension of the left side thoracotomy. As we reported earlier [7], left side rib-cross thoracotomy is another and better option to expose both the thoracic and thoracoabdominal aorta although meticulous reconstruction of the ribs is required. We applied this approach for case 4 (retrograde type A dissection with rupture of the descending aorta) to obtain better exposure quickly, because it was hard to predict the extent of the replacement preoperatively in this complicated case.

An aneurysm that included the area from the ascending aorta, aortic arch, descending aorta and thoracoabdominal aorta was the most challenging paradigm because multiple organs such as the myocardium, brain, spinal cord and visceral organs must be well protected during the procedure. Extracorporeal circulation was basically established with femoral artery return and right atrial drainage through the right femoral vein. In the right decubitus position, femoral vein cannulation was sometimes difficult and additional main pulmonary artery drainage was applied through maintaining negative drainage pressure. Myocardial protection was reliably obtained by cardioplegic solution delivered through a balloon-tipped catheter placed in the ascending aorta. Since the myocardial ischemic time averaged 83 min, myocardial recovery was sufficient enough in all cases without any drawbacks.

Brain protection during the procedure involving aortic arch replacement is another crucial issue in obtaining a satisfactory outcome since the duration of circulatory arrest has been demonstrated to be a predictor of early death [4]. We used the arch-first technique under deep hypothermia for total arch replacement in the earlier period and have shifted to a more reliable protection method of selective cerebral perfusion under deep hypothermia. Efficacy of this procedure was proved by the absence of permanent neurological deficits with the exception of temporary right hand paralysis in case 11.

There was no operative mortality (30-day mortality) but one patient died of accidental traumatic cerebral hemorrhage on day 145 (case 2). Our early results were comparable to those in other reports regarding mortality [5,10,11]. A major concern with this left posterolateral thoracotomy is the complication of intraoperative endobronchial hemorrhage under a fully heparinized condition. In the majority of cases, mild endobronchial hemorrhage was observed, but resolved without respiratory failure. Duration of intubation was a mean of 19.4 ± 17.0 h, and prolonged respiratory assistance over 48 h was required in three cases (cases 4, 7 and 16), one of which was due to phrenic nerve palsy. Pulmonary complications were observed in six patients (37.5%) but those were not lethal. We believe that this is an acceptable rate of pulmonary complications.

In conclusion, satisfactory exposure for extensive thoracic aneurysms can be achieved through a left posterolateral thoracotomy, which was possible even for the reconstruction of intercostal and visceral arteries for a thoracoabdominal aneurysm by its extension to retroperitoneal space.

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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.

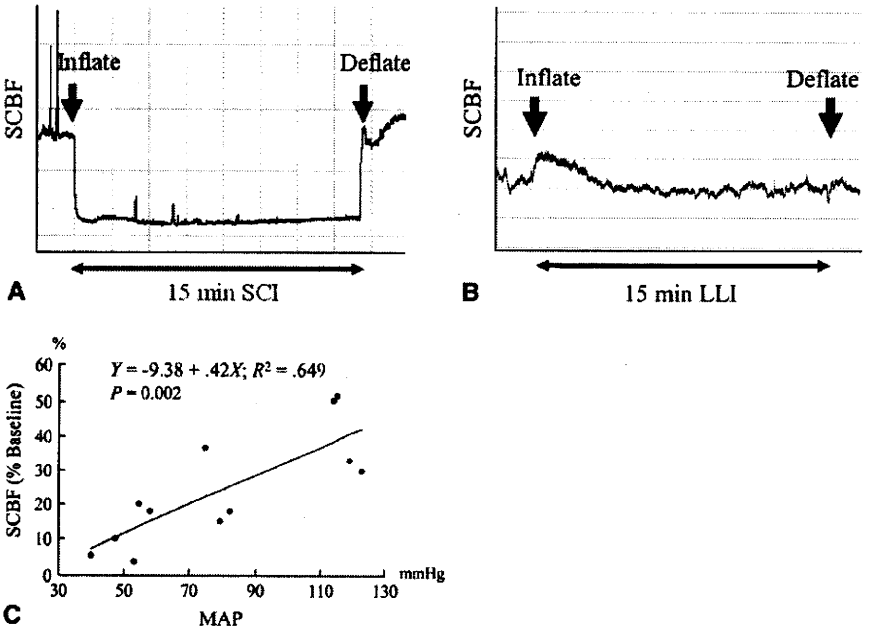

FIGURE 1. A, Spinal cord blood flow *(SCBF)* recordings in spinal cord ischemia *(SCI)* model. B, Spinal cord blood flow recordings in lower limb ischemia *(LLI)* model. C, Relationship between mean arterial pressure *(MAP)* and spinal cord blood flow during aortic occlusion in spinal cord ischemia model.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

