fibrinogen concentrate achieved sufficient hemostasis and reduced the use of blood products even in patients with SFL of 101–150 mg/dl. Hypofibrinogenemia less than 150 mg/dl may be a useful value as a cut-off criterion for when to administer fibrinogen concentrate.

The next concern is how much fibrinogen concentrate is required to achieve sufficient surgical hemostasis. The average SFL at ICU admission were 250 mg/dl, which may be the optimal target value for sufficient surgical hemostasis, because a sufficient SFL is necessary upon the neutralization of heparin. When the SFL are restored effectively and promptly at this point, the subsequent coagulation failure could be avoided. However, in cases without sufficient hemostasis, the surgical bleeding is prolonged, and the consumption of coagulation factors continues. This leads to a gradual decrease in the SFL, and leads to a vicious cycle of coagulopathy. Therefore, sufficient SFLs are mandatory before protamine injection, especially after complex and difficult surgeries. A dose of one gram of fibrinogen concentrate theoretically will increase the SFL by 20 mg/dl in a 65 kg patient with 5L of intravascular blood volume. When patients show a SFL of 150 mg/dl at CPB termination, 5 g of fibrinogen concentrate is therefore theoretically required to achieve the target SFL of 250 mg/dl.

The guidelines for blood transfusion also recommend that blood examinations, including fibrinogen, PT and APTT, are mandatory before the use of FFP. We have a quick measurement system to examine the coagulation in our laboratory, and can obtain a prompt response within 30 minutes even at night. We propose that such a quick measurement of the coagulation is mandatory for deciding whether to administer fibrinogen concentrate. The information obtained by this quick measurement of the coagulation is important for the surgical team to understand the patients' coagulation condition. A lack of factors such as fibrinogen or platelets should be noted and remedied before the neutralization of heparin and during surgical hemostasis. When the bleeding tendency is predicted to continue in the surgical field, additional measurements should be performed. Surgeons must understand the mechanisms underlying coagulopathy in order to achieve sufficient surgical hemostasis.

As noted above, fibrinogen concentrate has not been approved for hypofibrinogenemia during surgery in Japan. This situation is similar in many Western countries. Fibrinogen concentrate will be approved in the near future for intraoperative coagulopathy. Prior to this, the safety of the intraoperative use of fibrinogen concentrate should be confirmed. The present study was a retrospective observational study; however, there were observed no complications related to the fibrinogen concentrate. In addition, there is no evidence that fibrinogen concentrate increased the risk of major complications or mortality.

In conclusion, hypofibrinogenemia frequently was observed at the termination of CPB during thoracic aortic surgery. Hypofibrinogenemia is one of the major factors associated with intraoperative coagulopathy. Quick measurement of the coagulation status is mandatory for deciding whether to administer fibrinogen concentrate, and should provide important information to understand the patients' coagulation condition as well. Hypofibrinogenemia of < 150 mg/dl SFL may be a useful criterion to decide whether to administer fibrinogen concentrate. The intraoperative administration of fibrinogen concentrate appears to be an optimal strategy to increase the SFLs effectively and promptly. It can treat coagulopathy and reduce the need for a large blood transfusion, and can help to avoid massive bleeding during thoracic aortic surgery.

DISCLOSURE

All the authors have declared no competing interest.

REFERENCES

1) Tanaka KA, Egan K, Szlam F, Ogawa S, Roback JD, Sreeram G, Guyton RA, Chen EP. Transfusion and hematologic variables after fibrinogen or platelet transfusion in valve replacement surgery: preliminary data of purified lyophilized human fibrinogen concentrate versus conventional transfusion. *Transfusion*, 2014; 54: 109–118.
2) Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Flinck A, Skrtic S, Jeppsson A. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost*, 2009; 102: 137–144.
3) Ellis PR, Jr., Kleinsasser LJ, Speer RJ. Changes in coagulation occurring in dogs during hypothermia and cardiac surgery. *Surgery*, 1957; 41: 198–210.
4) Dirkmann D, Hanke AA, Gorlinger K, Peters J. Hypothermia and acidosis synergistically impair coagulation in human whole blood. *Anesth Analg*, 2008; 106: 1627–1632.
5) Clauss A. [Rapid physiological coagulation method in determination of fibrinogen]. *Acta Haematol*, 1957; 17: 237–246.
6) Williams JB, Phillips-Bute B, Bhattacharya SD, Shah AA, Andersen ND, Altintas B, Lima B, Smith PK, Hughes GC, Welsby IJ. Predictors of massive transfusion with thoracic aortic procedures involving deep hypothermic circulatory arrest. *J Thorac Cardiovasc Surg*, 2011; 141: 1283–1288.
7) Bilecen S, Peelen LM, Kalkman CJ, Spanjersberg AJ, Moons KG, Nierich AP. Fibrinogen concentrate therapy in complex cardiac surgery. *J Cardiothorac Vasc Anesth*, 2013; 27: 12–17.
8) Gielen C, Dekkers O, Stijnen T, Schoones J, Brand A, Klautz R, Eikenboom J. The effects of pre- and postoperative fibrinogen levels on blood loss after cardiac surgery: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*, 2014; 18: 292–298.
9) Walden K, Jeppsson A, Nasic S, Backlund E, Karlsson M. Low preoperative fibrinogen plasma concentration is associated with excessive bleeding after cardiac operations. *Ann Thorac Surg*, 2014; 97: 1199–1206.
10) Rahe-Meyer N, Hanke A, Schmidt DS, Hagl C, Pichlmaier M. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: results from a randomized, placebo-controlled trial. *J Thorac Cardiovasc Surg*, 2013; 145: S178–185.
11) Rahe-Meyer N, Solomon C, Winterhalter M, Piepenbrock S, Tanaka K, Haverich A, Pichlmaier M. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. *J Thorac Cardiovasc Surg*, 2009; 138: 694–702.

American Journal of Emergency Medicine 33 (2015) 308.e3–308.e4

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Case Report

Thrombus in acute aortic dissection with atrial fibrillation: a treatment dilemma

Abstract

Type B acute aortic dissection (AAD) is often successfully managed with medical therapy, with a lower mortality rate, compared with type A AAD. Although the number of AAD patients complicated with atrial fibrillation (AF) has increased, reflecting an aging society, there have only been a few reports regarding the association of AAD and AF. Furthermore, there is no consensus on anticoagulation therapy in ADD patients complicated with AF, despite the importance of anticoagulation therapy in AF treatment. Here, we discuss a 79-year-old man with type B AAD and chronic AF complicated with the rapid left atrial appendage (LAA) thrombus formation after discontinuation of anticoagulation therapy. Emergent contrast-enhanced computed tomography revealed type B AAD with a partially thrombosed false lumen from the bifurcation of the aorta and the left subclavian artery to above the diaphragm. Ulcer-like projection was observed in the proximal thrombosed false lumen. Ten days after discontinuation of anticoagulation therapy, LAA thrombus was detected on contrast-enhanced computed tomography, which was not observed on admission. After anticoagulation therapy was resumed, the LAA thrombus disappeared, but the partially thrombosed false lumen was enlarged. The second discontinuation of anticoagulation therapy stabilized the dissected aorta and did not cause recurrence of LAA thrombus. In conclusion, clinicians need to balance the prevention of LAA thrombus formation with the complete thrombosis of a false lumen in patients with AAD and AF.

Type B acute aortic dissection (AAD) is often successfully managed with medical therapy, with a lower mortality rate, compared with type A AAD, especially in cases of thrombosed type AAD [1]. Although the number of AAD patients complicated with atrial fibrillation (AF) has increased, reflecting an aging society, there have only been a few reports regarding the association of AAD and AF [2,3]. Furthermore, there is no consensus on anticoagulation therapy in AAD patients complicated with AF, despite the importance of anticoagulation therapy in AF treatment. Here, we discuss a 79-year-old man with AAD and chronic AF complicated with the rapid left atrial appendage (LAA) thrombus formation after discontinuation of anticoagulation therapy, which was given for the prevention of thromboembolism caused by AF.

A 79-year-old man with chronic AF was admitted to the hospital for severe back pain. His blood pressure was 176/88 mm Hg and had an irregular heart rate of 71 beats/min at presentation. Emergent contrast-enhanced computed tomography (CECT) revealed type B AAD with a partially thrombosed false lumen from the bifurcation of the aorta and the left subclavian artery to above the diaphragm (Figs. 1A and 2A, D). Ulcer-like projection was observed in the proximal thrombosed false lumen. We discontinued administration of warfarin and started administration of antihypertensive drugs, which included a β-blocker and intravenous morphine hydrochloride. The patient's pain and blood pressure was controllable. Laboratory examination after admission showed that prolonged prothrombin time was normalized after warfarin discontinuation, but that the elevation of D-dimer levels was sustained. Follow-up CECT performed 3 and 10 days after admission did not reveal any extension or enlargement of the dissected aorta. However, LAA thrombus was detected on CECT 10 days after admission, which was not observed before (Fig. 1A, B). After concurrent administration of heparin and warfarin, the LAA thrombus completely disappeared on day 18 without any embolic events (Fig. 1C). However, the partially thrombosed false lumen was enlarged and exerted pressure on the true lumen (Fig. 2A-F), despite stabilization of blood pressure and cautious rehabilitation. With respect to anticoagulation therapy, we needed to take balance between the prevention of an LAA thrombus and the complete thrombosis in the false lumen; therefore, we decided to again discontinue anticoagulation therapy. Fortunately, careful follow-up CECT and echocardiogram showed that discontinuation of anticoagulation therapy stabilized the dissected aorta without enlargement of the false lumen or extension of the dissected aorta and did not cause recurrence of an LAA thrombus. After confirmation of false lumen stabilization, we restarted warfarin on day 42 after AAD onset, and AAD remained stable without enlargement of the false lumen.

Although there are no current recommendations regarding the use of anticoagulants for patients with AAD, many physicians believe it would have a negative effect on thrombosis formation and the healing process in the dissected aorta's false lumen. On the other hand, Song et al [4] have also reported favorable effects of early anticoagulation on the AAD; therefore, the effect of anticoagulation on AAD remains unknown. To the best of our knowledge, this is the first description of the rapid formation of LAA thrombus in a patient with AAD. This case emphasizes the careful management required for patients with AAD and AF. Clinicians need to balance the prevention of LAA thrombus formation with the complete thrombosis of a false lumen in patients with AAD and AF. In patients who have a partially thrombosed false lumen with ulcer-like projections, discontinuing anticoagulants may prevent enlargement of the false lumen of the dissected aorta, at least during the acute phase. However, AAD is associated with hypercoagulation reaction, as evidenced by a significant elevation in coagulation marker. If rapid formation of LAA thrombus is observed, anticoagulation therapy needs to be started with careful follow-up of the dissected aorta. We also need to keep in close communication with the cardiovascular surgery team to prepare for emergent surgical intervention, including surgical or thoracic endovascular aortic repair.

