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An Update on Surgery for Acute Type A Aortic Dissection: Aortic Root Repair, Endovascular Stent Graft, and Genetic Research

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Abstract
Acute type A aortic dissection remains a lethal disease. With advances in operative methods and perioperative management, surgical outcomes continue to improve, but in-hospital mortality still ranges from 10% to 30% in most series. The surgical technique of choice for aortic root repair remains controversial. Thus, we review the surgical techniques and introduce endovascular stent graft treatment and genetic studies for acute type A aortic dissection.

Key words Acute type A aortic dissection · Aortic root repair · Aortic valve sparing · Endovascular stent graft · Genetics

Introduction

Acute type A aortic dissection remains a lethal disease. Complication rates associated with acute type A aortic dissection exceed 1%–2% per hour after the initial onset of symptoms.[1–3] Without treatment, approximately 75% of patients die within 2 weeks of the onset of symptoms,[4] as the result of aortic rupture, pericardial effusion and tamponade from aortic leak into the pericardial space, aortic insufficiency and ischemia of coronary arteries from dissection of the aortic root, innominate, carotid, or subclavian occlusion from dissection into their respective ostia or themselves, and malperfusion syndrome.

To prevent these lethal complications, immediate repair has been the treatment of choice. Acute type A aortic dissection remains one of the most challenging diseases facing cardiothoracic surgeons. With advances in operative methods and perioperative management, surgical outcome continues to improve,[5] but the in-hospital mortality still ranges from 10% to 30% in most series.[5–15]

On the other hand, the last decade has seen the development of endovascular stent-grafts for the treatment of aortic diseases. Endovascular stent grafting has been used to treat thoracic aortic dissection.[16–23]

Prevention might be the least invasive therapy for this kind of life-threatening disease. Thus, genetic research has recently been introduced to prevent aortic dissection.

Open Surgery: How to Repair the Aortic Root?

Acute type A aortic dissection has been treated surgically only in the last 60 years and despite recent advances, mortality rates remain high.[5–15] The best surgical technique for aortic root repair in acute type A aortic dissection remains controversial. Aortic valve regurgitation caused by leaflet prolapse is a major complication of aortic dissection, and is associated with increased morbidity and mortality.[24,25]

Supracommissural replacement of the ascending aorta or composite replacement of the aortic valve and ascending aorta are established surgical techniques for acute type A dissection in patients with deteriorated aortic root or valvular regurgitation. The Stanford group and others have advocated preservation of the aortic valve by resuspension whenever possible.[24,26–31] However, in the 1990s operative mortality remained high, at 20%–30%.[28–30] Most operative deaths resulted from intraoperative hemorrhage and left ventricular pump failure.[28] The latter complication may be caused by residual blood flow in the false lumen of the aortic root. Furthermore, supracommissural replacement was associated with the risks of redissection, pseudoaneurysm formation in the aortic root, and aortic regurgitation. Therefore, different techniques have been designed for proximal aortic

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reconstruction. Root replacement with a composite graft may prevent the need for reoperation.[32,33] However, postoperative anticoagulation therapy can interfere with thrombosis of the false lumen. Recently, valve-sparing techniques for replacement of the ascending aorta in patients with acute type A aortic dissection have gained attention. Here we review these techniques for repair of the aortic root.

Supracommissural Replacement (SCR)

Gelatin–Resorcin–Formalin (GRF) Glue

Gelatin–resorcin–formalin (GRF) glue was created in 1966 and first used for aortic root reconstruction in 1977 by Guilmet and colleagues.[34–36] The glue was applied between the two layers, as one or two drops of formalin–glutaraldehyde mixture (Fig. 1). The main reasons for using GRF glue were to reinforce the aorta, rendered fragile by acute dissection, and to strengthen the aortic anastomosis.

In 1999, Bachet and colleagues[37] reported 21% hospital mortality (39/204 patients) in operations using GRF glue. They concluded that although the results obtained with GRF glue have benefited from general progress in pre-, intra-, and postoperative management, there is no doubt that the operative procedures have been simplified by its use, as assessed by the mean duration of cardiopulmonary bypass and aortic cross-clamping. A 21% overall mortality does not seem low, but 20% of the patients were older than 65 years, and almost one-third underwent emergency replacement of the aortic arch.

