Aorta

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Original Research Article

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Advanced Glycation End Products and its Soluble Receptors in the Pathogenesis of Thoracic Aortic Aneurysm

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Abstract

Background: Matrix metalloproteinases (MMPs) have been implicated in the pathogenesis of thoracic aortic aneurysms (TAAs). Cytokines [Interleukin (IL)-1β, IL-2, IL-6, and TNF-α] increase the expression of MMP-2 and -3. Advanced glycation end products (AGEs) interact with cell receptors to increase the release of cytokines. Circulating soluble receptors for AGEs (sRAGE) and endogenous secretory RAGE (esRAGE) compete with membrane bound RAGE for binding with AGEs and reduce the production of cytokines. It is hypothesized that low levels of serum sRAGE and esRAGE and high levels of AGEs, AGEs/sRAGE and AGEs/esRAGE would increase the levels of cytokines that would increase the levels MMPs, thus contributing to the formation of TAAs.

Methods: The study population was composed of 17 control subjects and 20 patients with TAA. Blood samples were collected for measurement of serum sRAGE, esRAGE, AGEs, cytokines, and MMPs. AGEs, sRAGE, and esRAGE were measured using ELISA kits, whereas the remaining parameters were measured using the Luminex Multi-Analyte system.

Results: The levels of sRAGE were lower, while the levels of AGEs, AGEs/sRAGE, AGEs/esRAGE, cytokines and MMPs were higher in patients with TAA compared to controls. The levels of sRAGE were inversely correlated with cytokines and MMPs, while AGEs, AGEs/sRAGE and AGEs/esRAGE were positively correlated with cytokines and MMPs. Cytokines were positively correlated with MMPs.

Conclusions: The data suggest that the AGE-RAGE axis may be involved in the pathogenesis of TAA and that low levels of sRAGE and high levels of AGEs, AGEs/sRAGE, and AGEs/esRAGE are risk factors for TAA.

Key Words

Advanced glycation end products • Soluble RAGE • Cytokines • Matrix metalloproteinase • Aortic aneurysm • Thoracic aortic aneurysm

Introduction

The mechanism of development of thoracic aortic aneurysms (TAAs) is complex. The characteristic features of TAAs are destruction of collagen and elastin in media and adventitia, loss of smooth muscle cells with thinning of aortic wall, and transmural infiltration...
of lymphocytes and macrophages. Matrix metalloproteinases (MMPs) -2 and -3, which have elastolytic and collagenolytic activities, have been implicated in the development of (aortic aneurysm) AA [1, 2]. Cytokines interleukin (IL)-1β and tumor necrosis factor-alpha (TNF-α) increase the expression of MMP-2. IL-1β [3, 4], IL-2 [5], IL-6 [6], and TNF-α [4] regulate the expression of MMP-2 and MMP-3.

Advanced glycation end products (AGEs) are a heterogeneous group of irreversible adducts resulting from nonenzymatic glycation and oxidation of proteins, nucleic acids and lipids [7, 8]. AGEs interact with receptors for AGEs (RAGE) and activate nuclear-factor kappa-B (NF-κB), increasing gene expression and releasing inflammatory cytokines (IL-1β, IL-2, IL-6, and TNF-α) [8–10] and generating reactive oxygen species (ROS) [8, 11]. There are two isoforms of c-truncated RAGE: total soluble RAGE (sRAGE) [12] and endogenous secretory RAGE (esRAGE) [13]. Both sRAGE and esRAGE act as a decoy for RAGE ligands and compete with membrane-bound RAGE for ligand binding [14], thus reducing the production of cytokines [3–6] and ROS [15]. Earlier, based on the literature, we [16] had suggested that sRAGE plasma levels may differentiate patients with aortic disease from the general population.

It is hypothesized that low levels of sRAGE and esRAGE and high levels of AGEs, AGEs/sRAGE, and AGEs/esRAGE would increase the levels of cytokines, which in turn would increase the levels of MMPs, resulting in the formation of aortic aneurysms. The specific objectives are to determine whether serum levels of sRAGE and esRAGE are lower, and AGEs, AGEs/sRAGE, AGEs/esRAGE, cytokines (IL-1β, IL-2, IL-6, TNF-α), and MMPs (MMP-2 and MMP-3) are higher in patients with TAA compared to control subjects. The other objectives are to determine if sRAGE and esRAGE are negatively correlated with cytokines and MMPs; if AGEs, AGEs/sRAGE, and AGEs/esRAGE are positively correlated with cytokines and MMPs; and if cytokines are positively correlated with MMPs.

