Endovascular Stent Graft Repair for Thoracic Aortic Aneurysms: The History and the Present in Japan

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Stent-grafts for endovascular repair of thoracic aortic aneurysms have been commercially available for more than ten years in the West, whereas, in Japan, a manufactured stent-graft was not approved for the use until March 2008. Nevertheless, endovascular thoracic intervention began to be performed in Japan in the early 1990s, with homemade devices used in most cases. Many researchers have continued to develop their homemade devices. We have participated in joint design and assessment efforts with a stent-graft manufacturer, focusing primarily on fenestrated stent-grafts used in repairs at the distal arch, a site especially prone to aneurysm. In March 2008, TAG (W.L. Gore & Associates, Inc., Flagstaff, Arizona, USA) was approved as a stent graft for the thoracic area first in Japan, which was major turning point in treatment for thoracic aortic aneurysms. Subsequently, TALENT (Medtronic, Inc., Minneapolis, Minnesota, USA) was approved in May 2009, and TX2 (COOK MEDICAL Inc., Bloomington, Indiana, USA) in March 2011. Valiant as an improved version of TALENT was approved in November 2011, and TX2 Proform as an improved version of TX2 began to be supplied in October 2012. These stent grafts are excellent devices that showed good results in Western countries, and marked effectiveness can be expected by making the most of the characteristics of each device. A clinical trial in Japan on Najuta (tentative name) (Kawasumi Labo., Inc., Tokyo, Japan) as a line-up of fenestrated stent grafts that can be applied to distal arch aneurysms showing a high incidence, and allow maintenance of blood flow to the arch vessel was initiated. This trial was completed, and Najuta has just been approved in January of 2013 in Japan, and further development is expected. In the U.S., great efforts have recently been made to develop and manufacture excellent stent grafts for thoracic aneurysms, and rapid progress has been achieved. In particular, in the area of the aortic arch, in which we often experience aneurysmal change, but there are no commercially available devices which are urgently needed. Companies are competing keenly to develop devices. To our knowledge, more than 4 manufacturers are involved in the development of functionally new stent grafts in this area. The introduction of branched stent grafts may not be faraway.

Keywords: stent, stent graft, aneurysm, thoracic aortic aneurysm, endovascular surgery

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INTRODUCTION

Thoracic aneurysms have mainly been treated by graft replacement. However, this surgical technique is markedly invasive, and a decrease in invasiveness is important in improving treatment results. Endovascular aneurysm repair (EVER, TEVAR) has attracted attention due to its minimal invasiveness for more than 15 years, and is an indispensable technique for aneurysms at present. In Japan, in the thoracic area, homemade stents grafts constructed by implant surgeons themselves were initially used, but commercially available stent grafts were approved in 2008, which markedly increased cases treated using such stent grafts. The history of endovascular surgery for aneurysms started with the experimental study by Dotter in 1969. After some experimental studies, clinical experiences for abdominal and thoracic aneurysms were reported by Parodi, et al. in Argentina and Dake and Mitchell, et al. in the U.S., respectively, in the 1990s. In Japan, clinical results were occasionally reported in the latter half of the 1990s. The clinical application of endovascular stent grafting has annually been increasing, and its usefulness has been demonstrated. Since 2000, clinical trials and midterm results have been reported. I also initiated this treatment method in 1995, and have improved stent grafts, delivery system, and surgical procedures to the present. During the past 17 years, I have treated about 1700 cases in the thoracic aorta area using this method including cases treated in other institutions. In April, 2008, a clinical trial on Najuta (tentative name) (Kawasumi Labo., Inc., Tokyo, Japan) as a line-up of fenestrated stent grafts that can be applied to distal arch aneurysms showing a high incidence, and allow maintenance of blood flow to the arch vessel (Fig. 1) was initiated. This trial was completed, and Najuta has just been approved in January of 2013 in Japan, and further development is expected.

STANDARD DEVICES AND THEIR CHARACTERISTICS

Before 2008, there were commercially available endovascular stent grafts for thoracic aneurysms in western countries. In Japan, endovascular stent grafts for abdominal aneurysms were approved by the Ministry of Health, Labour and Welfare, but those for thoracic aneurysms were awaiting approval. In most institutions, stent grafts were constructed by surgeons themselves; the circumference of a self-expanding type Gianturco Z stent (COOK MEDICAL Inc., Bloomington, Indiana, USA) or Matsui-Kitamura (M-K) stent as a skeleton was covered with polyester fabric or a polytetrafluoroethylene (PTFE) film vascular prosthesis material and fixed with vascular suturing thread, or Inoue’s stent graft was used. However, in March 2008, TAG (W.L. Gore & Associates, Inc., Flagstaff, Arizona, USA) was approved as a stent graft for the thoracic area first in Japan. Subsequently, TALENT (Medtronic, Inc., Minneapolis, Minnesota, USA) was approved in May 2009, and TX2 (COOK) in March 2011. Valiant as an improved version of TALENT was approved in November 2011, and TX2 Proform as an improved version of TX2 began to be supplied in October 2012. These stent grafts are excellent devices that showed good results in Western countries, and marked effectiveness can be expected by making the most of the characteristics of each device.