Subsequently, GRF glue has been used widely in operations for acute type A aortic dissection, and good results have been achieved.[5,37–40] In these series, hospital mortality ranged from 6% to 22%. On the other hand, late complications possibly caused by the toxic effects of GRF glue have been reported.[5,41–45] In 2001, Kazui and colleagues[43] reported that redissection of the aortic root developed in 4 (7%) of 57 patients who had undergone root reconstruction using biologic glue. Reoperation revealed dehiscence of the proximal suture line where GRF glue was applied.

GRF glue was used in 221 patients in our series.[5] False aneurysms were found in 31 (16%) of 193 survivors from 1 to 65 months (mean, 30 months) after surgery for acute type A aortic dissection. Redissection, dehiscence of the proximal suture line (Fig. 2A), and aneurysm formation may have been caused by the toxic effects of GRF glue, because these complications and operative findings have never occurred in aortic operations without GRF glue. Our findings suggest that GRF glue is associated with an increased risk of potentially lethal complications ascribed primarily to the use of excess formalin. Only 2–3 droplets of formalin, or less, is considered sufficient to polymerize 1 ml of gelatin–resorcin mixture.[46,47] We used a small syringe to apply the formalin because too much formalin might be toxic to the aortic wall. The syringe could add a very small volume of formalin to the gelatin–resorcin. One drop from the syringe was equivalent to about 0.04 ml. We added 3–5 drops (0.12–0.20 ml) of formalin to 3–5 ml of gelatin–resorcin. However, this small volume of formalin might have had toxic effects on the aortic wall. Accordingly, we have discontinued using GRF glue. Macroscopic and microscopic findings suggest that the complications were related to the toxic effect of the formalin, the concentration of which (37%) in the GRF glue is too high (Fig. 2B).

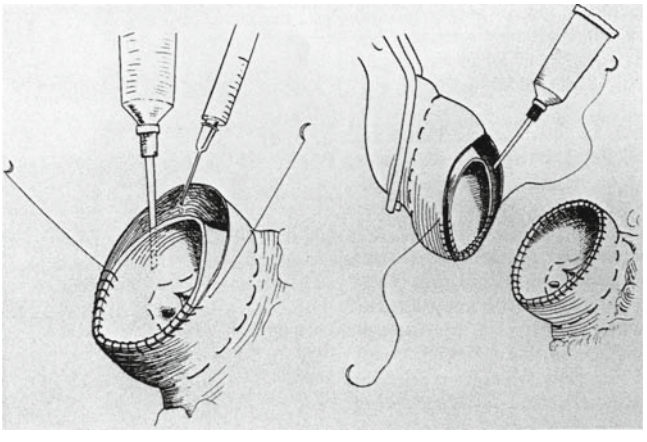

Fig. 1. Use of gelatin–resorcin–formalin (GRF) glue, which is applied between two layers. One or two drops of the formalin–glutaraldehyde mixture were necessary for each application. Simultaneous continuous suturing was done on the edges of the two cylinders. Reprinted with permission, from Guilmet et al.[35] Copyright Elsevier

BioGlue

BioGlue (Cryolife, Kennesaw, GA, USA) is composed of bovine serum albumin (BSA) and a relatively low concentration of glutaraldehyde (10%). BioGlue forms a covalent bond with tissue and reinforces flimsy or friable tissue into a tougher and more workable consistency. BioGlue was introduced in the United States in 1997, under a humanitarian device exemption, for use in acute aortic dissection.

At the American Association for Thoracic Surgery in 2001, Bavaria and colleagues[48] reported a prospective, randomized, multicenter study using BioGlue in acute aortic dissection. Patients who underwent surgery with BioGlue had shorter operative times, less blood loss, and shorter hypothermic arrest periods than control patients. The FDA approved BioGlue for general use as a hemostatic adjunct in cardiac and vascular surgery in December 2001.