Methods

Study Population

The study population was composed of 17 control and 20 patients with TAA. The control subjects were selected at the Royal University Hospital, University of Saskatchewan, Saskatoon, Canada. The following selection criteria for control subjects were used. They were in the age group of 35 to 50 years, nonobese, normotensive, nonsmokers, and had no history of angina, coronary artery disease, or diabetes. The patients with TAA were selected from Aortic Institute, Yale-New Haven Hospital, Yale University School of Medicine, (New Haven, Connecticut, USA) during the period of September 2011 to May 2012. The demographics and clinical characteristics of the patients with TAAs are shown in Table 1. The study protocol was approved by the Human Investigations Committee at Yale University, School of Medicine, New Haven, Connecticut, and the Ethics Committee for Human Studies at the University of Saskatchewan and by the Saskatoon Health Region. Written informed consent was obtained from control subjects and patients with TAA. TAA in figures has been represented as AA.

Measurements of Biochemical Parameters

Five milliliters of arterial/venous blood samples were collected from control subjects and intra-operatively from all patients undergoing surgery of thoracic aorta before heparin administration in a vacutainer without anticoagulant for measurement of serum sRAGE, esRAGE, AGEs, IL-Iβ, IL-2, IL-6, TNF-α, MMP-2, and MMP-3. Blood samples were immediately refrigerated at 4°C for 3 hours before centrifugation at 3000 rpm for 10 minutes at 4°C. The serum (supernatant) was collected and transferred into Eppendorf tubes and stored at –80°C until used for analysis. AGE levels in the serum were measured using a human AGE–enzyme-linked immunoassay (ELISA) kit (BioPCR, Beijing Zhonghao Shidai Co. Ltd. China). Serum levels of sRAGE and esRAGE were measured using the commercially available ELISA kit (R&D Systems, Minneapolis, Minnesota, USA). IL-1β, IL-2, IL-6, TNF-α, MMP-2, and MMP-3 were measured using Luminex Multi-Analyte Profiling System (Luminex, Austin Texas, USA, Bio-Rad) an instrument that measures multiple analytes simultaneously in one sample [17, 18].

Statistical Analysis

The data are reported as the mean ± SE. The data between the two groups were compared using a 2-tailed unpaired Student’s t test. Single linear univariate correlations (Pearson’s correlation coefficients) were performed to evaluate the relationship between AGEs, sRAGE, or esRAGE, and cytokines and MMPs, between AGEs, AGEs/sRAGE, or AGEs/esRAGE, and cytokines, and between cytokines and MMPs. A p value of less than 0.05 was considered significant.

Results

Serum AGEs, sRAGE, and esRAGE

The serum levels of AGEs, sRAGE, and esRAGE in control subjects and in patients with TAA are summarized in Figure 1.

The serum levels of sRAGE were 1.43-fold lower (997.5 ± 84.06 vs. 1425.0 ± 106.63 pg/ml), while levels
Cytokines

The serum levels of IL-1β, IL-2, IL-6, and TNF-α in patients with TAA and control subjects are summarized in Figure 3. The values of IL-1β, IL-2, IL-6, and TNF-α in control subjects were 0.587±0.10, 0.402±0.066, 1.375±0.363, and 8.09±0.810 pg/ml, respectively. The levels of IL-1β, IL-2, IL-6, and TNF-α in patients with AA were, respectively, 3.49-, 22.38-, 10.65-, and 3.35-fold higher than controls, but the values were significant only for IL-2 and IL-6.

Correlation of sRAGE with IL-1β, IL-2, IL-6, and TNF-α

Correlation data from 20 patients with TAA and 11 control subjects are summarized in Figure 4. The levels of serum sRAGE are negatively correlated with IL-1β, IL-2, and IL-6 but were significant only with IL-6. There was no correlation between sRAGE only and TNF-α.

