Successful Acute Endovascular Therapy of Cerebral Embolism for a Patient with Ventricle-assist Device: Case Report

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Objective: Ventricular assist devices (VAD) are used as a bridge to heart transplantation. Cerebral embolism can develop in patients with VADs despite a strict anticoagulation therapy. We report two cases of successful acute endovascular therapy with Penumbra system for cerebral embolism.

Case Presentations: Case 1: A 20-year-old woman with a VAD presented with right facial palsy and right monoplegia. 3D-computed tomography angiography (3D-CTA) demonstrated left middle cerebral artery (MCA) occlusion. We successfully performed endovascular recanalization of the left MCA with Thrombolysis in Cerebral Infarction (TICI) Grade 3 perfusion, and the patient's symptoms significantly improved. The patient's condition improved to nearly the pre-treatment state. However, due to repeated strokes, the patient developed disturbances of consciousness, aphasia, and complete paralysis of the left lower limb. Furthermore, the infection worsened, and the patient eventually developed a circulatory disorder of the VAD and died. Case 2: A 34-year-old man with VAD presented with sudden disturbances of consciousness and right hemiparesis. Computed tomography (CT) scan revealed no early abnormalities. We performed endovascular recanalization of the left internal carotid artery (IC) top with TICI 3 perfusion. After endovascular treatment, CT scan did not reveal a cerebral infarction. The patient eventually achieved an National Institutes of Health Stroke Scale (NIHSS) score of 0 point and received a heart transplant. In case 2, we pathologically analyzed the retrieved thrombus and confirmed the thrombus to be mainly composed of fibrin. There were no complications of hemorrhage in either case.

Conclusion: A suction-type thrombectomy device is believed to be the first choice for patients with VAD.

Keywords ► acute endovascular therapy, cerebral embolism, ventricle-assist device, penumbra, thrombectomy

Introduction

We previously reported a patient wearing a ventricular assist device (VAD) who developed acute cerebral embolism and

responded to aspiration thrombectomy.¹⁾ Thereafter, the connecting parts of VADs, as used in this patient, were substituted for titanium meshes, contributing to the prevention of thrombus formation through the induction of endothelial cells. However, the incidence of stroke remains high. According to a study regarding a VAD, EVAHEART (steady-flow type, SUN MEDICAL TECHNOLOGY RESEARCH CORP., Nagano), which was used in the two patients presented in this article, the incidence of cerebral infarction was 0.37 events per patient year (EPY), and that of cerebral hemorrhage was 0.21 EPY.²⁾ Structurally, VADs are characterized by a tendency toward blood flow stagnation (whirlpool)-related thrombus formation.^{3,4)} Patients with serious neurological sequelae may be excluded from candidates for transplantation. If severe cerebral infarction occurs, positive reperfusion therapy must be considered. However, in many patients, intravenous thrombolytic therapy with Alteplase (intravenous tissue plasminogen activator: I.V. t-PA) is excluded. On the other

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hand, coagulation disorder-based exclusion criteria for endovascular treatment are less strict than those for I.V. t-PA; therefore, endovascular recanalization treatment is indicated. Since the Organ Transplant Law was revised in July 2010, the number of patients undergoing heart transplantation in Japan has increased. However, the mean interval until transplantation is 980 days, and patients requiring heart transplantation are waiting for donors while wearing VADs. Currently, 90% of those waiting for heart transplantation are wearing VADs.^{5,6)} Although the waiting period temporarily reduced with the increase in the number of patients undergoing heart transplantation, the number of patients wishing to undergo heart transplantation rapidly increased, prolonging the waiting period in 2013; VAD-wearing patients are exposed to a high risk of stroke.

Recent randomized comparative studies established evidence regarding endovascular mechanical thrombectomy for occlusion of the major cerebral artery, but stent retrievers were primarily used in all studies.^{7–11)} A few case reports on endovascular treatment for occlusion of the major cerebral artery in VAD-wearing patients have been published. However, stent retrievers were primarily used.^{12,13)}

We report on two patients in whom endovascular mechanical thrombectomy with a Penumbra system (Penumbra Inc., CA, USA) led to favorable results.

Case Presentation

Case 1: A 20-year-old female

Complaints: Consciousness disorder, right hemiplegia

Medical history: At the age of 18 years, VAD [EVAHEART (steady-flow type), SUN MEDICAL TECHNOLOGY RESEARCH CORP., Nagano] implantation was performed due to hypertrophic cardiomyopathy.