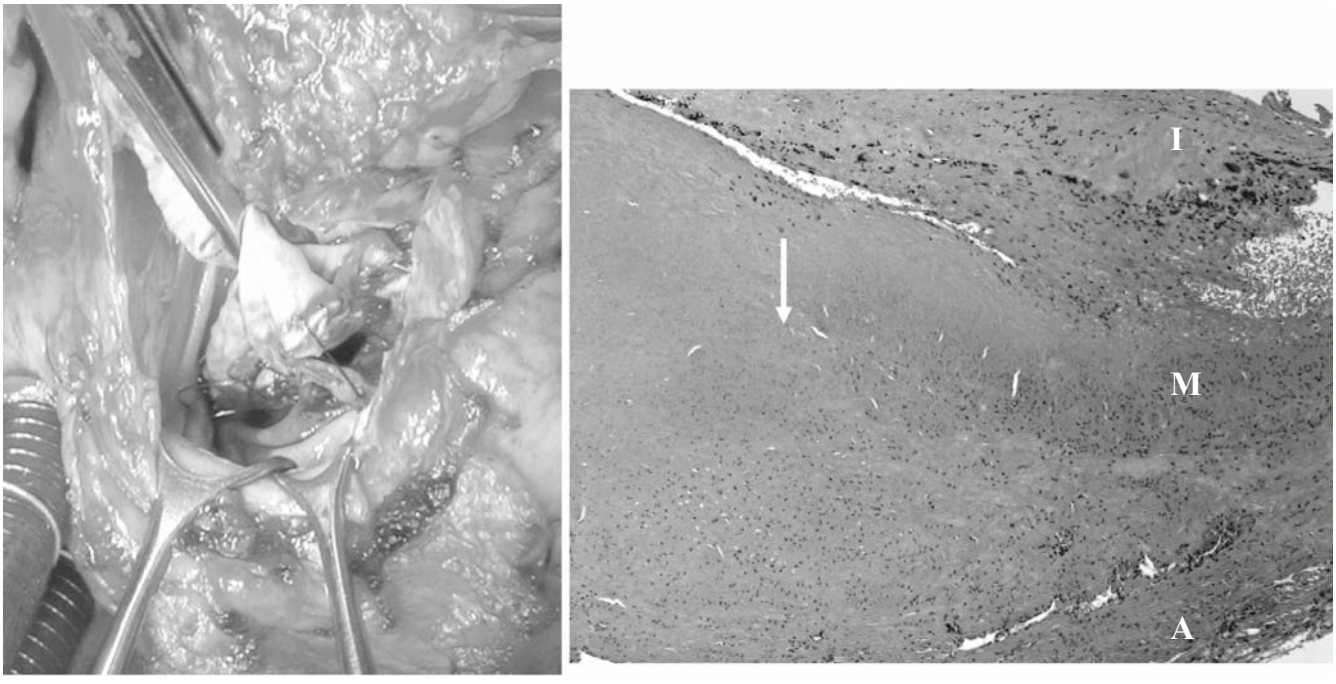

Fig. 2A,B. Findings of aortic root necrosis. **A** The anastomosis between the aortic root and prosthesis had opened. Necrosis of the right and noncoronary cusps where GRF-glue was used. **B** Microscopic findings. Nuclei of the medial smooth muscle cells had almost disappeared (*arrow*) (hematoxylin–eosin stain, × 40). *I*, tunica intima; *M*, tunica media; *A*, tunica adventitia

In 2003, Chao and colleagues[49] described its use in 13 patients and reported that, according to the manufacturer, as long as unmixed glutaraldehyde does not make direct contact with the tissue, BioGlue is not locally toxic. In 2004, Raanani and colleagues[50] reported using BioGlue to repair the aortic root in 22 patients, with two operative deaths. They concluded that BioGlue was less toxic and had a stronger adhesive effect than the older surgical glue.

In 2007, Mitrev and colleagues[51] reported a series of 20 consecutive patients treated for AAD using suction-assisted BioGlue application for aortic suture line reinforcement, with no bleeding complications and only two early deaths unrelated to bleeding. Thus, suction-assisted BioGlue application could prevent BioGlue embolization. However, Kazui and colleagues[43] reported pseudoaneurysm formation after using BioGlue for acute type A aortic dissection. Although glutaraldehyde in BioGlue is less toxic to the aortic wall than formalin in GRF glue, an overdose may still cause aortic wall necrosis and pseudoaneurysm formation.