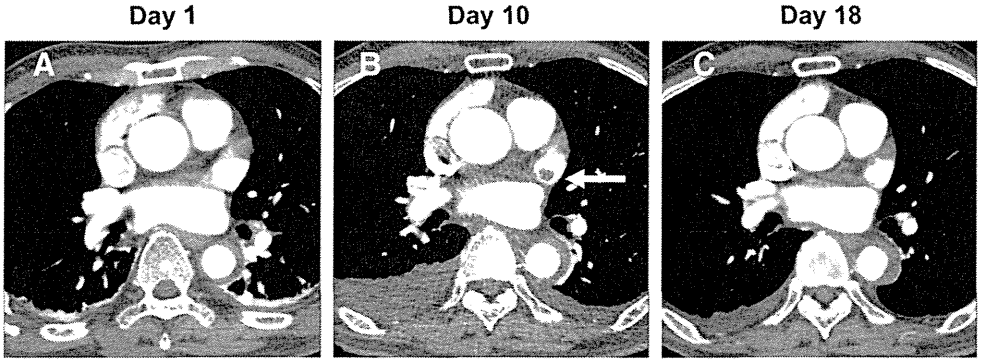


Fig. 1. Contrast-enhanced computed tomography showing thrombus in the LAA (B, arrow) on day 10 after AAD, which was not observed on admission (A). C, After resumption of anticoagulation therapy, LAA thrombus disappeared on day 18.

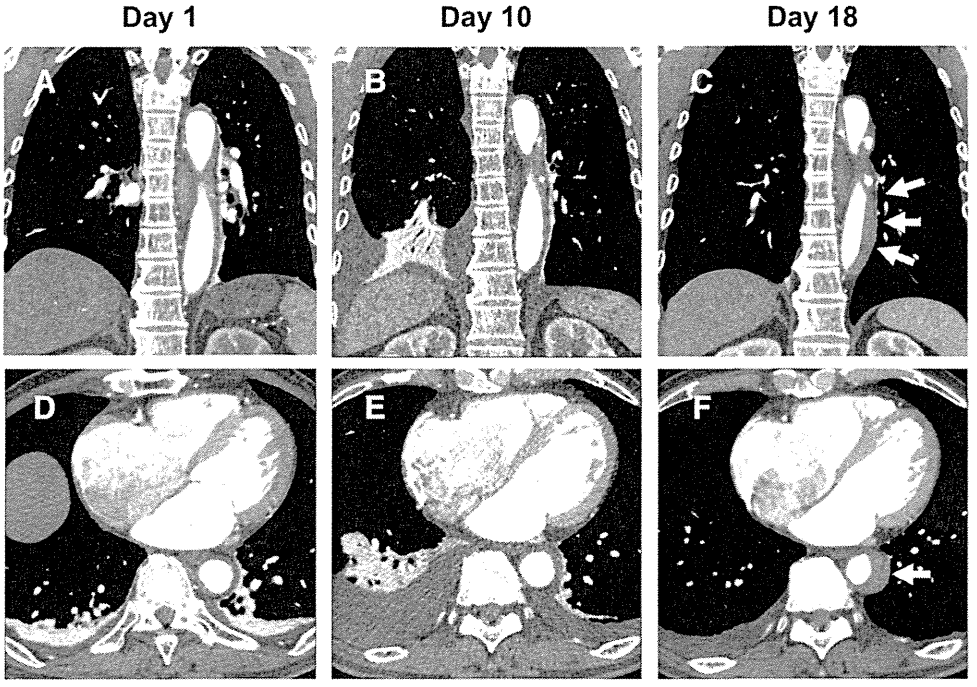


Fig. 2. Comparison of thrombosed aortic dissection seen on CECT on days 1 (A and D), 10 (B and E), and 18 (C and F). C and F, A partially thrombosed false lumen was enlarged (arrows) after resumption of anticoagulation therapy.

Yasuyuki Shiraishi, MD*
Takashi Kohno, MD
Toru Egashira, MD
Yuichiro Maekawa, MD
Division of Cardiology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan
*Corresponding author. Tel.: +81 3 5843 6702; fax: +81 3 5363 3875
E-mail address: yshiraishi@a3.keio.jp

Yoshitake Yamada, MD
Department of Diagnostic Radiology
Keio University School of Medicine Tokyo, Japan

Akihiro Yoshitake, MD
Hideyuki Shimizu, MD
Division of Cardiovascular Surgery
Keio University School of Medicine, Tokyo, Japan

Motoaki Sano, MD
Division of Cardiology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

Masahiro Jinzaki, MD
Department of Diagnostic Radiology
Keio University School of Medicine, Tokyo, Japan

Keiichi Fukuda, MD
Division of Cardiology, Department of Medicine
Keio University School of Medicine, Tokyo, Japan

http://dx.doi.org/10.1016/j.ajem.2014.07.040

References

[1] Tsai TT, Evangelista A, Nienaber CA, Myrmel T, Meinhardt G, Cooper JV, et al. Partial thrombosis of the false lumen in patients with acute type B aortic dissection. N Engl J Med 2007;357:349–59.
[2] Koracevic G, Djordjevic D, Glasnovic J. Is significance of atrial fibrillation in acute aortic dissection underestimated? J Emerg Med 2009;37:168–70.
[3] Chew HC, Lim SH. Aortic dissection presenting with atrial fibrillation. Am J Emerg Med 2006;24:379–80.
[4] Song SW, Yoo KJ, Kim DK, Cho BK, Yi G, Chang BC. Effects of early anticoagulation on the degree of thrombosis after repair of acute DeBakey type I aortic dissection. Ann Thorac Surg 2011;92:1367–74.

Interactive CardioVascular and Thoracic Surgery 19 (2014) 205–210
doi:10.1093/icvts/ivu148 Advance Access publication 14 May 2014

Embolism is emerging as a major cause of spinal cord injury after descending and thoracoabdominal aortic repair with a contemporary approach: magnetic resonance findings of spinal cord injury†

Hiroshi Tanaka*, Kenji Minatoya, Hitoshi Matsuda, Hiroaki Sasaki, Yutaka Iba, Tatsuya Oda and Junjiro Kobayashi

Department of Cardiovascular Surgery, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

* Corresponding author. National Cerebral and Cardiovascular Center, Department of Cardiovascular Surgery, 5-7-1 Fujishirodai, Suita, 565-8565 Osaka, Japan. Tel: +81-6-68335012; fax: +81-6-68335982; e-mail: hirtanak@hsp.ncvc.go.jp (H. Tanaka).

Received 6 September 2013; received in revised form 11 March 2014; accepted 12 March 2014

Abstract

OBJECTIVES: We reviewed magnetic resonance (MR) findings of the spinal cord in patients who had a spinal cord injury after descending and thoracoabdominal aortic repair, to speculate the specific cause of the injury.

METHODS: Between 2000 and 2012, 746 patients underwent descending or thoracoabdominal aortic surgery: 480 received an open repair with adjuncts of spinal cord protection [distal perfusion, cerebrospinal fluid (CSF) drainage, reattachment of intercostal arteries and hypothermia] and 266 received an endovascular repair. Twenty-six (3.5%) suffered a spinal cord injury. Of these, 18 (14 open repair and 4 endovascular repair) underwent postoperative spinal cord MRI. Preoperative identification of the Adamkiewicz artery (ARM) was obtained in all patients except 1. Aortic pathology was dissection in 2 and non-dissection in 16 patients.

RESULTS: There were 3 types MRI finding: sporadic infarction involving a range of spinal cord (sporadic); focal and asymmetrical infarction within a few segments of vertebra (focal); and diffuse and symmetrical infarction around the level of the ARM (diffuse). In endovascular repair, sporadic infarction was observed in all patients (4 of 4). In open repair, sporadic infarction was observed in 3 (21%), focal infarction in 7 (50%) and diffuse infarction in 4 (29%). In all patients who had sporadic or focal infarction, the aortic pathology was non-dissection.

CONCLUSIONS: From these findings, embolism is 1 of the major causes of spinal cord injury in the era of adjuncts to optimize spinal cord haemodynamics during aortic repair.

Keywords: Spinal cord injury • Aortic repair • Embolism

INTRODUCTION

Spinal cord injury (SCI) remains a devastating problem in descending and thoracoabdominal aortic repair. In 1988, Crawford reported that the use of distal aortic perfusion significantly reduced the incidence of SCI [1]. Spinal fluid drainage has been proved to be effective for spinal cord protection [2]. With these adjuncts combined with mild hypothermia, the incidence of SCI has been reduced to 3.5–5.0% in recent reports [3, 4]. Deep hypothermia, which is one of the most promising methods for organ protection, also provides excellent results with a low incidence of SCI [5, 6]. Preoperative identification of the Adamkiewicz artery (ARM) and collateral arteries to the anterior spinal artery by magnetic resonance (MR) angiography or computed tomographic angiography has given a better understanding of the circulation in the spinal cord [7, 8], which has contributed to lowering the incidence of SCI. In 1990, Mawad *et al.* [9] reported the MRI findings of SCI after thoracoabdominal aortic repair, which showed symmetrical high intensity of various degrees according to the severity of ischaemia. Since then, various adjuncts have evolved and the strategy for spinal cord protection has changed over time. To investigate the cause of SCI in patients who underwent aortic repair with a contemporary approach with various adjuncts for spinal cord protection, we reviewed MRI findings of SCI in these patients.

PATIENTS AND METHODS

Between 2000 and 2012, 746 patients underwent descending or thoracoabdominal aortic repair. Four hundred and eighty had open repair and 266 had endovascular repair. Of these, 233 (49%) had aortic dissection. In open repair, the mean age was 63 ± 10 years and 344 (71%) were men. In endovascular repair, their mean age was 75 ± 9 years and 64 (24%) were men.

†Presented at the Postgraduate Course of the 27th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 6 October 2013.

Operative procedures

In open repair, we used 2 methods for spinal cord protection during the period: mild hypothermia (30–32°C) with distal perfusion, spinal fluid drainage and reattachment of intercostal arteries under the guidance of motor evoked potentials (MEPs); and deep hypothermia (18–20°C). Since 2000, we have performed preoperative identification of ARM [10] and 90% could be identified. In patients with preoperatively identified ARM, reattachment of intercostal arteries, including the main source of the ARM, was performed in both methods. We used mild hypothermia with adjuncts in 307 (64%) patients and deep hypothermia in 173 (36%) patients. In mild hypothermia, we used the segmental clamp technique to reduce spinal cord ischaemic time and to close the patent intercostals, which should not be reconstructed immediately after opening the aorta. The target intercostals were decided according to a preoperative ARM study, and we reconstructed 2 or 3 pairs of intercostals around the identified ARM. These were also closed immediately after opening the aorta with balloon-tipped catheters or removable sutures. If ARM could not be identified in the preoperative study, we blindly reattached 2 or 3 pairs of intercostals between Th 8 and Th 12 levels. A spinal fluid drainage tube was inserted preoperatively and drained continuously to keep spinal fluid pressure at 10 mmHg or less if MEPs significantly change.

In endovascular repair, descending aortic repair was performed in 245 and thoracoabdominal aortic repair in 21 patients. Since 2008, we have performed spinal cord protection with spinal fluid drainage, intentional hypertension at the time of deployment and MEPs in high-risk patients who have a long segment of the aorta covered, closing the ARM [11].