Occlusion of the left middle cerebral artery (MCA) was observed one year before admission.¹⁾ Consciousness disorder, aphemia, and right hemiplegia (manual muscle testing (MMT), upper limbs: 0/5, lower limbs: 3/5) occurred, and the National Institutes of Health Stroke Scale (NIHSS) score was 16 points. Angiography confirmed that a lesion of the left MCA (M1) was responsible for these abnormalities. Using a Penumbra 041 system, thrombus aspiration was performed, leading to TICI2b recanalization. After one month, there were improvements in aphemia (daily living level) and right hemiplegia (MMT score: 4/5), and the modified Rankin Scale (mRS) score was 3. Subsequently, it reduced to 1, and the patient was followed-up at the outpatient clinic of the Department of Cardiovascular Surgery.

Present illness: To treat infection at the drive line-penetrating site of the VAD, the patient was admitted to the Department of Cardiovascular Surgery of our hospital. As right facial paralysis was noted when waking up (7:00 am), she was referred to our department. At the time of onset, she had taken Warfarin at 3.5 mg and aspirin at 200 mg.

Neurological findings: Consciousness was clear, and right facial paralysis and slight paralysis of the right upper limb (MMT score: 4/5) were observed. The NIHSS score was 3 points.

Hematological data: international normalized ratio of prothrombin time (PT-INR): 3.05.

Neuroradiological findings: Contrast-enhanced computed tomography (CT) revealed occlusion of the left MCA (M1). In the left putamen and caudate nucleus head, early CT signs were observed. The Alberta Stroke Program Early CT (ASPECT) score was 8 points (**Figs. 1A** and **1B**). Old infarcted foci were detected in the bilateral basal ganglia and pons.

As occlusion of the left MCA was observed, angiography was performed.

Endovascular treatment: The VAD used in the present case provided steady flow, and femoral artery pulsation was not detected. For this reason, a 4Fr. sheath was inserted into the right femoral artery under echo-guidance (8:45 am). The interval from detection until puncture was 1 h and 45 min.

Left cerebral angiography (CAG) revealed occlusion of the left MCA (M1) (**Figs. 2A** and **2B**). The collateral pathway from the left anterior cerebral artery (ACA) was advanced, and the peripheral artery was visualized. During CAG, the consciousness level reduced to a Japan Coma Scale (JCS) score of 10 or higher, and endovascular treatment was performed. As the activated clotting time (ACT) was abnormally high (not measurable), heparin was not administered. The sheath was exchanged for a 9Fr. sheath, and a 9Fr. Optimo device (Tokai Medical, Japan) was inserted into the left internal carotid artery (ICA). A Penumbra 5Max system (Penumbra Inc., CA, USA) was guided to the thrombotic site using a microwire (Chikai 0.014 inch: ASAHI INTEC, Japan) coaxial to a Penumbra 3Max system (Penumbra Inc., CA, USA). The site was continuously aspirated using a pump. There was no reversed vascular flow, suggesting that thrombus grasping was successful. A direct aspiration first pass technique (ADAPT) was performed, leading to recanalization (one pass). Occlusion of the M2 middle trunk persisted, but it had been confirmed that it was persistently occluded after endovascular mechanical thrombectomy about 1 year before; therefore, we considered that the lesion corresponded to TICI3,

Fig. 1 CT scan revealed parenchymal abnormalities in the left MCA area (head of caudate nucleus and putamen), and the ASPECT score was 8 points. Low density of the bilateral basal ganglia was attributed to a previous infarction (A, B). Only a minor infarction was found in the left basal ganglia at postoperative day 2 after endovascular recanalization (C, D). CT: computed tomography; MCA: middle cerebral artery; ASPECT: Alberta Stroke Program Early CT

and this procedure was completed (interval from puncture until recanalization: 90 min) (**Figs. 2D** and **2E**). For hemostasis, Angio-Seal™ (St. Jude Medical Inc., USA) was used. Postoperative course: After endovascular treatment, the consciousness level promptly improved. Postoperative CT revealed localized cerebral infarction involving the left basal ganglion (**Figs. 1C** and **1D**). Although slight weakness of the right face and upper limb persisted, recovery to the pre-treatment state was achieved. Five days after surgery, the NIHSS score was 1 point. However, subsequently, occlusion of the left ACA, left temporal lobe intracerebral hemorrhage, occlusion of the right MCA, and that of the right ACA/MCA occurred. The interval from cerebral infarction until the onset of these abnormalities was 3 months or less.