Correlation of AGEs with Cytokines

The correlation between AGEs and cytokines is shown in Figure 5. The serum levels of AGEs are positively correlated with only IL-1β and IL-6. Although there was a tendency for negative correlation of AGEs with IL-2 and TNF-α, the correlation was not significant.

Correlation of AGEs/sRAGE with Cytokines

The results are summarized in Figure 6 and Table 2. There was a positive correlation between AGEs/sRAGE, and IL-1β, IL-2, IL-6, and TNF-α but the correlation was significant only between AGEs/sRAGE and IL-2.

Correlation of esRAGE with Cytokines

There was a tendency for a positive correlation of serum esRAGE with serum IL-1β, IL-2, IL-6 and TNF-α, but the correlation was significant only between esRAGE and TNF-α (Table 2).

Correlation of AGEs/esRAGE with Cytokines

There was a tendency for a positive correlation between AGEs/esRAGE, and IL-1β and TNF-α, but the correlation was significant only between AGEs/esRAGE and IL-2 and IL-6 (Table 2).

Table 1. Demographics and clinical characteristics of the patients with aortic aneurysms.

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<td>Number of patients</td>
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<td>Age (years) ± SD</td>
<td>53.85 ± 13.76</td>
</tr>
<tr>
<td>Male</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>White</td>
<td>18 (90%)</td>
</tr>
<tr>
<td>Risk factors/comorbidities:</td>
<td></td>
</tr>
<tr>
<td>Smokers (or history of smoking)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>34.29±0.25</td>
</tr>
<tr>
<td>Obesity</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Previous aortic surgery</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Positive family history</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Mean size of ascending aorta, cm</td>
<td>5.07±0.56</td>
</tr>
</tbody>
</table>

SD = standard deviation

of AGEs were 6.3 folds higher (20.06±3.69 vs. 2.93±0.97 µg/ml) in patients with TAA compared to controls. The values for esRAGE were not significantly different from each other (0.372±0.0334 vs. 0.326±0.0391 ng/ml; controls vs. patient.)

AGEs/sRAGE, AGEs/esRAGE, MMP-2 and MMP-3

The ratio of AGEs/sRAGE, AGEs/esRAGE, and serum levels of MMP-2 and -3 for control subjects and patients with TAA are summarized in Figure 2. The ratio of AGEs/sRAGE and AGEs/esRAGE were 10.4- and 8.18-fold higher, respectively, in patients with TAA compared to controls. The values for MMP-2 and -3 were 29.60% and 142.1% higher in patients with TAA compared to controls, respectively.
**Figure 1.** The serum levels of sRAGE, esRAGE, and AGEs in control subjects and in patients with ascending thoracic aortic aneurysms (AA). Results are expressed as the mean ± SE. AGEs = advanced glycation end products; sRAGE = soluble receptor for AGEs; esRAGE = endosecretory soluble receptor for AGEs. *P < 0.05; control vs. patients with AA.

**Figure 2.** Ratios of AGEs/sRAGE, AGEs/esRAGE, and serum levels of MMP-2 and -3 in control subjects and patients with ascending thoracic aortic aneurysms (AA). Results are expressed as the mean ± SE. AGEs = advanced glycation end products; sRAGE = soluble receptors for AGEs; esRAGE = endosecretory soluble receptors for AGEs; MMP = matrix metalloproteinase. *P < 0.05, Control vs. patients with AA.
Correlation of MMP-2 or MMP-3 with sRAGE, esRAGE, AGEs, AGEs/sRAGE, and AGEs/esRAGE

The results are summarized in Figure 6 and Table 2. There was a tendency for a positive correlation between sRAGE and MMP-2, and a negative correlation between sRAGE and MMP-3 (Figure 6). There was a positive correlation of esRAGE with MMP-2 and -3 but not significant (Table 2). There was a weak positive correlation of AGEs with MMP-2 and negative correlation with MMP-3 (Table 2) and weak correlation of AGEs/sRAGE with MMP-2 and -3 (Figure 6), and between AGEs/esRAGE and MMP-2 and -3 (Table 2).

Correlation of Cytokines with MMP-2 and MMP-3

The correlation between cytokines and MMP-2 and -3 are summarized in Figure 7 and Table 2. There was a positive correlation between MMP-2 and IL-1β (significant), IL-2, IL-6, and TNF-α, and between MMP-3 and IL-1β (significant), IL-2, and TNF-α.