Concerning the characteristics of each device, TAG shows high conformability to the curved aorta with the great radius of curvature and also well fits the landing zone with slight wall irregularity. However, for aneurysms located in the distal arch or proximal descending aorta, the proximal end of TAG sometimes does not adequately conform to the curvature of the distal arch, and lack of graft fixation against the minor curvature of the Aorta (gap issue) is observed. Stent graft deployment can be readily performed by pulling the thread, and is only slightly affected by operator’s skills. However, the control at the time of stent graft release, i.e., positional adjustment in mm units, particularly distal adjustment is difficult and inappropriate. Therefore, an inadequate distance to the celiac artery (distal landing zone length) with a curved descending aorta, often causes Type Ib...
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allows safe stent grafting with high conformability to the distal arch. The bare stent portion at the tip accurately directs the device toward the ascending aorta reinforces stent fixation, and contributes to the prevention of endoleak. In addition, the line-up includes large caliber stent grafts (maximum, 46 mm), expanding the applicability of this device.

TX2 can be regarded as a device between TAG and Valiant. Based on our experience, its controllability during graft deployment is extremely fine and accurate. In the distal arch, although the slight gap issue is observed, this device is very appropriate for the treatment of aneurysms in the lesser curvature of the distal arch. Its expandability is also between those of TAG and Valiant. The line-up is rich, allowing use for various aneurysms.

Fig. 2 Commercially available stent grafts. There are the following 5 approved types in Japan (October 6, 2012): (a) TAG (Gore, USA); (b) TALENT (Medtronic, USA); (c) TX2 (COOK, USA); (d) Valiant Captivia (Medtronic); (e) TX2 Proform (COOK).

Valiant as an improved version of TALENT is a model with a delivery system called Captivia allowing the tip stent to open last. This is an excellent device that markedly overcame the conventional disadvantages and allows safe stent grafting with high conformability to the distal arch. The bare stent portion at the tip accurately directs the device toward the ascending aorta reinforces stent fixation, and contributes to the prevention of endoleak. In addition, the line-up includes large caliber stent grafts (maximum, 46 mm), expanding the applicability of this device.

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TX2 Pro-form as an improved version of TX2 is a device in which the gap issue has been improved. The stent graft of TX2 Pro-form is the same as that of TX2, but the method of its fixation to the delivery system has been changed. In addition, its performance was further improved by using a shape memory alloy for the central
lumen and improving the shape and material of the tip. Since fitting to the distal arch improved, this device is also appropriate for the treatment of aneurysms located on the greater curvature of the distal arch, and widely applicable. COOK also initiated global simultaneous clinical trials of TX2 low profile with a small sheath, and our institution is a participant in this clinical trial.

**Devices for the Arch and Distal Arch Aneurysms**

For the treatment of the arch and distal arch aneurysms in the arch or distal arch showing a high incidence, in patients in whom an adequate length of the landing zone from the left common carotid artery cannot be obtained, the covered stent should be landed proximal side of the site branching off the left common carotid artery. In this case, blood flow to the arch branch should be preserved, treatment is often impossible and difficult using approved commercially available devices alone. Therefore, blood flow in the arch branch should be maintained with an additional following bypass grafting for the carotid artery (debranch method), or an additional procedure in which a small covered stent is inserted like a branch from the aorta into the carotid artery (chimney method). However, these methods sometimes require an approach to the ascending aorta, increasing surgical invasion, and possibly causes other complications such as cerebral infarction due to bypass grafting or stent graft placement in a branch vessel, poor fitting to the proximal fixation, and prolongation of the procedure time. Thus, these methods have not yet been originally established as minimally invasive methods. In the present stage, the final form of stent grafts must be the branched stent graft which is definitely useful for arch or distal arch aneurysms. However, in the case of aneurysms which do not have enough inner space, the branch of the stent graft placed in the arch vessel may be bent in the aorta due to post operative aortic remodeling, resulting in stenosis or obstruction, and therefore, careful development should be required. At present, branched stent grafts and fenestrated stent grafts (Fig. 1), though not commercially available devices, have been developed and treatment using commercially available stent

