Aiming at One-Stage Corrective Surgery for Extended Thoracic Aortic Dilatation

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Abstract

Definitive treatment of extended thoracic aortic dilatation is a major surgical challenge. Histopathology of resected thoracic aortic wall may reveal undiagnosed aortitis affecting outcome. We sought to investigate the benefit of thorough histopathology after one-stage corrective surgery for the treatment of extended thoracic aortic dilatation. Five patients underwent one-stage corrective surgery using the hybrid open arch repair by the frozen elephant trunk together with endovascular aortic grafting. A representative sample of the resected aortic arch was procured for histology. T- and B-lymphocytes, plasma cells, macrophages, and immunoglobulin G4 (IgG4) positivity were evaluated by immunohistochemistry. The mean preoperative maximum aortic diameter was 54 mm (range, 41–79 mm). The mean follow-up was 18 months (range, 1–24 months). As confirmed by computed tomography (CT) upon follow-up, complete thrombosis of the false lumen at the level of the frozen elephant trunk was achieved in all patients with dissection. One patient was operated due to atherosclerotic dilatation of the thoracic aorta, and postoperative CT showed successful exclusion of the atherosclerotic dilatation; this 75-year-old man was diagnosed with IgG4-positive aortitis and experienced unexpected blindness after surgery without evidence of emboli or long-term neurological impairment upon repeated brain CT. The hybrid open arch repair by the frozen elephant trunk and simultaneous endovascular repair is a feasible choice for one-stage surgery through sternotomy aiming at definitive treatment of extended thoracic aortic pathology. However, systematic evaluation of inflammation may reveal concealed aortitis affecting postoperative outcome and need for long-term surveillance.

Keywords

- ▶ extended thoracic aortic dilatation
- ▶ IgG4
- ▶ frozen elephant trunk
- ▶ one-stage surgery

The incidence of extended thoracic aortic dilatation is relatively rare.¹ One-stage surgery for definitive treatment of extended thoracic aortic dilatation may be achieved using the hybrid open arch repair by the frozen elephant trunk prosthesis.^{1–5} We have recently adapted the technique by applying endovascular grafting via the frozen elephant trunk component for distal aortic remodeling. The aim is to perform both ascending thoracic aortic and arch surgery through

sternotomy while achieving descending thoracic and distal aorta remodeling with the frozen elephant trunk and additional endovascular repair.

Patients with extensive thoracic aorta disease such as dilatation and dissection may suffer from a systematic disease not only causing high blood pressure but affecting extension of aortic disease and recovery after surgery.^{6,7} Aortic inflammation may predispose to future extension of dilatation or

dissection of the aorta.^{8–11} We sought to investigate whether thorough histological evaluation of the resected aorta would reveal concealed aortitis in patients with extended thoracic aortic dilatation.

Materials and Methods

Study Protocol and Surgery

From October 2010 to August 2012, we encountered five patients with extended aortic dilatation. After the institutional review board approval, ascending aortic wall resection was obtained during surgery and processed for histology. Aortic dilatation was preoperatively confirmed and evaluated with computed tomography (CT). According to our institutional policy, aortic dilatation included an aortic diameter more than 5.5 cm wide or aortic growth more than 1 cm in a year. This definition was adjusted to the presence of gender, patient size, and symptoms including aortic dissection, according to the Yale Center criteria.¹²

The decision on the extension of resection and surgical technique was at the discretion of the operating surgeon. Whenever dilatation included the aorta root, a radical resection of the dilated ascending aorta together with the root and the aortic valve was performed. The graft size was estimated by the principal surgeon. Resection of the aortic arch was performed using the Evita Open Plus (Hechingen, Germany) hybrid graft. The histological sample was procured from the middle of the resected diseased area of the aortic arch at the vicinity of the left subclavian artery.

Before surgery, a pig-tail catheter was inserted from the left femoral artery up to the aortic arch at the height of the left subclavian artery to identify the true or narrow atherosclerotic lumen of the aorta. The right femoral and right axillary arteries were cannulated for arterial access, and after sternotomy, the double-lumen venous cannula was inserted through the right atrial appendix. After initiation of cardiopulmonary bypass, cardioplegia was administered using the antegrade or retrograde routes, via the ascending aorta, coronary ostia, or sinus venous. During 20°C hypothermia, the dilated aortic arch was resected and the proximal part of the descending aorta was fashioned for the open anastomose of the Evita Open Plus hybrid graft. Circulatory arrest was established, the aortic arch was transacted, and bilateral selective antegrade cerebral perfusion was instituted using direct endoluminal cannulation of the arch vessels. Thereafter, the arch was resected, and the frozen elephant trunk of this device was launched into the diseased true lumen of the descending aorta according to the manufacturer's instructions using the pig-tail catheter to identify the true lumen. Immediately thereafter, a metallic endovascular mesh stent (Evita XL endograft [Hechingen, Germany]) was inserted via the frozen elephant trunk to further dilate the true lumen against the false lumen. The metallic mesh structure of the stent endograft made it possible to prevent antegrade obstruction of allowed unobstructed flow into arterial branches of the distal aorta. The proximal part of the hybrid Evita Open Plus prosthesis was fashioned according to anatomical variances of the ascending aorta, the truncus, left carotid, and subclavian arteries.