The extent of aortic repair, aortic pathology and method of spinal cord protection are shown in Table 1. In all but 1 patient who had SCI and underwent spinal MRI, the left subclavian artery and the bilateral hypogastric arteries were patent. One patient who had emergent surgery had only a plain CT, so their patency was unknown.

Operative results and spinal cord injury

Operative mortality was 3.4% (26/746): 3.5% (18/480) in open repair and 3% (8/266) in endovascular repair. Twenty-six patients (3.5%) had SCI: 4% (19/480) in open repair and 2.6% (7/266) in endovascular repair. Twenty patients had paraparesis, 4 had paraplegia and 2 had monoparesis. Of them, 18 (14 open repair and 4 endovascular repair) had postoperative spinal cord MRI. The other 8 patients did not have spinal cord MRI because of their postoperative conditions.

Table 1: The extent of aortic repair and aortic pathology

	n	Dissection (%)	Deep hypothermia (%)
Open surgery	480	233 (49)	173 (36)
Descending	232	100 (43)	101 (44)
TAAA I	29	15 (51)	12 (41)
TAAA II	59	48 (81)	46 (78)
TAAA III	116	52 (49)	14 (12)
TAAA IV	44	8 (18)	0 (0)
Endovascular repair	266	10 (4)	
Descending	245	6 (2)	NA
TAAA	21	4 (19)	NA

TAAA: thoracoabdominal aortic aneurysm.

Analysis of spinal cord magnetic resonance findings

Spinal MRI was performed in all patients except 1 with SCI 2–4 weeks postoperatively. A patient who had renal failure and paraplegia had spinal MRI 2 months postoperatively. MRI abnormalities in SCI are best demonstrated on T_2-weighted images as high-intensity areas. Two radiologists analysed the MRI findings independently and classified them into 3 types:

Focal type: asymmetrical focal high intensity on axial T_2-weighted images within 2 segments of vertebra (Fig. 1).

Sporadic type: asymmetrical multiple high intensity on axial T_2-weighted images involving more than 3 segments of vertebra (Fig. 2).

Diffuse type: symmetrical high intensity on axial T_2-weighted images (Fig. 3).

The Review Ethics Board of the National Cerebral and Cardiovascular Center approved this study and individual consent for the study was waived.

RESULTS

Age, aortic pathology, the extent of operation, location of ARM, the adjuncts for spinal protection, MRI findings and the location of spinal infarction are shown in Table 2. In open repair, only 4 of 14 (29%) patients had diffuse-type spinal infarction, 7 (50%) had focal infarction and 4 (21%) had sporadic infarction. In endovascular repair, all patients had sporadic infarction. In all patients who had diffuse infarction, the location of the infarction was around the ARM. Aortic pathology was non-dissection in 16 and dissection in 2 patients. With regard to symptoms, 3 patients had paraplegia and the remaining 15 had paraparesis or monoparesis. Two patients who underwent surgery with deep hypothermia had SCI; in 1 who had undergone ascending aorta-to-iliac artery bypass because of lower body malperfusion because of aortic dissection, clamping the bypass graft at the time of thoracoabdominal repair for arterial cannulation caused SCI. In this patient, spinal MRI showed extensive diffuse infarction below the level of ARM. The other had sporadic-type infarction. The incidence of SCI in open surgery was 5.5% (17/307) in patients with mild hypothermia and 1.2% (2/176) in those with deep hypothermia.

DISCUSSION

SCI in aortic surgery has been regarded as provoked by intraoperative and postoperative deterioration of spinal cord circulation. Several authors have reported MRI findings of spinal cord infarction in aortic surgery [12, 13], and we have focused exclusively here on perioperative spinal cord circulation as the cause of ischaemia. However, because the causes of spontaneous spinal cord infarction have been reported [13, 14], we assumed that there would be 2 main causes of spinal cord infarction after aortic repair: infarction developing from ischaemia caused by intraoperative haemodynamic deterioration of the spinal cord, and embolism. Only a few cases of SCI in aortic surgery caused by embolism have been reported [15, 16]. Mawad reported MRI findings

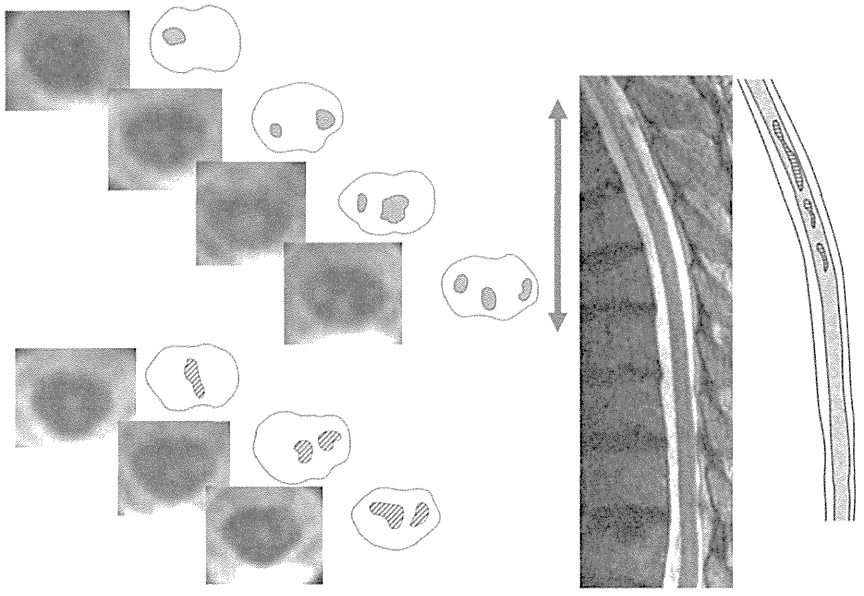


Figure 1: Sporadic type MRI findings: asymmetrical multiple high intensity on axial T_2-weighted images involving more than 3 segments of vertebra. Infarction is shaded on the illustration.

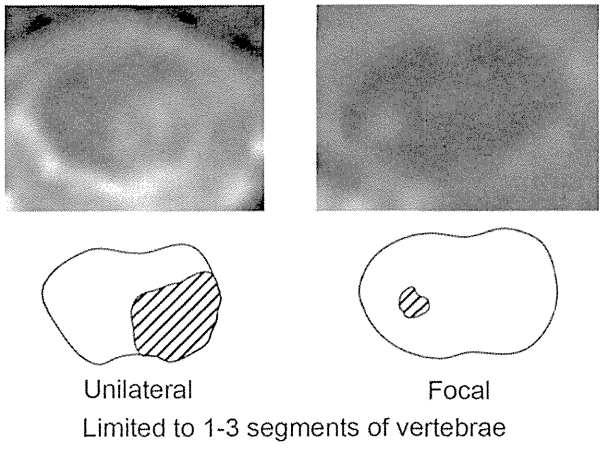


Figure 2: Focal type MRI findings: asymmetrical focal high intensity on axial T_2-weighted images within 2 segments of vertebra. Infarction is shaded on the illustration.

of SCI after thoracoabdominal aortic repair, all of which showed symmetrical high intensity in cross section, classified into 'diffuse type' in this study. These findings are different from those of this study. In Mawad's series, the currently available adjuncts for spinal cord protection had not been used properly at that time; therefore, the main cause of spinal cord infarction would have been haemodynamic deterioration of spinal cord circulation. Three major adjuncts for spinal cord protection, including distal aortic perfusion, mild hypothermia and cerebrospinal fluid drainage, have enabled better outcomes and a lower incidence of SCI, and these adjuncts alleviate intraoperative haemodynamic deterioration of the spinal cord. Despite their evolution, there is a still measurable incidence of SCI.

Over the past 12 years, we have experienced 4 patients with SCI after thoracoabdominal aortic repair who had an autopsy including the spinal cord. In 3 of 4 patients, microscopic findings showed scattered spinal cord infarction with atheroemboli in the anterior spinal artery and its branches, which supports our hypothesis (Fig. 4). The remaining patient showed symmetrical infarction without atheroemboli. Sporadic and focal infarction in MRI findings corresponding to scattered infarction microscopically is thought to be caused by atheroembolism.

In this study, we identified only 20% diffuse infarction, which was caused by haemodynamic deterioration, and the remaining 80% had focal or sporadic infarction, which was mainly caused by atheroemboli. Using the contemporary approach for spinal protection, embolism has become one of the major causes of SCI.

The source of atheroemboli is obviously aortic atheroma, so which procedure causes the embolism? Intraoperative MEPs serve as useful reference. In all patients who underwent open repair with mild hypothermia, we used MEPs for spinal cord functional monitoring. Of the patients whose MRI showed focal or sporadic infarction, 1 patient showed loss of MEPs (<20% of control) at the time of proximal double clamping outside the aneurysm, and 5 showed loss of MEPs during aortic clamping, including crucial segmental arteries. The MEPs never returned in these patients. Considering these findings, aortic manipulation is a major cause of atheroembolism. Two patients showed no change of MEPs intraoperatively, but they had hemiparesis because of a paralysed thigh and decreased lower leg strength, and their MRI showed a small focal infarction. The MEP device detects evoked potentials only at specific muscles; therefore, it is not reliable if a small part of the spinal cord is injured without segmental ischaemia. Most intercostals in non-dissecting aneurysms are occluded because of parietal thrombus formation; however, some intercostals are patent outside the aneurysm in patients. They can serve as a carrier for emboli at the time of clamping and reperfusion, although this is highly speculative.

In the patients with diffuse-type infarction, infarction occurred around the level of ARM in all patients and, in the patients with focal-type infarction, 14% (1/7) had infarction involving the level

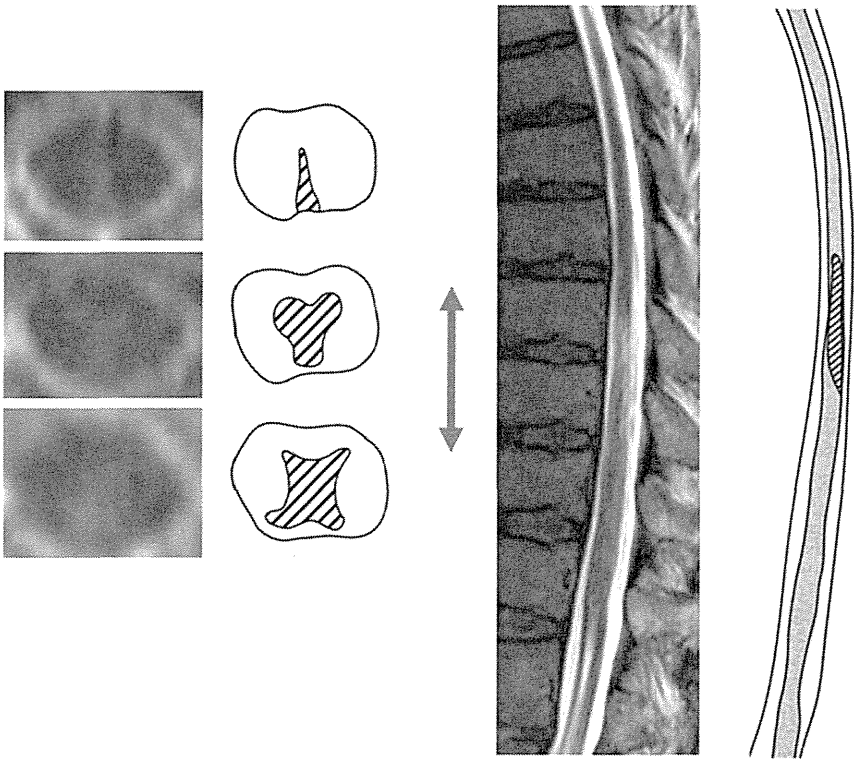


Figure 3: Diffuse type MRI findings: symmetrical high intensity on axial T_2-weighted images. Infarction is shaded on the illustration.

of ARM, but in the sporadic type, the level of ARM was not involved in spinal cord infarction.