Fibrin Glue

In 1994, Séguin and colleagues[52] reported one nonvalve-related early death (6.7%), but no late mortality after aortic valve repair with fibrin glue for acute type A aortic dissection. However, Casselman and colleagues[53] reported in 2000 that the use of fibrin glue for root reconstruction may compromise the long-term durability of repair compared with Teflon felt and GRF glue.

Since October 2003, we have been using fibrin glue for aortic root reconstruction. We infuse fibrin glue into the proximal false lumen and place Teflon felt strips on both the inner and outer surfaces of the aorta for reinforcement, using 3-0 polyester interrupted mattress sutures. We have used this method in 63 patients with acute type A dissection, with an in-hospital mortality rate of 15.9%.[54]

Nakajima and colleagues[14] reported low in-hospital mortality of 9.0% after repair of the aortic root using a fabric neomedia and fibrin glue in patients undergoing supracommissural aortic replacement (Fig. 3). Aortic reoperation was not required at 5 or 10 years in 98% ± 2% and 98% ± 2% of patients, respectively. The durability of using fibrin glue and any felts seems to be satisfactory, but long-term follow-up is mandatory.

Adventitial Inversion Technique

In 1995, Floten and colleagues[55] described the adventitial inversion technique to repair aortic dissection. During resection of the diseased ascending aorta and inner curve of the arch, the margin of the intima was

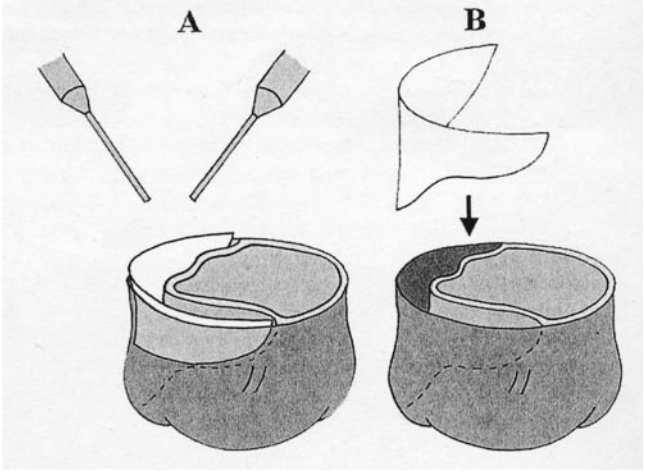

Fig. 3A,B. Use of fibrin glue. **A** The fibrinogen solution and the thrombin solution were applied to a fabric strip, placed between the dissected layers. **B** Geometrically fashioned fabric was soaked in fibrinogen solution and inserted into the false lumen of the aortic root to obliterate completely. Reprinted with permission, from Nakajima et al.[14] Copyright Elsevier

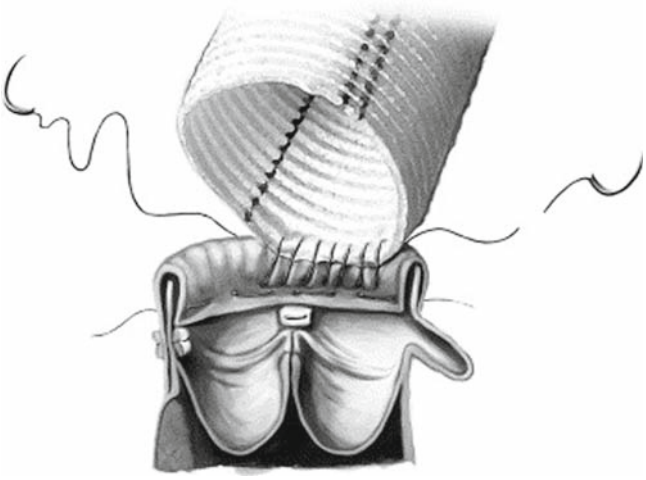

Fig. 4. Adventitial inversion technique. The redundant adventitia was inverted into the aortic lumen and tacked to the luminal surface of the intima using horizontal 6-0 polypropylene mattress sutures at the level of the sinotubular junction. Reprinted with permission, from Tanaka et al.[57] Copyright Elsevier