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**Fig. 3** Digital subtraction angiography (DSA) (left upper) and computed tomography (CT) (left lower) images before fenestrated stent grafting for distal arch aneurysms and DSA (right upper) and CT (right lower) images after the grafting. There was no endoleak, blood flow to the carotid artery was maintained, and complete thrombosis in the aneurysm was observed, showing a treatment success.
grafts without the debranch or chimney for distal arch aneurysms will be realized in the near future.\textsuperscript{15}

**Indications**

**Morphological indications**

The evaluation of the aortic shape and properties is the most important in determining indications for this method. Manufacturers often present morphological criteria for indications for each device and based on these issues, institutions often have their own indication criteria. The contraindication criteria for this method in our institution based on manufacturers' indication criteria are as follows.

a) The length of the healthy aorta (landing zone) from major aortic branches (such as carotid, celiac, superior mesenteric, and renal arteries) to the origin or end of the aneurysm is $<15$ mm. In particular, for distal arch aneurysms, the distance from the left common carotid artery to the origin of the aneurysm is $<15$ mm.

b) The landing zone is markedly tortuous or calcified.

c) The landing zone diameter is $>38$ mm (permitted for TALENT and Valiant) or $\leq 10$ mm.

d) The aorta, iliac artery, or femoral artery is severely tortuous or calcified, and advancement of the delivery sheath is expected to be difficult.

In addition to the above, difficulty in stent graft deployment suggested using diagnostic imaging and patients with a high risk of developing certain complications are sometimes included in the contraindications.

**Clinical indications**

Thoracic aneurysms, if untreated, rupture, leading to death. Despite improvement in recent surgical results, the operative death rate is not always satisfactory. In addition, in patients undergoing re-operation or having certain pre-operative risks, markedly invasive operation itself involves risks, and operation is not indicated in some of them. Therefore, endovascular stent grafting is useful as a minimally invasive method. When there are morphological indications, this method is indicated not only in high-risk patients but also in some low-risk patients.

**Limitations of This Treatment Method**

The above morphological contraindications represent the limitations of this treatment method at present. The stent graft is basically placed in the descending aorta. However, recently, we have actively placed a stent graft from the ascending aorta for distal arch aneurysms when necessary to improve long-term results, and have obtained good results (Fig. 3). If there are precise devices and skills, stent graft placement in almost all sites of aorta would be possible. The proximal landing zone from the left common carotid artery should be required at least $15$ mm, and the left subclavian artery (LSCA) is intentionally occluded with a stent graft in some cases to prolong the landing zone. In such cases, before operation, an occlusion test of the LSCA should be performed to confirm safety. When blood flow to the left vertebral artery is necessary, the risk of paraplegia or coronary bypass grafting using left internal mammary artery branching from LSCA is found, blood flow can be maintained by addition of a bypass operation to the LSCA. Some studies have suggested that aortic dissection with entry located in the descending aorta even including that accompanied by retrograde dissection toward the ascending aorta (DeBakey IIIb\textsuperscript{R}) is a good indication because entry closure is technically relatively straightforward.\textsuperscript{12,13} However, at present, we consider this case with the retrograde dissection in the ascending aorta as a contraindication, considering the risk of injury or degeneration of the intimal flap as a part of the landing zone during or late after stent grafting because dissection involves the proximal side of the landing zone as the most important area for stent grafting. Thus, the Stanford B which has healthy proximal landing zone is a good indication. However, since the distal landing zone is not healthy due largely to the dissection, late iatrogenic intimal flap injury caused by the end of the stent graft has also been observed. In addition, the false lumen may be enlarged because of untreated re-entry near the abdominal branch. There remain various problems to determine the limiting point of endovascular repair for aortic dissection.

**Preoperative Examinations**

For safe and accurate stent grafting, preoperative imaging diagnosis is indispensable. There are various imaging techniques such as computed tomography (CT) scanning, angiography, ultrasonography, and magnetic resonance angiography (MRA). Minimally invasive versatile CT scanning is indispensable, and in particular, 3-dimensional reconstruction CT images are very useful and optimal. Angiography may also provide much information although arterial puncture is slightly invasive for the patients.
and displacement of the stent graft can be prevented by deployment, pressing the stent graft against and along the greater curvature side of the distal arch. For delicate positional adjustments of the fenestrations of Najuta to the 3 vessels in the arch, accurate deployment is performed by gradual landing of the stent graft utilizing the blood flow force.

Although we should explain the method of the use of each commercially available stent graft, the details are omitted due to page limitation since the insertion method varies among the devices. Refer to the recommended usage by each manufacturer.