There is a possibility that ARM is a crucial source of spinal cord circulation; however, few published data show that ARM has a crucial role in spinal cord protection in thoracoabdominal aortic surgery. This study includes only a few patients with diffuse-type infarction; therefore, data focusing on this subject are necessary.

In endovascular repair, 2 papers have demonstrated a low incidence of SCI [17, 18]. All patients in this study showed sporadic infarction. Atheroemboli might be a more significant factor in endovascular repair, which does not aggravate the global circulation during the procedure.

We have discussed that focal and sporadic types are caused by atheroembolism, and the diffuse type is caused by haemodynamic deterioration; however, the part of the artery that is occluded might influence which type of infarction occurs. In fact, in an autopsy case that showed atheroemboli in the sulcal artery branching to the anterior part of the spinal cord from the anterior spinal artery, infarction involved the anterior part of the grey matter almost symmetrically in a microscopic section. Thus, even the diffuse type on MR might be atheroemboli-driven infarction. It might be too speculative that the type of MRI findings in SCI reflects the aetiology, but atheroemboli cause spinal cord infarction as the autopsies showed, and accumulation of a number of patients would be necessary.

The classic watershed area in the spinal cord had been regarded as the lower cervical and upper thoracic areas, but many articles have reported a low incidence of SCI in these areas, regardless of the cause of SCI. Anatomical variation, including the location of radicular arteries, would cause individual differences in the location of watershed areas. In watershed area infarction during aortic repair, intraoperative occlusion of the artery that has a crucial role in blood supply would cause deterioration of the circulation in that area, spinal cord ischaemia and, finally, infarction followed by ischaemia would occur and the end arteries would be thrombosed. This mechanism was probably the main cause in Mawad's series in 1990, before the era of various adjuncts, which showed diffuse-type infarction in all patients. No patients showed sporadic-type infarction. Although watershed infarction still occurs with the current approach for spinal cord protection, not only haemodynamic stability, but also embolism should be the focus. In horizontal plane of the cord, the radicular arteries form 2 distinct systems of intrinsic blood supply. The first system is a posterolateral and peripheral plexus formed primarily by the 2 posterior spinal arteries that run longitudinally along the posterolateral sulcus of the cord and are richly interconnected by anastomotic channels. This is a centripetal vascular territory with penetrating branches that supply from one-third to one-half of the outer rim of the spinal cord. The second arterial system is a centrifugal system formed by numerous alternating central arteries that arise from the anterior spinal artery, run horizontally in the central sulcus and turn alternately to the right and left. This centrifugal system supplies the central grey matter and an adjacent white matter, which includes the corticospinal tract. Owing to the higher metabolic rate in the grey matter than the white matter and the anatomical arterial distribution, the grey matter, particularly the anterior horn, is vulnerable to hypoperfusion, which corresponds to the severity of ischaemia as Mawad's series showed. In this study, the types of the infarction correlated with the severity of the symptoms: patients with sporadic and the focal types showed severe symptoms and patients with focal type showed mild symptoms, but it might be difficult to speculate the cause of ischaemia only by means of the MRI findings of the spinal cord.

Table 2: Type of spinal magnetic resonance abnormality in patients with spinal cord injury

	Age (years)	Gender	Pathology	Location of aneurysm	Preop ARM	Location of MRI abnormality	Type of MRI abnormality		
Patients who underwent TEVAR									
1	85	M	Non-dissection	Descending	L Th 12th	Th 4-7	Sporadic		
2	89	M	Non-dissection	Descending	NA	Th 4, 8, 10	Sporadic		
3	68	M	Non-dissection	Descending	NA	Th 4-10	Sporadic		
4	81	M	Non-dissection	Descending	L Th 11th	Th-4,5,11-12	Sporadic		
	Age	Gender	Pathology	Deep hypothermia	Preop ARM	Repair involving ARM	Location of MR abnormality	Type of MR abnormality	
Patients who underwent open descending aortic repair									
1	59	M	Dissection	Yes	Th11	No	Th 6-9	Sporadic	
2	82	M	Non-dissection	No	Th9	No	Th 3-12	Sporadic	
3	81	M	Non-dissection	No	Th11	No	Th 7, 12	Focal	
4	58	M	Non-dissection	No	L1	No	Th 5	Focal	
5	85	M	Infection	No	Th10	Yes	Th 6-10	Diffuse	
	Age	Gender	Pathology	Extent	Deep hypothermia	Preop ARM	Repair involving ARM	Location of MR abnormality	Type of MR abnormality
Patients who underwent open thoracoabdominal repair									
1	88	F	Non-dissection	II	No	Th11	Yes	Th 4-12	Sporadic
2	72	M	Non-dissection	I	No	Th8	Yes	Th 5-8	Focal
3	61	F	Non-dissection	II	No	Th11	Yes	Th 5, 6	Focal
4	71	M	Non-dissection	III	No	Th9	No	Conus	Focal
5	79	M	Non-dissection	III	No	Th8	No	Conus	Focal
6	68	M	Non-dissection	III	No	Indefinite	NA	Conus	Focal
7	69	M	Non-dissection	II	No	Th12	Yes	Th12	Diffuse
8	34	M	Dissection	II	Yes	Th11	Yes	Th10-Conus	Diffuse
9	74	M	Non-dissection	III	No	Th10	Yes	Th 9, 10	Diffuse

ARM: Adamkiewicz artery; M: male; F: female.

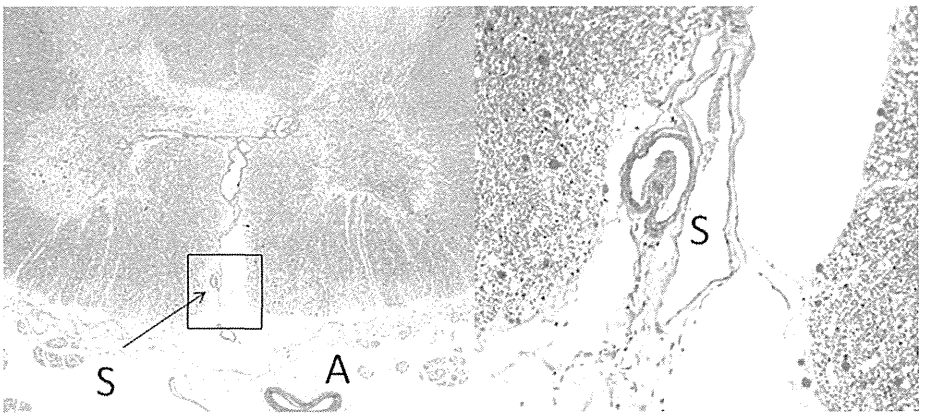


Figure 4: (A) Atheroemboli in the sulcal artery branching from the anterior spinal artery. (B) Magnification of the area indicated in (A). A: anterior spinal artery, S: sulcal artery.

Given that it has been reported that cerebral atheroembolism often occurs during extracorporeal circulation and aortic clamping, even if the patient is asymptomatic postoperatively [19, 20], spinal atheroembolism can potentially occur, but whether it is symptomatic depends on the extent and site of infarction. Reconstructed segmental arteries and vertebral and hypogastric arteries would reperfuse the spinal cord or the collateral artery would restore blood flow if the segmental arteries were occluded in the spinal cord [21], but intraoperative bleeding that would result in systemic hypotension and back-bleeding from the segmental arteries would reduce pressure on the anterior spinal artery, and vasoconstrictor in open surgery would impair blood flow from the arteries. Both atheroembolism and haemodynamic deterioration would adversely affect spinal cord circulation in open surgery. The association with atheroembolism but with less haemodynamic deterioration would be a major reason for the low incidence of SCI in endovascular repair. Therefore, avoiding multiple segmental aortic clamping to prevent atheroembolism seemed to be one of the major reasons for the low incidence of SCI in deep hypothermia, which provides longer ischaemic tolerance of organs and prevents reperfusion injury [22].

In conclusion, the incidence of SCI was lowered with a contemporary approach using various adjuncts to maintain intraoperative spinal cord circulation; however, embolism became a focal issue regarding SCI in descending and thoracoabdominal aortic repair.

STUDY LIMITATIONS

This is a study based only on the analysis of 18 MRI and 4 autopsies. The number of patients is small, and only 3 cases showed direct evidence of spinal cord infarction caused by embolism, proved by autopsies. The others are speculations from circumstantial evidence. Although there might be other reasons for SCI in these cases, some patients must have had embolism-driven infarctions, as shown in the autopsies. We need to accumulate more patients to investigate the specific causes of SCI and hope that this paper will help to lower the incidence of SCI, even if only slightly.

Conflict of interest: none declared.

REFERENCES

[1] Crawford ES, Mizrahi EM, Hess KR, Coselli JS, Safi HJ, Patel VM. The impact of distal aortic perfusion and somatosensory evoked potential monitoring on prevention of paraplegia after aortic aneurysm operation. J Thorac Cardiovasc Surg 1988;95:357–67.

[2] Coselli JS, LeMaire SA, Köksoy C, Schmittling ZC, Curling PE. Cerebrospinal fluid drainage reduces paraplegia after thoracoabdominal aortic aneurysm repair: results of a randomized clinical trial. J Vasc Surg 2002;35:631–9.

[3] Estrera AL, Sheinbaum R, Miller CC III, Harrison R, Safi HJ. Neuromonitor-guided repair of thoracoabdominal aortic aneurysms. J Thorac Cardiovasc Surg 2010;140(6 Suppl):S131–135.

[4] Lemaire SA, Price MD, Green SY, Zarda S, Coselli JS. Results of open thoracoabdominal aortic aneurysm repair. Ann Cardiothorac Surg 2012;1:286–92.

[5] Fehrenbacher JW, Siderys H, Terry C, Kuhn J, Corvera JS. Early and late results of descending thoracic and thoracoabdominal aortic aneurysm open repair with deep hypothermia and circulatory arrest. J Thorac Cardiovasc Surg 2010;140(6 Suppl):S154–160.