trimmed back 1 cm distal to the adventitial resection line. The redundant adventitia was then inverted into the aortic lumen and tacked to the luminal surface of the intima by horizontal 6-0 Prolene (Ethicon, Somerville, NJ, USA) mattress sutures. They also used this technique for proximal anastomosis in patients requiring supracoronary grafts and for both anastomoses in a type B aortic dissection. This technique creates a tough but soft aortic cuff. It allows the use of small needles, which decreases the risk of a new intimal tear, and avoids the use of felt strips which narrow the aortic lumen. In 1998, Garcia-Rinaldi and colleagues[56] confirmed that this technique was safe and useful for the surgical treatment of acute aortic dissection.

In 2005, Tanaka and colleagues[57] reported using the adventitial inversion technique (Fig. 4) in 18 patients, with overall hospital mortality of 11.1%, but no second-stage operation for aortic root or distal aortic lesions was needed during the follow-up period of 7–51 months (mean: 28 ± 14 months). They concluded that the adventitial inversion technique provides an excellent immediate hemostasis and allows thrombotic closure of the proximal and distal false lumen in the treatment of acute type A dissection. However, few operations performed with this technique have been reported and long-term follow-up is lacking.

Composite Replacement

Historically, some surgeons believed that radical root replacement carried a higher risk, so conservative root repair or separate aortic graft and valve replacement was preferred for acute dissections. However, because Marfan syndrome, annuloectasia, and extensive aortic root dissection may have a high incidence of aortic root redissection or pseudoaneurysm formation after only supracommissural replacement, composite replacement has been recommended.[32,33]

Recently, root replacement with a composite graft carrying mechanical valve prosthesis has represented an established surgical treatment with excellent results.[58–62] Ergin and colleagues[60] reported the influence of total composite replacement of the ascending aorta and the root on operative risk and long-term survival. Nineteen patients who underwent radical root replacement (group I) were compared with 54 patients who underwent conventional valve-preserving root reconstruction (group II). Group I represented a higher operative risk subset as the result of having substantial aortic regurgitation and coronary dissection, but there was no difference in operative mortality (15.7% vs 12.9%). Moreover, paradoxically, Group I had substantially better event-free survival estimates at 5 years (88% ± 12% vs 67% ± 9%) and 9 years (88% ± 22% vs 63% ± 19%); thus, these authors recommended that root replacement be considered more frequently.

Moon and colleagues[61] reported that operative mortality was higher for a separate aortic graft and valve (50% ± 16%) than for a composite valve graft (20% ± 7%) ($P < 0.05$). However, the lifelong need for anticoagulation with its risk for bleeding and possible thromboembolic events after mechanical valve replacement

causes complications with an annual incidence of 2%–4%.[63] Gott and colleagues[58] reported that the rate of thromboembolic events was 0.42 events/100 patient-years (4 events/962 patient-years of follow-up).

Aortic Valve-Sparing Techniques

Valve-sparing techniques for replacement of the aorta have gained recent attention for use in acute type A aortic dissection. The David "reimplantaion"[64] or Yacoub "remodeling"[65] techniques, which preserve the native aortic valve, have become popular. The advantage of the valve-sparing techniques is that anticoagulant therapy can be avoided, which benefits patients requiring second operations for a dissected distal aortic aneurysm.

In 2002, David and colleagues[66] reported that 230 patients underwent aortic valve-sparing operations for aortic root aneurysms or ascending aortic aneurysms with aortic insufficiency, including 25 acute type A aortic dissections. The mortality was 1.3% (3/230 patients), and the freedom from reoperation at 8 years was 99% ± 1% for aortic root aneurysms and 97% ± 2% for ascending aortic aneurysms with aortic insufficiency.

Valve-sparing aortic root replacement (reimplantation/remodeling) was originally developed for patients presenting with aortic valve incompetence caused by an aneurysm of the ascending aorta, but was applicable to a wide range of patients with various indications. The indications for aortic root implantation procedures have increased to include patients scheduled for operations. These techniques are appealing for patients with acute type A aortic dissection, as the sinus is frequently involved in the disease process and can be completely replaced by prosthetic material. However, acute type A aortic dissection must be considered an emergency requiring immediate surgery for any chance of survival.[67] It remains debatable if this technique should be used for emergency patients with acute type A aortic dissection.