Histology and Immunohistochemistry

Up to five blocks of resected aorta tissue were embedded in paraffin and cut to 4-μm-thick segments. Histology was evaluated from the following: hematoxylin and eosin, Verhoeff-van Gieson or elastase-van Gieson, and periodic acid-Schiff. A representative 1-cm-long piece of aortic wall corresponding to all different staining was evaluated systematically for all resected samples procured during surgery. Immunohistochemistry was performed using Benchmark XT Staining module (Ventana Lifesciences, Tucson, Arizona, United States). The antibodies and dilutions, respectively, were immunoglobulin G4 (IgG4) (1:100, binding site), CD68 (1:200, Dako, Glostrup, Denmark), CD3 (1:50, Novocastra, Nusloch, Germany), CD31 (1:100, Dako), CD20 (1:1000, Dako), and CD138 (1:150, ABD Serotec, Kidlington, United Kingdom). Antibody Dilution Buffer (Ventana Lifesciences) was used for dilution media.

The samples were blindly evaluated for each primary antibody, categorized on a scale of 0 to 3 and expressed as point score unit (PSU) by four authors, and arbitrarily five fields (× 40) were reviewed for each 1-cm-long aortic sample. Inflammatory and endothelial cells, medial degeneration, and intima thickness were estimated as previously described and expressed as PSU.¹³ Histological analysis included the evaluation of cystic medial degeneration (CMD) and intimal thickness. CMD was estimated on a scale from 0 to 3 (0, normal media; 1, mild degeneration; 2, moderate degeneration; and 3, severe degeneration). Intimal thickness were estimated according to an arbitrary scale from 0 to 3, where 0 indicated normal intima with a single endothelial cell layer; 1, intima thickness less than 25% as compared with the media; 2, thickness more than 25% but less than 50% as compared with the media; and 3, intensive intima thickness more than 50% as compared with the media. If patchy lesions of the aortic wall were identified, we chose the field area including the respective media, intima, and adventitia layers as mapped according to the thickest intima layer.

Results

► **Tables 1 and 2** show preoperative and operative details, respectively. Mean cardiopulmonary bypass time was 326 minutes (range, 246–415 minutes), mean selective antegrade cerebral perfusion time was 79 minutes (range, 60–96 minutes), and mean cardioplegic arrest time was 238 minutes (range, 187–289 minutes). Four of the patients were operated due to aneurysmatic progression of dissection either antegrade or retrograde type A dissection. Two of these patients had previous surgery for acute dissection of the ascending aorta with a straight Dacron prosthesis from the sinotubular junction reaching to the proximal arch. All but one patient had a systemic disease such as adrenal adenoma with rheumatoid arthritis, hypophyseal tumor associated with hypothyreosis, and hypoadosteronism. However, all patients suffered from malignant hypertension. The mean preoperative maximum aortic diameter was 54 mm (range, 41–79 mm).

The first patient was a 59-year-old man with onset of chronic B-type aortic dissection 6 years before the detection of new retrograde dissection at CT. Altogether, aortic arch

Table 1 Preoperative data

Variable	Case no.				
	1	2	3	4	5
Gender	Male	Male	Female	Female	Male
Age (y)	59	63	65	56	75
Dissection	Complicated chronic type B	Acute type B, progression to type A	Complicated chronic type B	Complicated chronic type B	No
Atherosclerosis	No	No	No	No	Yes
Hypertonia	Yes	Yes	Yes	Yes	Yes
CAD	No	No	No	No	Yes
Tobacco	No	Yes	No	No	No
Other conditions	No	Rheumatoid arthritis	COPD	Cardiac hypertrophy	Rectum and bladder carcinoma
Previous operations	No	No	Prosthesis for type A dissection	Prosthesis for type A dissection	Rectum and bladder operations
EF (%)	61	66	70	74	63
Maximal diameter of aorta (mm)	79	41	55	55	41
FEV ₁ (L)	3.14	3.0	1.52	2.5	3.0
Extension of disease	Arch to iliac arteries	Aortic root to iliac arteries	Aortic arch to renal arteries	Ascending aorta to descending aorta	Ascending aorta to descending aorta

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EF, E section fraction; FEV₁, functional expiratory volume in one minute.

dissection extended till both iliac arteries including a narrow true lumen with takeoff for coeliacus, superior and inferior mesenteric, and right renal arteries. Complete exclusion of the dilatation was performed using the hybrid open arch prosthesis, a distal stent endograft through the frozen elephant trunk, and resection of the ascending aorta replaced by a straight Dacron prosthesis. During a 24-month follow-up, the patient has recovered uneventfully.