**RESULTS**

We define initial success of endovascular stent grafting for aneurysms as complete thrombosis in and exclusion of the aneurysm (Fig. 1). To evaluate the performance of stent grafts and delivery systems, whether the stent graft could be implanted safely and accurately at the planned site is important, and the clarification of delivery failure is also necessary for the evaluation of early results. Concerning mid- and long-term results, the most important item for the evaluation of results is changes in the aneurysm diameter. Stent graft migration and deformation are also important. No changes or a decrease in the aneurysm diameter indicate favorable results. When the aneurysm diameter increases, its cause should be closely examined, and additional treatment should be necessary.

We have performed endovascular stent grafting in about 1900 patients with thoracic aneurysms in both this and other institutions for about 17 years since 1995. The number of patients in the institution we belong to was 1160, and their results are shown in the following. The ratio of non-dissection: dissection was 3:1. The location of aneurysms was the distal arch – proximal descending aorta in 679 patients and the descending aorta in 481.

**Early results**

The initial success rate without endoleak on postoperative CT images was 97.2%. As complications, cerebral infarction due to embolism was observed in 3.0%, paraplegia in 2.4% (paraparesis, 2.0%), aortic injury in 0.8%, and iliac/femoral artery injury in 3.9%. The initial success rate annually improved due to evolution of devices while the cerebral infarction rate transiently increased, with more proximal implantation, but is recently decreasing.
Midterm results

Patients in whom the vascular diameter could be measured 1 year or more after the operation were evaluated. A decrease, no change, and an increase in the aneurysm diameter were observed in 57.7, 35.5, and 6.8%, respectively, of patients with non-dissection true aneurysms, 82.4, 15.7, and 1.9%, respectively, of patients with non-dissection pseudoaneurysm, 36.9, 42.9, and 20.2, respectively, of patients with aortic dissection (double barrel type), and 76.6, 20.2, and 3.2%, respectively, of patients with partial aortic dissection. When only patients with distal arch aneurysms encountered from 2004 were evaluated, a decrease, no change, and an increase in the aneurysm diameter were observed in 42, 46, and 12%, respectively. Most patients showing an increase in the aneurysm diameter had inadequate proximal landing zone and had been treated during the early period. These patients frequently showed a second endoleak, which was coped with an additional stent grafting or coiling, or open surgical repair. In 80% of these patients, open surgery could be avoided by an additional stent grafting or coiling. The aneurysm diameter increased in a high percentage (20.2%) of patients with aortic dissection. However, in most of them, since occlusion of re-entry in the thoracoabdominal aorta had been impossible, the cause of the increase in the aneurysm diameter may have been an increased pressure in the false lumen due to blood flow through the re-entry into the false lumen. As complications, stent graft fracture was observed in 1.5% and migration in 4.8%, but an improvement in devices caused no migration observed in patients treated during recent years. The postoperative 5-year survival rate was 62.8% when deaths unrelated to treatment were included. The follow-up rate was 97.0%.

Future Prospects and Problems

Compared with conventional surgical repair, endovascular stent grafting has advantages such as a small surgical wound, decreases in the duration of procedure and blood loss, and no need for extracorporeal circulation. This method has improved surgical results, allowed early bed-leaving, shortened the hospitalization period, and decreased patients' physical and psychological burdens. In addition, a decrease in the medical cost can be expected. The problem of endovascular stent grafting is that its safety and accuracy have not adequately been established because devices and surgical procedures are still in the process of development, and long-term results have not sufficiently been evaluated in Japan. The history of endovascular stent grafting for the thoracic aortic aneurysms from its clinical introduction is not enough long. Although the treatment results have been satisfactory, there is still room for improvement in devices including not only stent grafts but also devices for stent graft delivery, and long-term durability has not adequately evaluated. Therefore, at present, endovascular stent grafting is not a treatment method brought to completion. To improve and obtain stable surgical results in the future, ease of the manipulation of stent grafts themselves and also delivery system is important, and further participation of medical equipment manufacturers in the development of devices is necessary for dramatic advances. In the U.S., great efforts have recently been made to develop and manufacture excellent stent grafts for thoracic aneurysms, and rapid progress has been achieved. In particular, in the area of the aortic arch, in which we often experience aneurysmal change, but there are no commercially available devices which are urgently needed. Companies are competing keenly to develop devices. To our knowledge, more than 4 manufacturers are involved in the development of functionally new stent grafts in this area. The introduction of branched stent grafts may not be faraway.

Conclusions

In Japan, TAG was approved in March, 2008, which was the major turning point in treatment for thoracic aortic aneurysms. For the acceptance of this endovascular repair as general medical treatment in the future, it is important to further expand the indications for this method to the arch or distal arch area by developing more excellent systems and technical improvement, and achieve the accuracy and safety of treatment.

Disclosure Statement

The authors have no conflict of interest to declare.

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