Leyh et al.[68] and others[69,70] reported the first results of valve-sparing aortic root replacement in acute type A aortic dissection, demonstrating relatively low perioperative mortality and a favorable clinical outcome. In 2002, Leyh and colleagues[71] reported that 30 patients with acute type A aortic dissection underwent valve-sparing aortic root replacement, as remodeling in 8 and reimplantation in 22. The mean follow-up was 22.6 ± 15.4 months. The overall 30-day mortality was 17% (5/29), and the late mortality 4% (1/24). During the observation period, 4 patients needed reoperation; for acute aortic valve regurgitation after aortic root remodeling ($n = 3$) and for acute aortic valve endocarditis after aortic root reimplantation ($n = 1$). They concluded that aortic root reimplantation leads to a favorable midterm outcome. In 2003, Miller[72] stated that the David reimplantation concept is better for acute aortic dissection because it is more hemostatic, as the only suture lines that can bleed are the coronary buttons and the distal aortic anastomosis.

The durability of the aortic valve-sparing repair is a surgical concern. David and colleagues[73] reported a series of 220 valve-sparing operations, as 167 reimplantations and 53 remodeling operations, for aortic root aneurysms. There were 3 operative and 13 late deaths, and patient survival at 10 years was 88% ± 3%. Freedom from moderate or severe aortic valve regurgitation at 10 years was 94% ± 4% after reimplantation and 75% ± 10% after remodeling ($P = 0.04$). They concluded that the aortic valve-sparing operation is associated with a low rate of valve-related complications. The probability of late aortic insufficiency was lower after the implantation procedure than after remodeling in their experience.

In 2004, Kallenbach and colleagues[74] assessed the outcome of three different surgical approaches, namely AVS, comp, and SCR, in the treatment of 295 patients with acute type A aortic dissection between October 1990 and October 2003. The aortic valve reimplantation technique had been used for AVS ($n = 48$). The perioperative mortality did not differ significantly among the groups (AVS 10.4% versus comp 28% versus SCR 26%; $P = 0.05$). However, the frequency of using the three techniques has changed over the years. Whereas SCR was used most commonly in the first half of the 1990s, the AVS technique was first applied in 1995, then became increasingly popular and accounted for up to half of all operations performed for acute type A aortic dissection. In conclusion, for acute type A aortic dissection the results of the reimplantation technique are comparable with those of established techniques. Complete removal of diseased tissue, a low incidence of reoperation, and the fact that there is no need for anticoagulants may favor this approach in selected patients.

In 2000, De Paulis and colleagues[75] introduced the Valsalva-shaped Dacron tube (Gelweave Valsalva graft, Vascutek, Ann Arbor, MI, USA) to reduce stress on the preserved native aortic valve. Recently, De Paulis et al.[76] and others[77,78] have used the Valsalva graft for reimplantation in patients with acute type A aortic dissection. The use of a Valsalva graft may contribute to good results.

Fazel and David[79] stated that patients with acute type A aortic dissection may also benefit from the aortic valve-sparing operation, but as these are complex operations they should be performed only in centers with much experience. Thus, the surgeon must be well trained in elective surgery to be confident of using the valve-

sparing technique when emergency surgery is performed for acute type A aortic dissection. We need to investigate if these benefits will outweigh the potential risk for reoperation.

Endovascular Stent Graft Treatment

Endovascular stent graft (ESG) treatment of the aorta was initially proposed by Parodi and colleagues[80,81] as a minimally invasive technique for endovascular surgery in high-risk patients with abdominal aortic aneurysms. Investigators from Stanford University used this technique to successfully treat thoracic aortic aneurysms in 1992.[82,83]

Endovascular stent graft has been proposed as a method to treat DeBakey type III aortic dissection including type A dissection.[16–18] The objectives of ESG in patients with DeBakey type III aortic dissection are to cover the entry in the descending thoracic aorta with the stent graft, cause thrombosis of the false lumen, and prevent the formation and rupture of false-lumen aneurysms. At our institute,[18] ESG was first used for the treatment of aortic diseases in 1996. Dake and colleagues[16] reported the application of ESG in 19 patients with acute aortic dissection in 1999, 4 of whom had type A and 15, type B dissection.