The second patient was a 63-year-old man referred to hospital with acute type B dissection. The patient suffered from seronegative rheumatoid arthritis, and soon developed delirium, bradycardia, pneumonia, and pulmonary embolism while nonoperative treatment was initially decided to apply. The dissection progressed in a retrograde fashion and instant surgery was executed. The dissection encompassed the whole

of the aorta though sparing the root, and the hybrid open arch prosthesis, the distal stent endograft, and a proximal prosthesis were successfully used. However, 3 months after surgery, CT revealed a less than 1-cm gap between the frozen elephant trunk and the distal metallic stent endograft. A left adrenal adenoma was detected. During the 24-month follow-up, no endoleak has though been detected.

The following two patients, 65 and 56 years old, were both previously operated on due to acute ascending aortic dissection. The aortic valve insufficiency was dealt with an aortic valve replacement using a bioprosthesis, the aortic root was partly resected and replaced with a prosthesis, and the hybrid open arch prosthesis together with a distal stent endograft were applied in the 65 years old. This patient was soon diagnosed of hypothyroidism, transient epilepsy, and a

Table 2 Operative data

Variable	Case no.				
	1	2	3	4	5
Hybrid open arch + frozen elephant trunk	Yes	Yes	Yes	Yes	Yes
Distal endograft	Yes	Yes	Yes	No	Yes
Proximal prosthesis	Yes	Yes	Yes	Yes	Yes
Proximal prosthesis including root	No	No	Yes	No	Yes
Aortic valve replacement	No	No	Bioprosthesis	No	No
Additional surgery	No	No	No	No	CABG

Abbreviation: CABG, coronary artery bypass surgery.

Fig. 1 Representative photograph of aortic wall during extended thoracic aortic dilatation (×40) showing IgG4-positive inflammation (dark staining color) of patient no. 5.

hypophyseal tumor. The 56-year-old patient was postoperatively found to suffer from aldosteronism.

The fifth patient had a history of urinary bladder and rectum carcinoma without metastasis. Due to severe arteriosclerosis and extension of dilatation from the ascending aorta including the arch and the distal descending aorta with coronary artery stenosis, the patient was operated on using the hybrid open arch prosthesis, including two invaginated sequentially interposed aortic endografts to exclude the distal dilatation and a prosthesis to replace the supracoronary ascending aorta excluding the aortic root. Simultaneous coronary artery bypass operation was performed. Postopera-

tively, total blindness occurred without any acute CT changes in the brain. Histological evaluation revealed global atherosclerosis with dilatation of the descending thoracic aorta including severe IgG4-positive aortitis (PSU 2; range, 0–2; ▶Fig. 1).

▶Table 3 summarizes the histological findings and postoperative outcome. The mean follow-up was 18 months (range, 1–24 months). All patients recovered from surgery, and none of the patients developed endoleaks or endotension postoperatively.

Discussion

On the basis of this pilot study, we were able to safely adapt and modify the hybrid open arch repair with the Evita prosthesis. After deployment of the hybrid graft, a bare-metal nitinol stent was inserted antegrade via the frozen elephant trunk for distal aortic remodeling of the true lumen in four patients with complicated type B dissection, of which two patients had been previously operated for acute type A dissection. Instead, one patient had a thoracic endograft for complete exclusion of an atherosclerotic aortic dilatation. Despite complete success with the one-stage surgical strategy employed, one patient out of five revealed severe IgG4-positive aortitis.