Discussion

The data show that serum levels of sRAGE are lower, and the levels of AGEs, AGEs/sRAGE, and AGEs/esRAGE are higher, in patients with TAA compared to...
control subjects. These are new findings. The levels of MMP-2, MMP-3, IL-1β, IL-2, IL-6, and TNF-α are higher in patients with TAA than in control subjects. Other investigators [19, 20] have also reported that the serum levels of IL-1β, IL-2, IL-6, and TNF-α are elevated in patients with abdominal aortic aneurysm [19–21]. In the present study, although the levels of TNF-α were higher in patients with TAA compared to controls, they were not significantly different from each other. The elevated serum levels of MMP-2 and MMP-3 also have been reported in patients with abdominal aortic aneurysm and TAA [22–25].

In the present study there was a tendency for an inverse correlation between sRAGE and IL-1β, IL-6, and IL-2. There was no significant inverse correlation between esRAGE and IL-1β, IL-2, and IL-6 except with TNF-α, which had a positive correlation with esRAGE. This positive correlation was not expected and the reason for this is not clear. There was a positive correlation between AGEs and cytokines (IL-1β and IL-6) and between AGEs/sRAGE and IL-1β or IL-6, but not with IL-2 or TNF-α. We had expected that there would be significant positive correlation between AGEs or AGEs/sRAGE and cytokines. It is possible that IL-1β and IL-6 are more frequently associated with the pathogenesis of TAA than are IL-2 and TNF-α.

There was a significant positive correlation of AGEs/esRAGE with IL-2 and IL-6 but not with TNF-α and IL-1β. Again it is not known why there was no positive correlation between AGEs/esRAGE and IL-1β and between AGEs/esRAGE and TNF-α. May be that the sample size was too small to evoke all correlations that may eventually prove positive.

It was expected that low sRAGE and esRAGE would have negative correlation with MMP-2 and MMP-3, and AGEs/sRAGE would have positive correlation with MMP-2 and -3. However, it was found that only sRAGE have negative correlations with MMP-2 and AGEs/sRAGE have weak positive correlations with MMP-2 and -3.

Figure 4. Correlation of sRAGE with IL-1β, IL-2, IL-6, and TNF-α. IL = interleukin; TNF-α = tumor necrosis factor-alpha; sRAGE = soluble receptor for advanced glycation end products.
Figure 5. Correlation of AGEs with IL-1β, IL-2, IL-6, and TNF-α. AGEs = advanced glycation end products; IL = interleukin, TNF-α = tumor necrosis factor-alpha.

Figure 6. Correlation of AGEs/sRAGE with IL-1β, IL-6, MMP-2, and MMP-3, and of sRAGE with MMP-2 and -3. IL = interleukin; AGEs = advanced glycation end products; sRAGE = soluble receptor for AGEs; MMP = matrix metalloproteinase.
Our hypothesis was that there would be positive correlation between IL-1β, IL-2, or IL-6 and MMP-2 and -3. There was significant positive correlation of IL-1β with MMP-2 and -3, and a weak positive correlation of IL-2 with MMPs and IL-6 with MMP-2.

The data in general show that low levels of sRAGE and high levels of AGEs/sRAGE and AGEs/esRAGE are associated with an increase in the serum levels of cytokines and MMPs. Also, there is an inverse correlation between sRAGE and cytokines or MMP-3, and a positive correlation between AGE/sRAGE or AGE/esRAGE, and cytokines and MMPs. The serum levels of cytokines are positively correlated with MMPs.

In conclusion, the data suggest that low levels of sRAGE, and high levels of AGEs/sRAGE and AGEs/esRAGE, increase the levels of cytokines that in turn increase the levels of MMPs resulting in the formation of TAAs. The data suggest also that the AGE-RAGE axis may be involved in the pathogenesis of TAAs and that low levels of sRAGE and high levels of AGEs, AGEs/esRAGE may be new risk factors for TAAs. This new mechanism of development of TAAs may open new avenues for the prevention, regression, and slowing of TAA progression. These findings may also help for