Thrombectomy for cerebral hemorrhage was performed under craniotomy. To treat cerebral infarction, endovascular treatment was conducted thrice. After confirming the absence of postoperative hemorrhage on CT the day after thrombectomy under craniotomy, heparin administration was started. Considering the risk of hemorrhage, the target activated partial thromboplastin time (APTT) was established as 40 s or more, and aspirin was discontinued. However, cerebral infarction occurred 1 week after cerebral hemorrhage; therefore, the subsequent APTT was established as 50 s or more, and aspirin administration was started early after onset. As occlusion of the left ACA was present prior to the pericallosal and callosomarginal arteries, mechanical clot disruption was performed using a microcatheter and microguidewire.

Fig. 2 Angiography before the treatment revealed complete obstruction of the left MCA (M1 horizontal segment) (A, B). Angiography after the treatment revealed recanalization with TICI 3 perfusion (D, E). Branches of the MCA were previously obstructed, and sufficient perfusion via the leptomeningeal collaterals from the ipsilateral ACA was observed (C, F). MCA: middle cerebral artery; TICI: Thrombolysis in Cerebral Infarction; ACA: anterior cerebral artery

To treat occlusion of the right MCA and that of the right ACA/MCA, ADAPT was performed using a Penumbra system, and recanalization (TICI2b) was achieved. However, the number of infarcted cerebral foci gradually increased, and neurological findings after recanalization for occlusion of the right ACA/MCA included consciousness disorder (JCS: 3), aphasia, and complete paralysis of the left lower limb. Subsequently, infection deteriorated, leading to VAD circulatory disorder (mRS: 6).

Case 2: A 34-year-old male

Complaints: Consciousness disorder, right hemiplegia

Medical history: At the age of 11 years, he developed dilated cardiomyopathy. At the age of 31 years, he underwent implantation of a VAD, EVAHEART (steady-flow type, SUN MEDICAL TECHNOLOGY RESEARCH CORP., Nagano). At the age of 33 years, hemorrhage of the right frontal lobe occurred. At the age of 34 years, left cerebral infarction occurred, but there were no symptoms in the left

MCA anterior trunk region, and endovascular treatment was not performed. Subsequently, hemorrhage of the right occipital lobe occurred. He had the above history, but the mRS score was zero.

Present illness: To treat infection at the drive line-penetrating site of the VAD, the patient was admitted to the Department of Cardiovascular Surgery of our hospital. The patient suddenly developed consciousness disorder in our hospital at 7:30 pm, and right hemiplegia was noted. On CT, the ASPECT score was 10 points (Figs. 3A and 3B). It was impossible to indicate i.v. t-PA due to a history of intracerebral hemorrhage, and emergency angiography was performed.

Neurological findings: Consciousness disorder (JCS: 3), complete aphasia, slight drooping of the right corner of the mouth, and right hemiplegia (MMT: upper limb, 1/5; lower limb, 2/5) were observed. The NIHSS score was 15 points. Hematological data: PT-INR, 1.58

Endovascular treatment: As described for Case 1, inguinal artery pulsation was not detected, and echo-guided femoral

Fig. 3 CT scan revealed no early abnormalities in the left MCA area, and the ASPECT score was 10 points. Low density of the right frontal area was attributed to a previous brain hemorrhage (A, B). CT scan revealed that the left MCA area was intact after endovascular recanalization (C, D). MCA: middle cerebral artery; ASPECT: Alberta Stroke Program Early CT; CT: computed tomography

puncture was performed (8:40 pm). The interval from detection until puncture was 1 h and 10 min.