Extended thoracic aorta disease including dissection and dilatation requires meticulous surgery. Our patients with extended thoracic aorta disease were dealt using the hybrid open arch repair with the Evita prosthesis. The technique has recently been well established among clinics of expertise in Europe.^{1–6} In our patients, an additional stent of the distal aorta was inserted to induce complete remodeling or

Table 3 Histological evaluation and postoperative outcome

Variable	Case no.				
	1	2	3	4	5
Pathological report	Chronic dissection	Chronic dissection	Chronic dissection	Chronic dissection	IgG4-positive aortitis
Cystic media degeneration	0	0	1	1	0
Intimal thickness	0	0	2	0	1
Plasma cells	0	0	2	1	1
B cells	0	0	2	0	1
T cells	1	2	1	1	2
Endothelial cells	2	3	3	2	3
Macrophages	2	2	1	2	2
Systematic disease	None	Left adrenal adenoma	Hypophyseal tumor	Hypoaldosteronism	IgG4 positivity
Postoperative symptoms	None	Delirium, bradycardia, pulmonary embolia	Hypothyreosis, epilepsy, pneumonia	Left recurrent nerve palsy	Blindness
Follow-up (mo)	24	24	18	12	10
Progression of disease	No	No	No	No	No

exclusion of the entire diseased aorta whenever the frozen elephant trunk Evita prosthesis itself was not sufficient in length. This strategy is in alignment with a recently presented technique including combined proximal stent grafting plus distal bare metal stenting for management of aortic dissection.⁷ Using the Evita prosthesis while inserting the distal stent endograft via the frozen elephant trunk, we aimed for definitive one-staged surgery. From a technical point, we discovered that only custom-made insertion knobs of the Evita device are appropriate to use, since otherwise the frozen elephant trunk part of the prosthesis may be difficult to apply distally to the descending aorta. Second, instead of using a hard wire during identification of the true lumen of the diseased aorta, we preoperatively used a pig-tail catheter that helped us to keep impeccable sterility.

We encountered four patients with dissection and one with atherosclerosis, all of which experienced extensive thoracic aorta disease together with hypertension, a well-known risk factor for aortic dilatation and dissection.¹⁴ All but one patient with dissection had a systematic disease such as rheumatoid arthritis with adrenal adenoma, hypoadosteronism, and hypophyseal tumor upon closer examination. The common denominator for these patients upon thorough histopathological examination was aortic wall inflammation including occasional plasma cells, macrophages, and T and B cells. In addition, the patient with atherosclerosis had IgG4-positive aortitis and experienced unexpected postoperative blindness.

The degree of ascending aortic wall inflammation may determine the extension of aortic wall dilatation.¹⁵ The diagnosis of inflammation is fundamental as aortitis and ascending aortic dissection are associated with increased mortality.^{14–16} Recent attempts to elucidate the association of inflammation with aortic dilatation and dissection have generated theories on activation of aortic wall inflammation together with aortic wall remodeling.^{8,17} IgG4 positivity has been linked earlier to various immunological conditions and has recently also been introduced to the literature of isolated thoracic aortitis.^{18–20} Interestingly, the association of extensive aortic dilatation with IgG4-positive aortitis has been proposed earlier.^{19,20} It is tempting to speculate that the presence of IgG4 positivity of the aortic wall is associated with a developing aortitis predisposing to progression of aortic dilatation.^{19,21} Currently, we have no proven explanation for the postoperative blindness, since repeated brain CT did not confirm evidence of emboli or long-term neurological impairment in our patient. Optic neuropathy and bilateral retinal infarction have been reported to occur in less than 0.1% of patients undergoing cardiopulmonary bypass.²² Clearly, as previously shown by Laco et al, microscopic examination of the aorta resected for dilatation is mandatory, as there are often no evident clinical signs of inflammation.¹⁸ We are to evaluate for IgG4 and total IgG antibody levels in the patient with atherosclerosis to seek for possible follow-up treatment aiming at eradicating IgG4.^{23,24}

In conclusion, the hybrid open arch repair by the frozen elephant trunk and simultaneous endovascular repair seems a feasible choice for one-stage surgery through sternotomy

aiming at definitive treatment of extended thoracic aortic pathology. However, despite the successful outcome of the one-stage surgical strategy, we strongly advocate for the importance of systematic histopathological evaluation of the aorta to further facilitate a tailored follow-up protocol and treatment of the individual patient. It remains to be proven whether the histological findings are associated with long-term outcome after major aortic surgery in these patients.