Table 2. Correlation coefficients (n=31).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pearson correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β vs. esRAGE</td>
<td>0.223</td>
<td>0.227</td>
</tr>
<tr>
<td>IL-2 vs. esRAGE</td>
<td>0.291</td>
<td>0.113</td>
</tr>
<tr>
<td>IL-6 vs. esRAGE</td>
<td>0.124</td>
<td>0.507</td>
</tr>
<tr>
<td>TNF-α vs. esRAGE</td>
<td>0.380</td>
<td>0.035</td>
</tr>
<tr>
<td>MMP-2 vs. esRAGE</td>
<td>0.081</td>
<td>0.665</td>
</tr>
<tr>
<td>MMP-3 vs. esRAGE</td>
<td>0.007</td>
<td>0.969</td>
</tr>
<tr>
<td>IL-2 vs. AGEs/sRAGE</td>
<td>0.568</td>
<td>0.001</td>
</tr>
<tr>
<td>TNF-α vs. AGEs/sRAGE</td>
<td>0.277</td>
<td>0.131</td>
</tr>
<tr>
<td>IL-1β vs. AGEs/esRAGE</td>
<td>0.315</td>
<td>0.084</td>
</tr>
<tr>
<td>IL-2 vs. AGEs/esRAGE</td>
<td>0.371</td>
<td>0.040</td>
</tr>
<tr>
<td>IL-6 vs. AGEs/esRAGE</td>
<td>0.495</td>
<td>0.005</td>
</tr>
<tr>
<td>TNF-α vs. AGEs/esRAGE</td>
<td>0.159</td>
<td>0.392</td>
</tr>
<tr>
<td>MMP-2 vs. AGEs/esRAGE</td>
<td>0.152</td>
<td>0.415</td>
</tr>
<tr>
<td>MMP-3 vs. AGEs/esRAGE</td>
<td>0.015</td>
<td>0.934</td>
</tr>
<tr>
<td>MMP-2 vs. TNF-α</td>
<td>0.293</td>
<td>0.110</td>
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<tr>
<td>MMP-3 vs. TNF-α</td>
<td>0.017</td>
<td>0.927</td>
</tr>
<tr>
<td>MMP-2 vs. AGEs</td>
<td>0.176</td>
<td>0.343</td>
</tr>
<tr>
<td>MMP-3 vs. AGEs</td>
<td>-0.042</td>
<td>0.824</td>
</tr>
</tbody>
</table>

IL = interleukin; TNF-α = tumor necrosis factor-alpha; MMP = matrix metalloproteinase; AGEs = advanced glycation end products; esRAGE = endosecretory soluble receptors for AGEs.

Figure 7. Correlation of IL-1β, IL-2, and IL-6 with MMP-2 and -3. IL = interleukin; MMP = matrix metalloproteinase.
screening of population for early detection of TAAs via biomarkers chosen from the pathophysiology herein demonstrated.

Acknowledgments

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Type B Aortic Dissection Repair Using a Thoraflex Hybrid Prosthesis in a Complex Aortic Arch Anatomy

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Abstract
Thoracic endovascular aortic repair (TEVAR) is recognized as an attractive option to treat complicated Type B aortic dissection. Nevertheless, TEVAR is not always technically possible. We report the case of a 53-year-old male with complicated Type B aortic dissection, in the setting of a complex anomalous aortic arch anatomy with an aneurysmal aberrant right subclavian artery. He was successfully treated by the frozen elephant trunk technique using the Thoraflex hybrid graft.

Key Words
Bovine arch • Dissection • Aorta

Introduction
Extensive aortic pathologies involving the aortic arch and the proximal descending aorta remain challenging for cardiac surgeons. After the introduction of the frozen elephant trunk technique in 1996 [1], several types of prosthesis have been developed to repair this combined disease of the aortic arch and the proximal descending aorta.

Thoraflex, the hybrid prosthesis of Vascutek (Scotland-UK), is a new commercially available prosthesis. It is composed of a distal endograft and a proximal 4-branched Gelweave graft, with an incorporated sewing collar in between [2].

Case Presentation
A 53-year-old man, with past history of hypertension, dyslipidemia, Type 2 diabetes, obesity (body mass index 40), sleep apnea, and smoking, was admitted to our service for surgical management of a complicated Type B aortic dissection.