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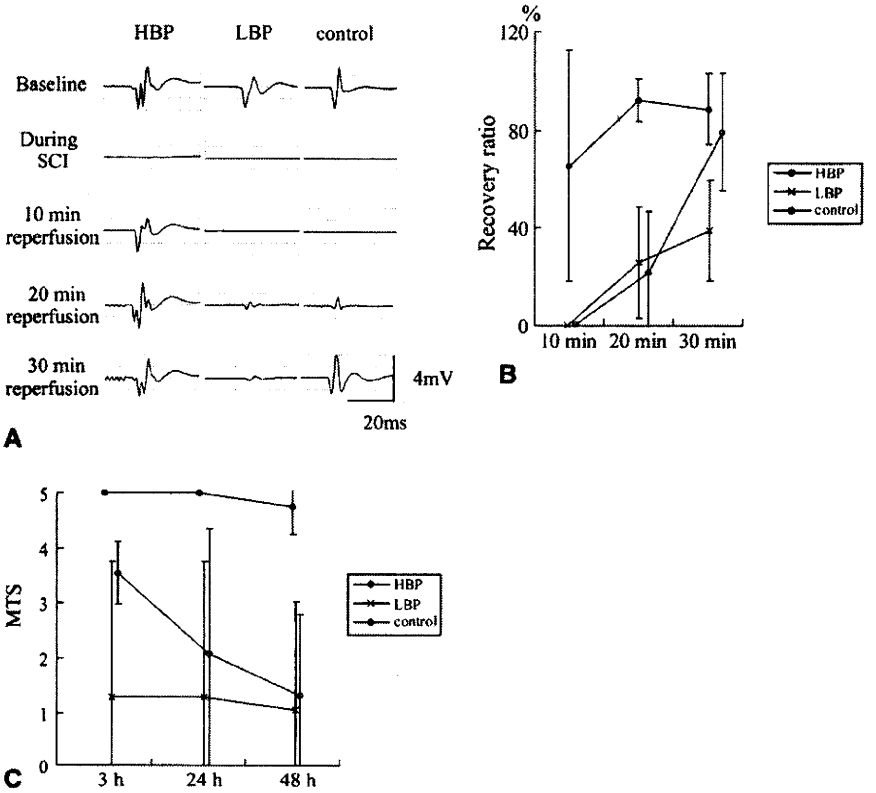

FIGURE 2. Intraoperative and postoperative neurologic assessments. A, Representative transcranial motor evoked potential *(tc-MEP)* complex. B, Recovery ratios of transcranial motor evoked potential amplitude at 10, 20, and 30 minutes after spinal cord ischemia *(SCI)*. C, Neurologic scores with modified 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