Angiography revealed occlusion at the terminal of the left ICA (**Figs. 4A and 4B**). After heparinization (3000 units of heparin, ACT: 214 s), endovascular treatment was performed. An 8Fr. Lancher (Medtronic, Minneapolis, MN, USA) was inserted into the left ICA, and the thrombus was aspirated using a Penumbra 5Max system (Penumbra Inc., CA, USA). Continuous aspiration with a separator and pump was successful. Angiography confirmed recanalization involving M1. Subsequently, we tried to insert a 3Max system as an inner catheter and a 5Max system to an area adjacent to the occlusive site of M1, but the 5Max system did not reach the area unless the 3Max system was inserted to an area distal to the occlusive site; lesion crossing with the 3Max system was conducted. Subsequently, the 3Max system was pulled back while aspirating it using the separator, and continuous aspiration using

the separator through the 5Max system was conducted, leading to recanalization. As the left M2 anterior trunk was occluded due to the previous infarction, endovascular treatment was completed with recanalization corresponding to TICI3, considering that the finding was similar to that before occlusion (**Figs. 4D and 4E**) (interval from puncture until recanalization: 2 h and 50 min). Hemostasis was performed using Angio-Seal™ (St. Jude Medical Inc., USA).

Postoperative course: Mild dysarthria was noted, and the NIHSS score was 1 point. However, postoperative CT did not reveal any infarcted focus (**Figs. 3C and 3D**). Finally, the NIHSS score reached zero, and heart transplantation was performed 2 months after surgery, leading to withdrawal from the VAD. In Case 2, pathological examination of the collected thrombus was conducted. On Elastica Masson/PAS/Gram staining, there was no organization or infection, and a diagnosis of a fibrin thrombus was made (**Figs. 5A and 5B**).

Fig. 4 Angiography before the treatment revealed L occlusion (A, B). Angiography after the treatment revealed ICA recanalization with TICI 3 perfusion (D, E). Branches of the MCA were previously obstructed, and sufficient perfusion via the leptomeningeal collaterals from the ipsilateral ACA was observed (C, F). ICA: internal carotid artery; TICI: Thrombolysis in Cerebral Infarction; ACA: anterior cerebral artery

Fig. 5 (A) Hematoxylin & Eosin (H&E) staining revealed a thrombus composed mainly of fibrin. (B) Thrombi were composed of fibrin with neutrophils and erythrocytes.

Discussion

After the Organ Transplant Law was revised in 2010, the annual number of patients undergoing heart transplantation markedly increased from 10 to 40. Furthermore, medical expense reimbursement for implantation-type VADs by insurance was started in April 2011, making it possible for patients to wait for transplantation at home. With an improvement in implantation-type VADs' performance, a multi-occupational examination/support system for patients was arranged, and the annual number of patients who newly apply for transplantation increased to approximately 100. Currently, more than 400 patients are waiting for transplantation. As a result, the interval until transplantation increased to approximately 900 days; although the number of heart transplantation series increased, it did not meet an increase in the number of patients waiting for transplantation, prolonging the interval until transplantation. Thus, the number of patients waiting for VAD insertion also increased, and, currently, the number of implantation-type VAD-wearing patients is 385.⁵⁾

According to a multi-center, cooperative, prospective, observational study (J-MACS Registry) after EVAHEART reimbursement in Japan, the 6-month, 1-year, and 2-year survival rates after EVAHEART implantation were 93.4, 87.4, and 87.4%, respectively. Concerning complications, the incidence of cerebral infarction was 0.37 EPPY, and that of cerebral hemorrhage was 0.21 EPPY. As described above, the interval until transplantation is long (approximately 900 days); therefore, the risk of stroke is high. Furthermore, patients with serious neurological sequelae may be excluded from candidates for transplantation; therefore, if severe cerebral infarction occurs, positive treatment should be selected. However, criteria to indicate I.V. t-PA include a PT-INR of <1.7, and this procedure is not indicated for most VAD-wearing patients in whom the PT-INR is controlled to 2.5 to 3.5; therefore, endovascular treatment is the only treatment in many cases.

For endovascular treatment for VAD (especially EVAHEART)-wearing patients, the following two points must be considered:

EVAHEART is a system to transmit blood to the ascending aorta through an inflow cannula at the left ventricular cardiac apex, blood pump, and outflow graft. Its structure differs from those of conventional pulsation-type assisted artificial hearts in which blood is retained and transmitted; blood is continuously transmitted through a blood pump impeller (continuous flow-type VAD). Therefore, there is no arterial

pulsation. In EVAHEART-wearing patients, there is no arterial pulsation on femoral puncture; echo-guided puncture must be performed (first point). In the field of cerebral endovascular treatment, echography is not always necessary, and, to shorten the interval until recanalization, physicians should confirm the place of echograph storage and establish a system in which echographs are always available.