[6] Kouchoukos NT, Kulik A, Castner CF. Outcomes after thoracoabdominal aortic aneurysm repair using hypothermic circulatory arrest. J Thorac Cardiovasc Surg 2013;145(3 Suppl):S139–141.

[7] Yamada N, Takamiya M, Kuribayashi S, Okita Y, Minatoya K, Tanaka R. MRA of the Adamkiewicz artery: a preoperative study for thoracic aortic aneurysm. J Comput Assist Tomogr 2000;24:362–8.

[8] Yoshioka K, Niinuma H, Ohira A, Nasu K, Kawakami T, Sasaki M *et al.* MR angiography and CT angiography of the artery of Adamkiewicz: noninvasive preoperative assessment of thoracoabdominal aortic aneurysm. Radiographics 2003;23:1215–25.

[9] Mawad ME, Rivera V, Crawford S, Ramirez A, Breitbach W. Spinal cord ischemia after resection of thoracoabdominal aortic aneurysms: MR findings in 24 patients. AJR Am J Roentgenol 1990;155:1303–7.

[10] Ogino H, Sasaki H, Minatoya K, Matsuda H, Yamada N, Kitamura S. Combined use of adamkiewicz artery demonstration and motor-evoked potentials in descending and thoracoabdominal repair. Ann Thorac Surg 2006;82:592–6.

[11] Matsuda H, Ogino H, Fukuda T, Iritani O, Sato S, Iba Y *et al.* Multidisciplinary approach to prevent spinal cord ischemia after thoracic endovascular aneurysm repair for distal descending aorta. Ann Thorac Surg 2010;90:561–5.

[12] Masson C, Pruvo JP, Meder JF, Cordonnier C, Touzé E, De La Sayette V *et al.* Study Group on Spinal Cord Infarction of the French Neurovascular Society. Spinal cord infarction: clinical and magnetic resonance imaging findings and short term outcome. J Neurol Neurosurg Psychiatry 2004;75:1431–5.

[13] Weidauer S, Nichtweiss M, Lanfermann H, Zanella FE. Spinal cord infarction: MR imaging and clinical features in 16 cases. Neuroradiology 2002;44:851–7.

[14] Cheshire WP, Santos CC, Massey EW, Howard JF Jr. Spinal cord infarction: etiology and outcome. Neurology 1996;472:321–30.

[15] Miyairi T, Kotsuka Y, Morota T, Kubota H, Shibata K, Ikeda Y *et al.* Paraplegia after open surgery using endovascular stent graft for aortic arch aneurysm. J Thorac Cardiovasc Surg 2001;122:1240–3.

[16] Miyairi T, Kotsuka Y, Ezure M, Ono M, Morota T, Kubota H *et al.* Open stent-grafting for aortic arch aneurysm is associated with increased risk of paraplegia. Ann Thorac Surg 2002;74:83–9.

[17] Czerny M, Eggebrecht H, Sodeck G, Verzini F, Cao P, Maritati G *et al.* Mechanisms of symptomatic spinal cord ischemia after TEVAR: insights from the European Registry of Endovascular Aortic Repair Complications (EuREC). J Endovasc Ther 2012;19:37–43.

[18] Bobadilla JL, Wynn M, Tefera G, Acher CW. Low incidence of paraplegia after thoracic endovascular aneurysm repair with proactive spinal cord protective protocols. J Vasc Surg 2013;57:1537–42.

[19] Fearn SJ, Pole R, Wesnes K, Faragher EB, Hooper TL, McCollum CN. Cerebral injury during cardiopulmonary bypass: emboli impair memory. J Thorac Cardiovasc Surg 2001;121:1150–60.

[20] Rodriguez RA, Rubens FD, Wozny D, Nathan HJ. Cerebral emboli detected by transcranial Doppler during cardiopulmonary bypass are not correlated with postoperative cognitive deficits. Stroke 2010;41:2229–35.

[21] Etz CD, Kari FA, Mueller CS, Brenner RM, Lin HM, Griepp RB. The collateral network concept: remodeling of the arterial collateral network after experimental segmental artery sacrifice. J Thorac Cardiovasc Surg 2011;141:1029–36.

[22] Kouchoukos NT, Rokkas CK. Hypothermic cardiopulmonary bypass for spinal cord protection: rationale and clinical results. Ann Thorac Surg 1999;67:1940–2.

止血戦略におけるフィブリノゲン製剤の役割

前田琢磨
Maeda Takuma
国立循環器病研究センター輸血管理室

Summary

大量出血症例では，初期から凝固障害が存在する可能性が高いにもかかわらず，救命や循環動態改善を優先し，まず，赤血球濃厚液輸血や晶質液，人工膠質液の大量投与がおこなわれるために，ますます希釈性，消費性凝固障害を増悪させている可能性がある．止血のためにフィブリノゲン製剤（クリオプレシピテートやフィブリノゲン濃縮製剤）を用いると輸血量が大幅に減少するという報告があいついでいる．今後わが国においてフィブリノゲン製剤が導入されれば，大量出血においてはまずフィブリノゲン製剤を投与という日がくる可能性もある．

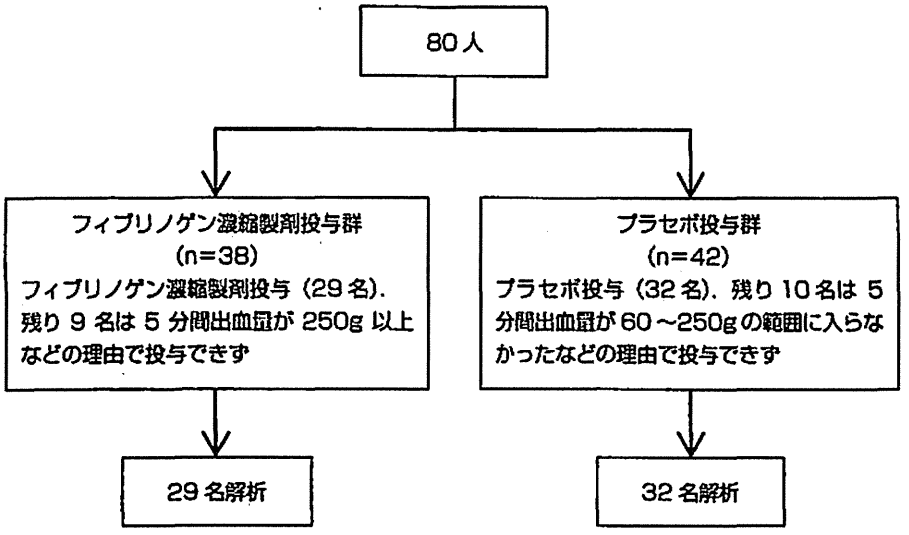
Key Words

・大量出血　・フィブリノゲン製剤　・止血　・フィブリノゲン

はじめに

大量出血症例では，初期から凝固障害が存在する可能性が高いにもかかわらず，救命や循環動態改善を優先し，まず，赤血球濃厚液輸血や晶質液，人工膠質液の大量投与がおこなわれるために，ますます希釈性，消費性凝固障害を増悪させている可能性がある．また出血性ショックやそれに伴う低体温，アシドーシスなどが，さらに凝固障害を増悪させている[1]．フィブリノゲンは，凝固因子のなかでの最終基質であり，血液凝固のメカニズムの最終段階でフィブリン（不溶性の網状線維素）となり，血栓を形成することで，止血に大変重要な役割を果たしている．したがって，ほかの凝固因子が活性化されても，フィブリノゲンがなければ，止血機構が十分にはたらかないこととなる．また，大量出血時に，凝固因子のなかで一番早期に止血に必要な血中濃度（約100mg/dL）を保てなくなるという特性をもち[2]，出血による急性低フィブリノゲン血症にいかに対応するかが，大量出血を早期に止血する際の大変重要な課題であることが指摘されている．このため，米国の輸血ガイドライン，輸血アルゴリズムについて記載されている文献では，心臓血管外科手術の大量出血などで低フィブリノゲン血症をきたした場合，止血のためにフィブリノゲン製剤（クリオプレシピテートやフィブリノゲン濃縮製剤）の使用が推奨されている[3][4]が，わが国では一般化されていない．しかし，その必要性は長きにわたり叫ばれつづけている．