References

- Hoffman A, Parker JATC, Raweh A, Autschbach R. Restoration of the thoracic aorta in Type A dissection with hybrid prosthesis. *Asian Cardiovasc Thorac Ann* 2011;19(2):123–127
- Uchida N, Kodama H, Katayama K, et al. Endovascular aortic repair as second-stage surgery after hybrid open arch repair by the frozen elephant trunk technique for extended thoracic aneurysm. *Ann Thorac Cardiovasc Surg* 2013;19(3):257–261
- Pacini D, Tsagakis K, Jakob H, et al. The frozen elephant trunk for the treatment of chronic dissection of the thoracic aorta: a multicenter experience. *Ann Thorac Surg* 2011;92(5):1663–1670, discussion 1670
- Uchida N, Shibamura H, Katayama A, Sutoh M, Kuraoka M, Ishihara H. Long-term results of the frozen elephant trunk technique for the extensive arteriosclerotic aneurysm. *J Thorac Cardiovasc Surg* 2010;139(4):913–917
- Schoenhoff FS, Schmidli J, Eckstein FS, Berdat PA, Immer FF, Carrel TP. The frozen elephant trunk: an interesting hybrid endovascular-surgical technique to treat complex pathologies of the thoracic aorta. *J Vasc Surg* 2007;45(3):597–599
- Ruggieri VG, Anselmi A, Abouliatim I, Verhoye JP. Management of postdissection thoracoabdominal aneurysm after previous frozen elephant trunk procedure with the E-vita Open Plus stent-graft. *J Thorac Cardiovasc Surg* 2012;144(1):e5–e7
- Hofferberth SC, Newcomb AE, Yli MY, et al. Combined proximal stent grafting plus distal bare metal stenting for management of aortic dissection: Superior to standard endovascular repair? *J Thorac Cardiovasc Surg* 2012;144(4):956–962, discussion 962
- Homme JL, Aubry MC, Edwards WD, et al. Surgical pathology of the ascending aorta: a clinicopathologic study of 513 cases. *Am J Surg Pathol* 2006;30(9):1159–1168
- Collins MJ, Dev V, Strauss BH, Fedak PW, Butany J. Variation in the histopathological features of patients with ascending aortic aneurysms: a study of 111 surgically excised cases. *J Clin Pathol* 2008; 61(4):519–523
- Burke AP, Tavora F, Narula N, Tomaszewski JE, Virmani R. Aortitis and ascending aortic aneurysm: description of 52 cases and proposal of a histologic classification. *Hum Pathol* 2008;39(4):514–526
- Pacini D, Leone O, Turci S, et al. Incidence, etiology, histologic findings, and course of thoracic inflammatory aortopathies. *Ann Thorac Surg* 2008;86(5):1518–1523
- Elefteriades JA. Thoracic aortic aneurysm: reading the enemy's playbook. *World J Surg* 2008;32(3):366–374
- Levula M, Paavonen T, Valo T, et al. A disintegrin and metalloprotease -8 and -15 and susceptibility for ascending aortic dissection. *Scand J Clin Lab Invest* 2011;71(6):515–522
- Narayan P, Rogers CA, Davies I, Angelini GD, Bryan AJ. Type A aortic dissection: has surgical outcome improved with time? *J Thorac Cardiovasc Surg* 2008;136(5):1172–1177
- Nuenninghoff DM, Hunder GG, Christianson TJ, McClelland RL, Matteson EL. Mortality of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis Rheum* 2003;48(12):3532–3537

- 16 Stevens L-M, Madsen JC, Isselbacher EM, et al. Surgical management and long-term outcomes for acute ascending aortic dissection. *J Thorac Cardiovasc Surg* 2009;138(6):1349–1357, e1
- 17 He R, Guo DC, Estrera AL, et al. Characterization of the inflammatory and apoptotic cells in the aortas of patients with ascending thoracic aortic aneurysms and dissections. *J Thorac Cardiovasc Surg* 2006;131(3):671–678
- 18 Laco J, Steiner I, Holubec T, Dominik J, Holubcova Z, Vojacek J. Isolated thoracic aortitis: clinicopathological and immunohistochemical study of 11 cases. *Cardiovasc Pathol* 2011;20(6):352–360
- 19 Stone JH, Khosroshahi A, Deshpande V, Stone JR. IgG4-related systemic disease accounts for a significant proportion of thoracic lymphoplasmacytic aortitis cases. *Arthritis Care Res (Hoboken)* 2010;62(3):316–322
- 20 Kasashima S, Zen Y, Kawashima A, et al. A clinicopathologic study of immunoglobulin G4-related sclerosing disease of the thoracic aorta. *J Vasc Surg* 2010;52(6):1587–1595
- 21 Stone JR. Aortitis, periaortitis, and retroperitoneal fibrosis, as manifestations of IgG4-related systemic disease. *Curr Opin Rheumatol* 2011;23(1):88–94
- 22 Nuttall GA, Garrity JA, Dearani JA, Abel MD, Schroeder DR, Mullany CJ. Risk factors for ischemic optic neuropathy after cardiopulmonary bypass: a matched case/control study. *Anesth Analg* 2001;93(6):1410–1416
- 23 Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum* 2010;62(6):1755–1762
- 24 Strehl JD, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol* 2011;64(3):237–243