In 2001, Kato and colleagues[17] reported treating ten carefully selected patients with type A aortic dissection (DeBakey type III) with ESG. Seven patients had acute dissection and three had subacute dissection. Entry closure was achieved successfully in all. Moreover, during a mean follow-up period of 20 months, no aortic rupture or aneurysm formation was noted in either the ascending or the descending thoracic aorta. Their findings suggested that this method is a promising alternative to surgical graft replacement.

Although the development of ESG for thoracic aortic diseases remains in its formative stages, the cumulative clinical experience with an estimated 5000 implants worldwide has yielded short- to mid-term data demonstrating promising results. Endovascular stent graft treatment of descending aortic disease has developed as a less invasive alternative for patients with advanced age and multiple comorbidities.[84,85]

Recently, ESG has been extended to the aortic arch and ascending aorta.[86,87] Zhang et al.[19] and others[20–23] reported the successful ESG treatment of patients with acute type A aortic dissection (DeBakey type I or II). The stent graft was deployed in the ascending aorta for exclusion of the dissection. This method bears the risk of compromising the aortic valve, the coronary arteries, and the supra-aortic vessels because of the special anatomy of the ascending aorta. Preoperative accurate assessment of the ascending aorta, aortic valve, and the localization of the primary entry tear may promote superior procedural results.

At present the long-term outcome is unclear, but ESG for acute type A aortic dissection (DeBakey type I or II) is a promising option, at least for patients with multiple comorbidities who are not candidates for conventional surgical repair.

Prevention and Presymptomatic Diagnosis

Prevention might be the least invasive therapy for this kind of life-threatening disease. Genetic research has been introduced to prevent aortic dissection.[88–103]

It has been known for several years that acute type A aortic dissection occurs in conjunction with several genetic syndromes, in particular Marfan syndrome (MFS), and initial research focused on the genetic basis of syndromic acute type A aortic dissection. In 1991, Lee and colleagues[88] reported that aortic disease in MFS was the result of defects in the fibrillin-1 (FBN1) gene that localized to chromosome 15q15–31. In addition to MFS, FBN1 mutation may also result in a range of clinical manifestations including not only other genetic diseases such as Shprintzen–Goldberg syndrome[89] and autosomal dominant Weill–Marchesani syndrome,[90] but also nonsyndromic acute type A aortic dissection.[91] Thus, recent studies have focused on defining the genetic component for nonsyndromic acute type A aortic dissection.[96–98,101]

In 2004, Mizuguchi and colleagues[92] reported that a heterozygous mutation in TGFBR2 (the transforming growth factor beta receptor II), leading to a splicing error in the kinase domain, was identified as the cause of disease in MFS. Recently, TGFBR1 and TGFBR2 mutations were found in a newly described aortic aneurysm syndrome (Loeys–Dietz aortic aneurysm syndrome)[93] and vascular Ehlers–Danlos syndrome.[94]

In 2005, Pannu and colleagues[95] reported that germline TGFBR2 mutations were responsible for the inherited predisposition to familial acute type A aortic dissection in 5% of 80 unrelated familial cases. Genetic studies[99,100,102] have demonstrated that mutations in the kinase domain of TGFBR2 cause type A aortic dissection. Therefore, families with members who have aortic dissection are advised to consider testing for TGFBR2 mutations. Individuals who carry the TGFBR2 mutation may be advised to have surveillance of the thoracic aorta done routinely and to have prophylactic repair of the aorta when the aortic diameter approaches 5.0 cm.

In 2007, Guo and colleagues[103] reported that missense mutations in smooth muscle α-actin (ACTA2) were responsible for 14% of inherited ascending thoracic aneurysms and dissection. Since then, we have been

conducting genetic research on mutations in aortic dissection. If mutations are found, preventive therapy for aortic dissection might be established. We recommend strict antihypertensive therapy for people at risk of aortic dissection, with lifelong regular imaging of their aorta, to decrease the number of operations for a dissecting aortic root.

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