本稿では大量出血においてのフィブリノゲン製剤の効能をエビデンスにもとづいて解説し，大量出血におけるフィブリノゲン製剤を用いた戦略にも言及する．



図❶ Hannover大学における二重盲検ランダム化比較試験

（Rahe-Meyer N *et al*, 2013[5]より引用）

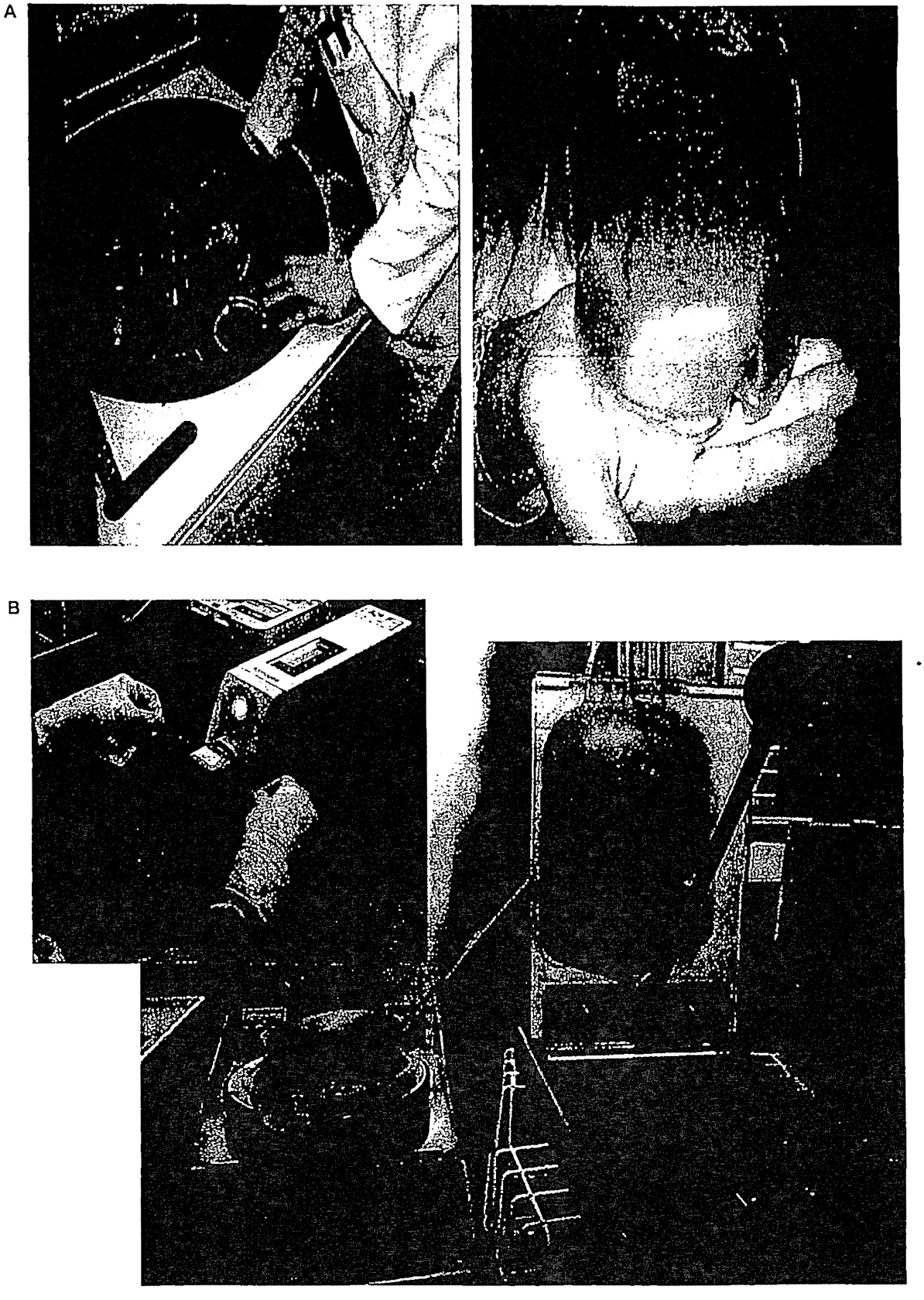
● 1．大量出血への対応の鍵はフィブリノゲン補充にあり

2013年にドイツのHannover大学から衝撃的な論文が発表された[5]．この試験は一施設による18歳以上の人工心肺を用いた，胸部および胸腹部大動脈置換術を受けた患者に対し，人工心肺離脱後の5分間出血量が60～250gであった場合にフィブリノゲン濃縮製剤もしくは生理食塩水を投与するという二重盲検ランダム化比較試験である（図❶）．フィブリノゲン濃縮製剤投与群では平均8gのフィブリノゲンが投与されていた．驚くべきことに，フィブリノゲン濃縮製剤で介入した群では，同種血輸血が回避された割合は45％にも及ぶ一方で，プラセボ群において同種血輸血回避率は0％であった．さらに，術後24時間の総輸血量はプラセボ群と比較してフィブリノゲン濃縮製剤投与群で85％削減が認められた．この研究においては，血栓症や有害事象が増加していないかの検討もされているが，とくに有意な有害事象の増加はなかったとされる．

フィブリノゲン濃縮製剤については，後ろ向き研究ではあるものの，外傷の領域でも輸血頻度や患者予後改善につながるという報告もあり[6]，この領域においてもフィブリノゲン製剤に対する今後の動向が注目される．

2014年9月現在，わが国においては安全なフィブリノゲン濃縮製剤の供給が十分でなく，またクリオプレシピテートが供給されないことから，大量出血時にはフィブリノゲン上昇を目指して新鮮凍結血漿（fresh frozen plasma：FFP）が投与されることが多い．当院においては輸血部でクリオプレシピテートを作製しており，とくに大血管外科において積極的に使用している．図❷Aに示すように，FFP480を4℃で30時間程度かけて低温融解し，遠心分離するとフィブリノゲンが多く含まれる白い沈殿物を認めるが，これがクリオプレシピテートである．つづいて，おもにアルブミンなどが含まれる上清部分を無菌操作で別バックに移動させ（図❷B），残った20～50mLをフィブリノゲンが濃縮されたクリオプレシピテートとして出庫している．原料のFFPに含まれるフィブリノゲンに個人差があるため，フィブリノゲン濃縮製剤と違いばらつきが多少あるものの，3パック（FFP480×3本分）でおおむねフィブリノゲンは約2g程度含まれることになる．しかも容量としては3パックでせいぜい150mL程度なので，容量負荷なくすぐに投与できるので，大量出血時には重宝している．

今後，わが国においてフィブリノゲン製剤が導入されれば，輸血のストラテジーが大きく変わる可能性がある．



図❷ 当院におけるクリオプレシピテート作製の様子

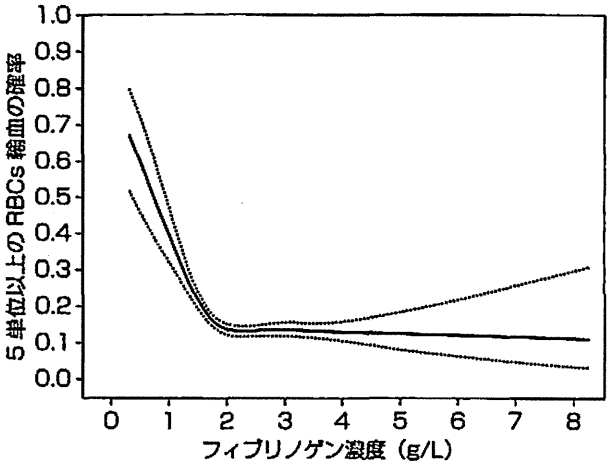
2. 止血のメカニズム ～なぜフィブリノゲン高値が止血につながるか～

フィブリノゲン値が高いほうが止血によいのは感覚的には理解できるが，ここはおさらいの意味もふくめて，止血のメカニズムからその理由を紐解いていく．止血のメカニズムは一次止血と二次止血に区別できる．一次止血においては，外傷などで血管内皮細胞が破綻し，露出したコラーゲンに von Willebrand factor（vWF）が結合する．血小板は血小板膜糖蛋白の GPIb（glycoprotein Ib）受容体を介して vWF と結合し，血管内皮細胞下組織に粘着，凝集して血小板血栓ができる．粘着した血小板は形態を変え，従来の円盤状の形態から偽足を出した形態となる．活性化した血小板はさまざまな顆粒を放出，血小板表面には血小板膜糖蛋白の GPIIb/IIIa 受容体が発現される．この GPIIb/IIIa に対してフィブリノゲンが結合し，血小板血栓を強固にする．つまり，フィブリノゲンは二次止血だけでなく，一次止血にも重要なはたらきを担っているのである．このようにフィブリノゲンは血小板血栓の安定化につながっているので，高いフィブリノゲン量は，血小板数の低下を補正できる可能性も指摘されている[7]．

二次止血の舞台は，凝集した血小板のリン脂質に富んだ膜である．内因系にせよ，外因系にせよ，凝固カスケードにはこのリン脂質と凝固因子が関与し，最終的にはトロンビンが産生されて，フィブリノゲンがフィブリンになって血栓が完成する．このように，一次止血においても血小板血栓を強固にする意味と，二次血栓において最終基質として血栓を完成させるという二つの側面から，止血においてフィブリノゲン値が高いことは重要であることが分かる．

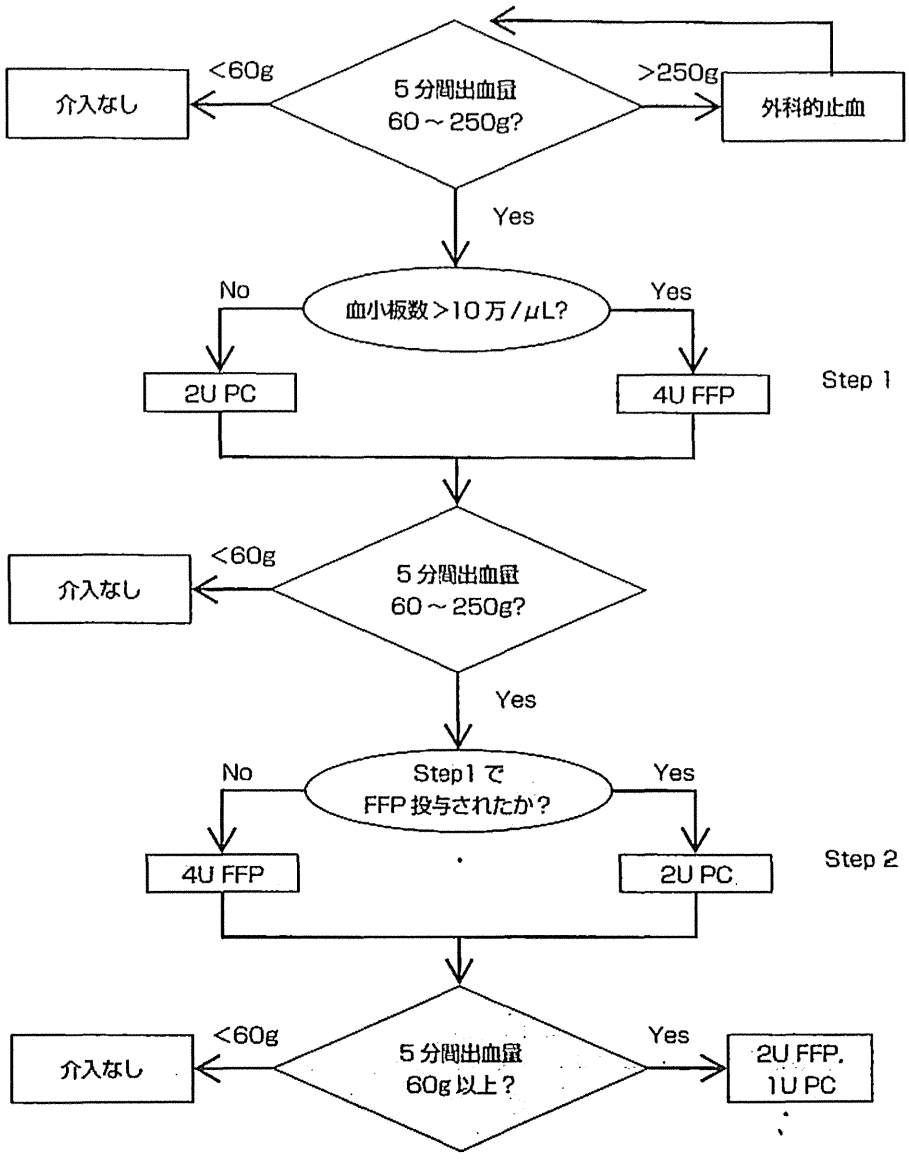
3. フィブリノゲン補充のカットオフ値は？

フィブリノゲン補充の目安として，多くのガイドラインで 100mg/dL があげられていることが多いが，じつはこの推奨についてのエビデンスレベルは低く，エキスパートオピニオンにもとづいている．しかしながら，このカットオフ値はじつは低すぎるのではないかという可能性が指摘されている．2013 年に出た報告[8]ではフィブリノゲン濃度 200mg/dL 未満群では大量輸血症例が増加していたとされる．（図❸）これは単施設後ろ向き観察研究で，人工心肺使用心臓手術 4,606 例を対象としている．フィブリノゲン濃度 200mg/dL 未満群は 42%の症例で，そのうち 18.9%が大量輸血を受けていた．一方，200mg/dL 以上群では 13.5%が大量輸血を受けていた（$p<0.0001$）．リスク因子を調整後でも，大量出血のオッズ比は，1.8（1.4～2.2）であり，傾向スコアを用いた解析でも 1.5（1.2～2.0）であったとされる．