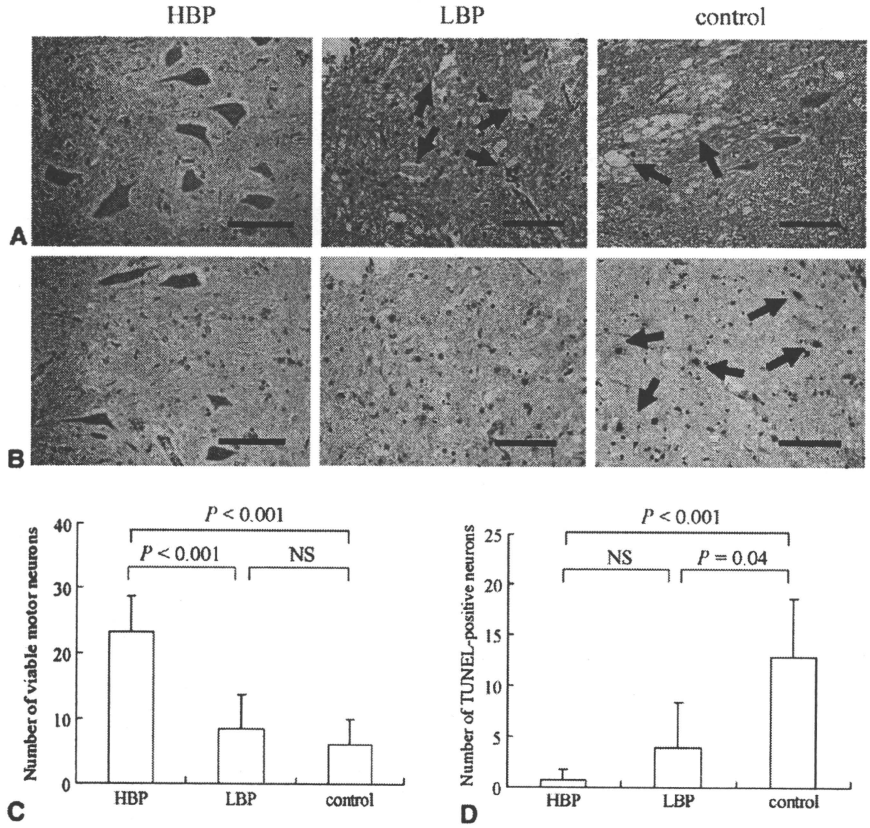

FIGURE 3. Photomicrographs of histologic sections in rabbit spinal cord at 48hours after spinal cord ischemia. A, Hematoxylin and eosin staining of ventral gray matter. Spinal cords in low blood pressure *(LBP)* and control groups show necrotic change *(arrows)*. B, Terminal deoxynucleotidyl transferase-mediated 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*).

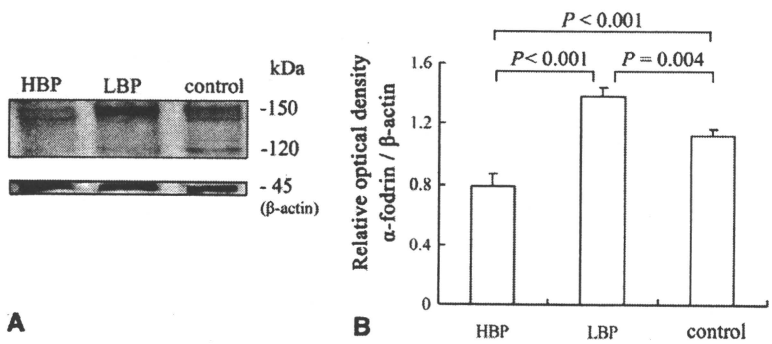

FIGURE 4. A, Western blot analysis of α-fodrin fragments at 48 hours after spinal cord ischemia. B, Relative optical densities of total α-fodrin fragments in each group at 48 hours after spinal cord ischemia. *HBP*, High blood pressure; *LBP*, low blood pressure.

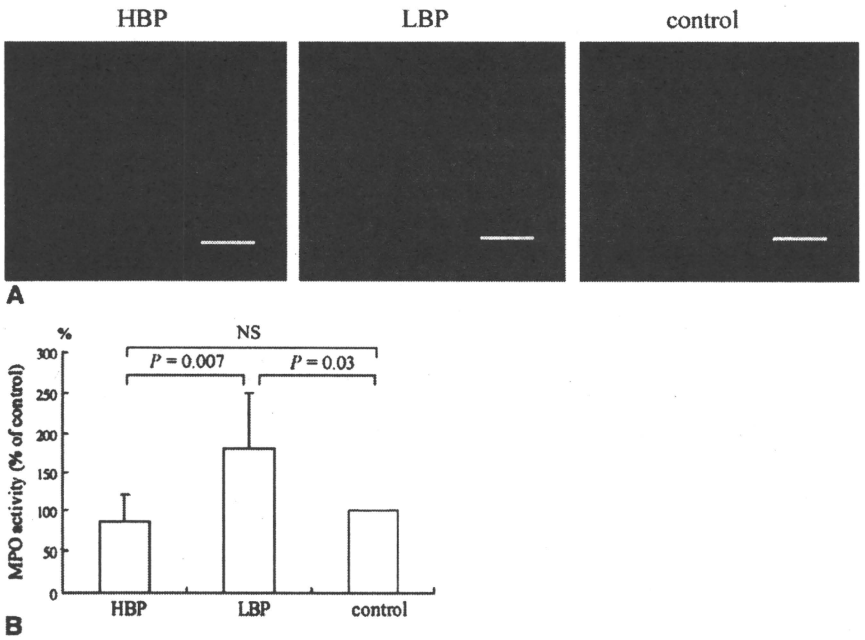

FIGURE 5. A, Fluorescence micrographs of histologic sections in rabbit spinal cord at 3 hours after spinal cord ischemia. Dihydroethidium staining (red fluorescence when oxidized to ethidium bromide by superoxide) of ventral horn. B, Myeloperoxidase *(MPO)* activities in each group at 3 hours after spinal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

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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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