With respect to VAD thrombus formation, several mechanisms have been proposed: (1) foreign body response-related thrombus formation (thrombus formation at the titanium junction of an inflow cannula),¹⁴⁾ (2) thrombus formation related to blood flow stagnation (whirlpool) between the cardiac apex and a blood-removing cannula, and (3) thrombus formation related to left ventricular collapse associated with a marked increase in the number of pump rotations.¹⁵⁾ It is suggested that thrombi appearing through the (2) or (3) mechanisms resemble fibrin thrombi related to atrial fibrillation. In Case 2, pathological findings of the collected thrombus confirmed a non-organized fibrin thrombus. Of course, foreign body response-related thrombus formation may occur, but the junction of the latest EVAHEART system was improved to titanium mesh; endothelial cells are induced, preventing thrombus formation. For the above reasons, VAD-wearing patients require anticoagulants and antiplatelet drugs for the prevention of cerebral infarction. Warfarin control targets a PT-INR of 2.5 to 3.5. As an antiplatelet drug, aspirin at 100 to 300 mg is orally administered.²⁾ In our hospital, Warfarin control targets a PT-INR of 2.5 to 3.0, and aspirin at 100 to 200 mg is orally administered as antiplatelet therapy.

As the second precaution, the risk of hemorrhage related to potent antiplatelet therapy must be considered.

If hemorrhage occurs, Warfarin administration must be reversed or discontinued. This may lead to thrombus formation, and, even if Warfarin is additionally administered, cerebral infarction may develop before its efficacy appears, or cerebral hemorrhage may be induced by increasing the intensity of the anticoagulant, resulting in a negative spiral. Physicians must recognize that cerebral infarction/hemorrhage may be repeated, as demonstrated in Case 1. From such a viewpoint, echo-guided puncture of the anterior wall should be accurately performed, and high-position puncture should be avoided. Furthermore, it is important to select procedures to avoid intracranial hemorrhagic complications, if possible.

Concerning the selection of devices, a few case reports on endovascular treatment for occlusion of the major cerebral artery in VAD-wearing patients have been published. However, procedures with a stent retriever were primarily adopted.

A recent randomized comparative study showed that endovascular mechanical thrombectomy with a stent retriever more markedly improved the outcome compared with medical treatment, but it is known that this procedure induces subarachnoid hemorrhage (SAH) at a specific percentage (SWIFT PRIME study using a Solitaire FR: 4%,⁷⁾ TREVO2 study conducted by Trevo and Merci: 12%¹⁶⁾). The results of treatment with aspiration catheters, such as the Penumbra system, were favorable with the recent introduction of large-diameter 5MAX ACE and ADAPT catheters.¹⁷⁾ In addition, several studies indicated that there was no SAH in any patient.^{17,18)} The pathogenesis of Merci Retriever-related SAH may involve device development-related vascular perforation, vascular-wall invasion on thrombus capture/collection, vascular dissociation associated with several sessions of lesion passage, and avulsion injury of vessels.^{19,20)} In the presence of stent retrievers, similar mechanisms may also function, although the degree differs. Of these points, stent development- or lesion passage-related mechanisms can be avoided using ADAPT catheters by Penumbra Inc. Avulsion injury may be less marked than after treatment with a stent retriever due to slight vascular linearization.

As a method to prevent hemorrhage, the dose of heparin is controversial, but the post-analysis of the Multi MERCI trial showed that, even when heparin at 3000 units (median) was used for endovascular treatment, there were no significant differences in the incidence of hemorrhage or mortality rate in comparison with a non-heparin-treated group, and that the clinical outcome was favorable.²¹⁾ Heparin at 3000 units may be available.

This is the first report on endovascular treatment with a Penumbra system for occlusion of the major cerebral artery in VAD-wearing patients. To minimize hemorrhagic complications, aspiration thrombectomy may be more advantageous with respect to the safety. In the future, further examination involving a large number of patients should be conducted.

Conclusion

This is the first report on the use of a Penumbra system for VAD-wearing patients. In these patients, hemorrhagic complications must be avoided, and a device to reduce the risk of hemorrhage should be selected. With respect to the safety, aspiration-type devices may be the most appropriate for VAD-wearing patients.

Disclosure Statement

There is no conflict of interest for the author or co-authors.

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