図❸ フィブリノゲン濃度と輸血量の関係
RBCs：red blood cells（赤血球）
（Karkouti K *et al*, 2013[8] より引用）

このほかにも，ドイツの Hannover 大学からの報告で，上行大動脈および大動脈弁置換術の患者を対象に，フィブリノゲン濃縮製剤を治療の最初に介入し，その後は輸血アルゴリズム（図❹）[9]に従うことで，総輸血量や術後出血量の大幅な減少が認められたとしているが，この試験においてはフィブリノゲン値が平均 200mg/dL 程の所でフィブリノゲン濃縮製剤が投与されている[9]．また，冠動脈バイパス術において出血を防ぐために必要なフィブリノゲン値は 100mg/dL よりずっと高いのではないかとする報告も散見されている[10]．麻酔科医の感



図❹ Hannover大学の報告におけるフィブリノゲン濃縮製剤介入後の輸血アルゴリズム
注）ドイツにおけるPC1U＝日本のPC約14単位
FFP：fresh frozen plasma（新鮮凍結血漿），PC：platelet concentrate（濃厚血小板）
（Rahe-Meyer N *et al*, 2009[9] より引用）

覚としてもフィブリノゲン補充のカットオフ値は100mg/dLよりは高いというのは頷けることではあるが，どれくらいが適切なのかについてはいまだに明確ではない．

4. これからの大量出血における戦略

大量出血において，早期から積極的にFFPや濃厚血小板を使えば出血量を減らし，患者予後を改善するという報告があいついでいる．イラク戦争において，外傷患者に赤血球濃厚液：FFP：濃厚血小板を1：1：1で投与することで，大量出血の患者の予後を改善したとの報

告[11]から，通常の外傷患者，またそれ以外の大量出血患者においてもこの考え方が拡大されてきている．しかしながら，この最適比に関しては明確な結論は出ていない．その理由として，大量出血の患者においてランダム比較試験をおこないにくいことがあげられる．したがって，さまざまなバイアスが入りやすく，たとえば生存バイアスの存在が指摘されている．つまり，死亡している患者にはFFPの投与量が少なかったので，FFPの使用が多いほうが予後がよいと結論付けられる．しかし，FFPは融解に時間がかかるために，大量出血で早期に死亡した患者には投与できないので，どうしても生存した患者にFFPが多く入りやすいのである．実際にこの生存バイアスは過去の論文[12]でも指摘され，この生存バイアスを除くため，時間経過を考慮し解析をおこなうと，死亡率とFFP：赤血球濃厚液は関係なかったとされる．

大量出血症例においてフィブリノゲンを補充することが出血を減らすということは，前述のHannover大学からの論文に代表されるように，大きな流れとなっている．したがって，今後わが国においてフィブリノゲン製剤が導入されれば，大量出血においてはまずフィブリノゲン製剤を投与という日がくる可能性もある．しかしながら，フィブリノゲン製剤の使用によって，深部静脈血栓症などの血栓症が増加する懸念もあり，フィブリノゲン製剤を新規の効果的な止血剤として使用することには慎重な意見もある[7]ことを付け加えておきたい．

おわりに

2014年9月現在，フィブリノゲン濃縮製剤と生理食塩水の国際共同多施設二重盲検プラセボ対照ランダム比較試験であるREPLACE study (Randomized Evaluation of fibrinogen versus PLACEbo in complex cardiovascular surgery) の症例登録が終了し，解析待ちの状況である．これは人工心肺使用大動脈置換術患者を対象とし，フィブリノゲン濃縮製剤または生理食塩水で介入し，総輸血量や治験薬投与後24時間以内の同種血輸血量の比較をおこなうものであるが，この治験によりフィブリノゲン濃縮製剤の有効性が示されれば，わが国においてもフィブリノゲン製剤の薬事承認が得られる可能性があり，大量出血における輸血のストラテジーに大きな変化をもたらすと思われる．今後の動向に注目したい．

文献

1) Sihler KC *et al*：Massive transfusion：new insights. *Chest* **136**：1654-1667, 2009
2) Hiippala ST *et al*：Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg* **81**：360-365, 1995
3) Hardy JF：Endpoints in clinical trials on transfusion requirements：the need for a structured approach. *Transfusion* **45** (1 Suppl)：9S-13S, 2005
4) Despotis G *et al*：A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. *Transfusion* **48** (1 Suppl)：2S-30S, 2008
5) Rahe-Meyer N *et al*：Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery：a randomized, placebo-controlled trial. *Anesthesiology* **118**：40-50, 2013
6) Levy JH *et al*：Fibrinogen and hemostasis：a primary hemostatic target for the management of acquired bleeding. *Anesth Analg* **114**：261-274, 2012
7) Sørensen B *et al*：A critical evaluation of cryoprecipitate for replacement of fibrinogen. *Br J Haematol* **149**：834-843, 2010
8) Karkouti K *et al*：The relationship between fibrinogen levels after cardiopulmonary bypass and large volume red cell transfusion in cardiac surgery：an observational study. *Anesth Analg* **117**：14-22, 2013
9) Rahe-Meyer N *et al*：Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level：a pilot study. *Br J Anaesth* **102**：785-792, 2009
10) Karlsson M *et al*：Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery：a prospective observational study. *Transfusion* **48**：2152-2158, 2008
11) Borgman MA *et al*：The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma* **63**：805-813, 2007
12) Snyder CW *et al*：The relationship of blood product ratio to mortality：survival benefit or survival bias? *J Trauma* **66**：358-362；discussion 362-364, 2009

▷第60回学術集会
シンポジウム14：危機的出血(大量出血・大量輸血)におけるチーム医療(4)◁

危機的出血に対する臨床検査部門の対応

河 原 好 絵*1 渡 辺 愉 美*2 友 田 豊*3 紀 野 修 一*4

Contribution of Central Hospital Laboratory to Critical Bleeding

Yoshie KAWAHARA *1, *Yumi WATANABE**2,
*Yutaka TOMODA**3 and *Shuichi KINO*, MD, PhD*4

It has been reported that fibrinogen products, such as fibrinogen concentrates, cryoprecipitate (CRYO), and fresh frozen plasma, are beneficial for treating coagulopathy due to massive blood transfusion. For the appropriate use of these products, it is necessary to evaluate the status of coagulopathy and determine the trigger level of the fibrinogen concentration for the administration of fibrinogen products.

In our institution, we established a treatment procedure for coagulopathy due to massive transfusion in 2011. This procedure includes determination of the trigger level for administration of CRYO (150 mg/dL), timing of sample collection for the evaluation of coagulation parameters (prothrombin time, activated partial thromboplastin time, and fibrinogen) and concentration status during the operation, and a method for rapid coagulation testing (turnaround time within 15 minutes) in critical bleeding.

Since 2011, we have performed 56 rapid coagulation tests for patients suffering from critical bleeding. The average turnover time was 13 minutes. According to the rapid coagulation test results, CRYO was administered to 27 patients. These results are satisfactory for treating critical bleeding patients.

We stress the need for the establishment of a rapid coagulation test system in the central hospital laboratory. 【Review】

[Rinsho Byori **62** : 1286～1294, 2014]

Corresponding author: *Yoshie KAWAHARA*, Department of Medical Laboratory and Blood Center, Asahikawa Medical University Hospital, Asahikawa 078-8510, Japan. E-mail: kawahara@asahikawa-med.ac.jp

【Key Words】 critical bleeding(危機的出血), cryoprecipitate: CRYO(クリオプレシピテート), fibrinogen(フィブリノゲン), coagulation test(凝固検査), turnaround time: TAT(所要時間)

危機的出血時には大量の輸液および輸血により体内の血漿成分が希釈され，希釈性凝固障害が惹き起こされる。この希釈性凝固障害に対応するためには，失われた凝固因子の中でも特にフィブリノゲンの補充が必要であり，クリオプレシピテート(以下，クリオ製剤)やフィブリノゲン製剤投与の有用性が報告されている[1)2)]。しかし，それらの使用には基準が示されておらず，適正使用のためにも各施設においてマニュアルが整備され，使用基準が明確化される必要がある。

当院では2011年11月よりクリオ製剤の供給を開始している。供給開始にあたって院内マニュアルを

*1～4旭川医科大学病院臨床検査・輸血部(〒078-8510 旭川市緑が丘東2条1-1-1)

作成し，その使用基準にフィブリノゲン値を設定した。クリオ製剤の使用基準に検査結果を使用するためには，凝固検査結果の迅速報告が必要となる。そこで，危機的出血時に限定して，日常検査とは明確に区別した方法で行う“迅速凝固検査”の運用を開始した。今回，“迅速凝固検査”運用開始までの準備および運用方法について紹介する。

I. 危機的出血時における迅速凝固検査の必要性

危機的出血時には，出血が持続することにより患者病態が刻々と変化するため，より迅速な検査結果の報告が求められる[3)4)]。また，既に患者には大量の補液および輸血が行われているため，止血困難もしくは止血困難な状態に陥ることが予測されている。この場合の凝固検査は，凝固止血能の評価もあるが，血液製剤を投与するか否か，およびその投与量の判断指標としての意義が大きくなる。検査結果が迅速に得られない場合は，術者や麻酔科医の感覚や慣習によって，投与の是非，また投与量の決断をしなくてはならない。このような状況は，血液製剤投与の過不足を生ずる危険性があり，血液製剤の有効利用の面からも回避しなくてはならない問題である。したがって，危機的出血時であっても，客観的な判断基準による血液製剤の適正使用に向けた検査体制の構築が求められる。

一方，凝固検査は採血手技や検体の処理条件によって結果が大きく左右されることが知られている。採血時の組織液混入や駆血などは凝固因子活性化の要因となり，長時間の室温保存は凝固因子低下の原因となる。また，不十分な遠心処理による血小板残存は，凝固異常の検出感度を低下させる[5)〜7)]。故に，凝固止血能を正しく評価するためには，適切な採血手技と検体処理を行う必要がある。

当院の凝固検査の turnaround time(TAT)は，30〜60分となっている。仮に危機的出血患者の凝固検査の結果報告までの所要時間が60分であった場合，出血量が100mL/min を超える患者に対して，60分後の検査結果は既にその病態を反映する結果でないことは明らかである。つまり，通常の凝固検査体制では，血液製剤投与の判断指標としては意味をなさないことになる。当院では，このような現場の状況に対応するために，「血液製剤適正使用のための凝固検査」という面を重視し，“迅速凝固検査”の運用を検討した。

II. 運用開始までの準備

A. TAT 短縮に向けた検体の取り扱い

迅速凝固検査の最大の目標は TAT の短縮であり，TAT 短縮を図るため，以下に示す事項について検証した。

1. 遠心時間短縮による検査結果への影響の調査

TAT に影響を与える要因の一つが前処理の遠心分離時間であると考えられた。そのため，遠心時間短縮による測定結果への影響を検討した[8)]。その結果，通常の遠心条件(3,000 rpm，10 min，10℃)と遠心時間を5分間短縮した条件(3,000 rpm，5 min，10℃)を比較したところ，後者の方が血漿中に5倍以上の血小板が残存していた。しかし，プロトロンビン時間(PT)，活性化部分プロトロンボプラスチン時間(APTT)，フィブリノゲンの結果には，良好な相関が認められた。5分間遠心では，乏血小板血漿が得られない可能性があり，日常の凝固検査には不向きであると考えられるが，血液製剤投与の判断を目的とした検査であるという観点から，迅速凝固検査では，遠心時間を5分間短縮する運用を採用した。

2. 項目の限定と優先測定の徹底

検査項目は，血液製剤の投与判断に最低限必要な凝固検査3項目(PT, APTT, Fib)と血算に限定し，オーダリングシステムでの入力作業の煩雑さを軽減させるため，セット化した。また，検査室では迅速凝固検査の検体を最優先検体として扱い，分析装置の緊急ポートを用いて測定することをルールとした。

上記 **1.**, **2.** によって，TAT の目標時間を15分とした。

B. 院内ルールの整備(Fig. 1〜3)

危機的出血時における現場の負担軽減のため，検査依頼には専用の伝票(**Fig. 1**)を準備した。専用伝票に医師が記入する項目は，患者氏名，ID，検査依頼医師名，連絡先の必要最低限とし，検査オーダーは，この専用伝票を受け取った検査技師が代理で入力することとした。また，迅速凝固検査からクリオ製剤の使用基準までをまとめた「手術時の大量出血患者に対する輸血療法マニュアル」(**Fig. 2**)を作成し，院内関係部署に周知した。

検査部門では，オーダー入力方法を含めた検査手順のマニュアル(**Fig. 3**)を独自に作成し，365日24時間の対応が出来るように夜間休日の検査業務を行うスタッフを含めたトレーニングも実施した。

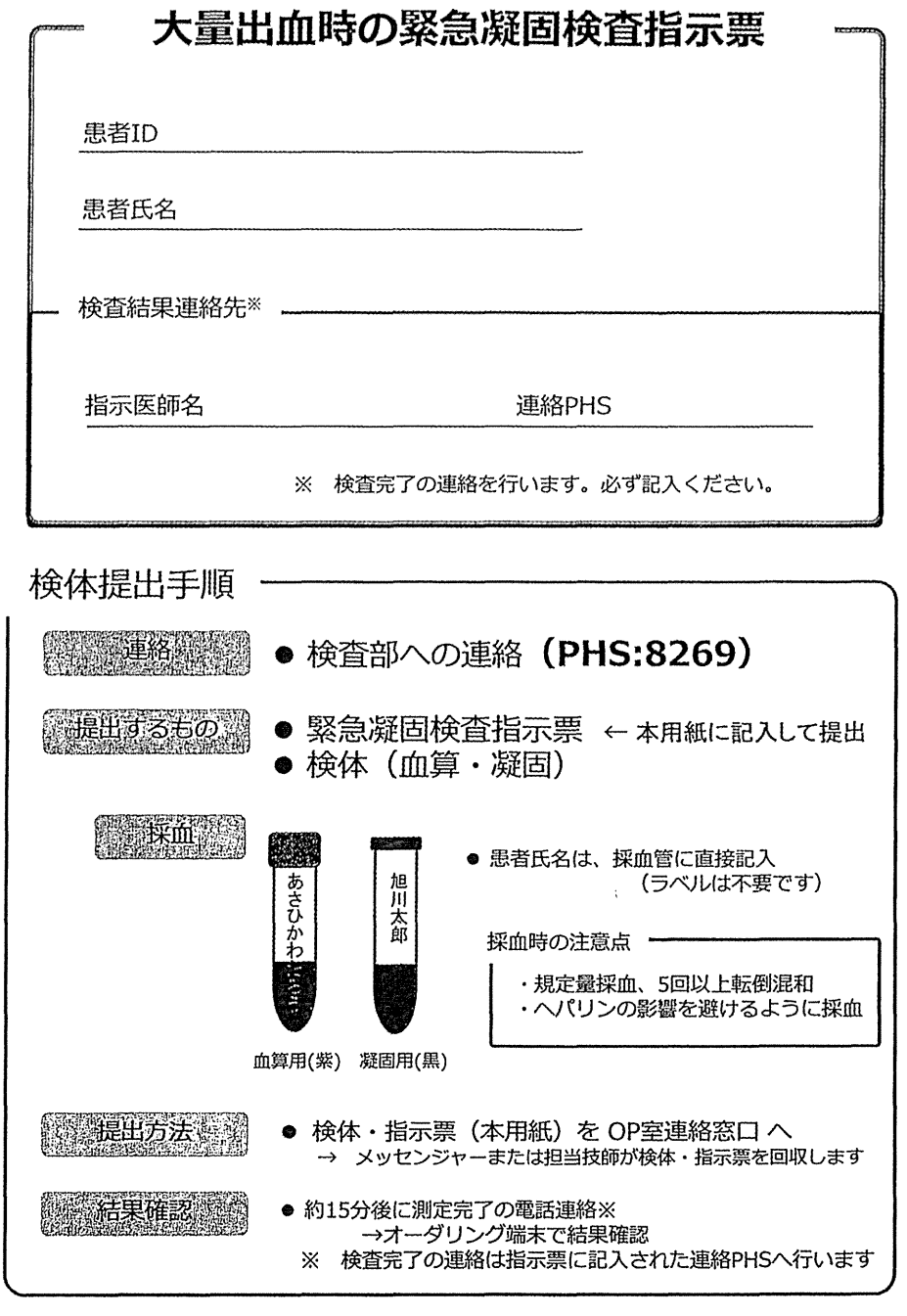


Figure 1　大量出血時の緊急凝固検査指示票

III. 実際の運用

A. 危機的出血発生現場における運用

迅速凝固検査は，原則として出血量が循環血液量の 1/2 になった時点から行われ，手術部から検査部へ依頼伝票と検体が提出される。具体的な手順は以下の通りである。

まず，検査依頼者（主として麻酔科医）は専用伝票に必要事項を記載し，採血を行う。そして，検査技師が 365 日 24 時間携帯している専用 PHS に『迅速凝固検体を提出する』ことを伝える。検査技師から搬送依頼を受けた院内メッセンジャーが手術室から検査室に検体を搬送する。検査依頼者は採血を行い，検査技師へ連絡するのみでよいため，術中の患者管理に集中できる。検査結果は最終的にオーダリングシステムに送信されるが，フィブリノゲン値の結果が出た時点で，検査技師から検査依頼者の PHS に一報が入る。フィブリノゲン値の報告が優先される

手術時の大量出血患者に対する輸血治療マニュアル

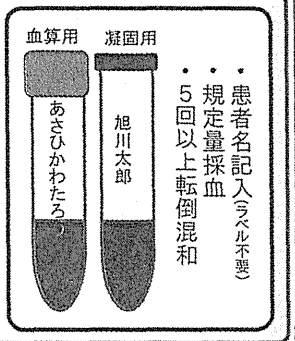
2012/10/29 改訂 旭川医科大学病院輸血療法連絡協議会

説明と同意

○大量出血の可能性のある手術を予定する患者については、術前に未交差同型赤血球濃厚液（未交差同型血）、異型適合赤血球濃厚液（異型適合血）、クリオ製剤（AB型FFPから院内で作成）の使用に関して説明し同意を得る。
○不測の大量出血で術前に説明がされていない場合には、術後に未交差同型血、異型適合血、クリオ製剤（AB型、院内製剤）の使用に関して説明し同意を得る。

大量出血時の凝固検査

準備	● 緊急凝固検査実施の連絡（PHS:8269） ● 緊急凝固検査指示票の記載（オーダ医師名、PHS番号、患者名、ID、必須）
採血	● ヘパリンの影響を避けるように採血
検体搬送	● 緊急メッセンジャー（検査部より連絡）
結果送信	● 約15分後に測定完了の電話連絡（再検の場合も） →オーダリング端末で結果確認



検査実施のタイミング【検体提出前に8269へ電話】	オーダ	血算	FIB	PT	APTT	FDP D-dimer
		紫採血管	黒キャップ採血管（必ず規定量を採血する）			
1. 入室前、又は入室後執刀前（前値として必須）	医師又は技師	●	●	●	●	△
2. 出血量が循環血液量の50%	技師	●	●	●	●	×
3. 以後、適宜	技師	●	●	●	●	×
4. 出血量が循環血液量の100%	技師	●	●	●	●	×
5. 以後、適宜	技師	●	●	●	●	×
6. クリオ輸注後（20～30分間隔）	技師	●	●	●	●	×
7. 止血完了後	技師	●	●	●	●	×
8. 手術直後	医師	●	●	●	●	●
9. 手術翌朝	医師	●	●	●	●	●

＊採血は可能な限り皮膚を穿刺して行う。
（動脈ルートからの採血は、ヘパリンの混入や検体の希釈の可能性があるのでできるだけ避ける。特にAPTTはヘパリンの影響で延長する。測定結果への影響を避けるため、動脈ルートからの採血の際には、ルート内の血液を十分に逆流させてから検体を採取する。）
＊循環血液量は、体重（Kg）x70mL で概算できる。

FIB（フィブリノゲン）濃度

クリオ使用には臨床検査・輸血部長の許可が必要。時間内（3381）、時間外（8269）に連絡下さい。

- **150mg/dL以上**：● 他の凝固因子の補充目的に必要に応じFFPを投与 ● 凝固検査を継続
- **150mg/dL以下**：● **FIB補充　クリオ＞FFP使用**

使用済クリオのバッグは、輸血部門まで返却して下さい。

血小板数

＊予約製剤なので、使用予定が立ち次第速やかに、輸血部門または緊急検査室へ連絡する。
＊必要とする単位数のABO同型血小板はすぐに準備できない場合があるので、そのような場合には危機的出血への対応ガイドラインに示されるABO異型適合血小板を用いる。

- **50,000/μl以上**：●血小板補充は必要なく、むしろフィブリノゲン値が重要
- **50,000/μl以下**：● 出血症状が顕著でなくても血小板輸血を考慮

クリオの投与法（FFPの使用手順と同じ。）

1））クリオの使用許可がでたら、輸血オーダからクリオ15単位（3バッグに相等）をオーダ。
・時間内：輸血部門から手術部にクリオを搬送します。
・時間外：夜間メッセンジャー（8538）へ連絡し、輸血依頼伝票を手渡します。宿直検査技師がクリオの持ち出し登録をし、夜間メッセンジャーが搬送します。
2）クリオ3バッグを37℃で解凍する
3）PDAで照合（患者血液型がAB型以外の場合は「△」がでますが、異型適合血なので使用可能です。）
4）クリオ3バッグを5～10分で一気に静脈内（CVが望ましい）投与する（出血が続いている患者でも100mg/dLほどの血中フィブリノゲン値の上昇が期待される）。
5）投与後にはフィブリノゲン値を確認する。
＊十分な効果が得られなかった場合は、クリオ15単位を追加投与する（追加分は再度オーダを立て、手順1）から繰り返す）。それでも不足の場合は、予備として10単位残っています。
＊速やかな止血のためには、有効なフィブリノゲン補充を行った上での血小板輸血が効果的です。
6）止血が完了するまで20～30分毎に凝固検査を継続する。

Figure 2　手術時の大量出血患者に対する輸血治療マニュアル（簡易版）