He presented first to the emergency room with a sudden onset of chest pain. His chest computed tomography (CT) angiogram showed a Type B aortic dissection with a complex anomalous aortic arch anatomy. His first aortic arch branch is a common trunk dividing into the right common carotid artery and the left common carotid artery (truncus bicaroticus). The second aortic arch branch is the left subclavian artery, followed by a large aneurysmal aberrant right subclavian artery running a retroesophageal course (arteria lusoria). The descending aortic dissection starts at the level of the arteria lusoria and extends to the renal arteries with both the celiac trunk and the superior
mesenteric artery perfused by the false lumen, without any clinical or radiological signs of organ malperfusion. The main port of entry for the dissection into the false lumen was at the level of the arteria lusoria, 1 cm distal to the origin of the left subclavian artery, with multiple additional ports of entry along the rest of the descending aorta (Figure 1A and B).

His transthoracic cardiac ultrasound showed a normal left ventricular ejection fraction (60%). His coronary angiogram showed no significant coronary stenosis.

Medical treatment was initiated and another CT scan was performed one week later because of recurrence of chest pain. That CT scan demonstrated a complicated subacute Type B aortic dissection with rapid enlargement of the maximal aortic diameter (>1cm in 1 week) at the level of the proximal third of the descending aorta.

After a multidisciplinary discussion, thoracic endovascular aortic repair (TEVAR) was discussed but not retained as a reasonable option, considering the complex, aberrant anatomy of this patient. A two-stage surgical treatment was chosen. The first stage consisting of a right carotid to right subclavian bypass, with occlusion of the arteria lusoria using an intravascular plug. The second stage consisting of a complete arch replacement and an antegrade deployment of a

Figure 1. Panel A. Type B aortic dissection starting at the level of the aortic isthmus. Panel B. Aberrant right subclavian artery crossing behind the esophagus with retrograde dissection in the aberrant artery. Panels C and D. Three-month postoperative CT scan. Note: Thoraflex prosthesis in place with no leaks, no false aneurysm, and a thrombosed false lumen down to the level of the diaphragm.
stented endograft in the descending aorta using the Thoraflex hybrid graft (Figure 2).

The first surgery consisted of a right carotid-subclavian bypass with an 8 mm Dacron prosthesis with insertion of an occlusive plug (PLUG 2 Amplatzer 16mm) into the aberrant right subclavian artery. The plug was delivered through the right brachial artery in a retrograde fashion.

Six weeks after this successful bypass, the patient was readmitted for surgical management of his aneurysmal dissection. The hybrid Thoraflex prosthesis was inserted using the frozen elephant trunk technique.

This second stage surgery was performed under cardiopulmonary bypass (CPB) with right femoral artery cannulation, moderate hypothermia, short hypothermic circulatory arrest (8 min) and selective anterograde cerebral perfusion into both carotid arteries (61 min). Myocardial protection was achieved by continuous retrograde infusion of cold blood into the coronary sinus.

The endovascular part of the Thoraflex device was first deployed into the open true lumen of the descending aorta. Then, the distal anastomosis was performed with interrupted sutures proximal to the origin of the aberrant right subclavian artery, using the sewing collar that separates the distal endograft from the proximal 4-branched graft. This sewing collar contains many folds that disappear when the stent is completely deployed at 37°C; that is why in moderate hypothermia when the deployment is still incomplete, the collar folds makes interrupted sutures much easier than running sutures.

The supra-aortic trunks were reimplanted separately in the three ad hoc branches, after which CPB was anterogradely reinitiated via the fourth branch. Finally, the proximal anastomosis was performed at the level of the sino-tubular junction by continuous suture of Prolene 4-0 reinforced by circumferential Teflon felt. The patient was rewarmed during the antegrade reperfusion and CPB was easily discontinued after 167 minutes.

The postoperative course was uneventful. The patient was discharged home on postoperative day 7 after a good postoperative control CT scan.

Three months later, the patient continues to do well. Another control CT angiogram showed no leaks or false aneurysms, demonstrating a thrombosed false lumen (Figure 1C and D).

Discussion

Ateria lusoria is a well-known common congenital vascular anomaly of the aortic arch, with an incidence ranging between 0.5% and 2.5% [3]. Truncus bicaroticus, a bovine aortic arch variant in humans, is another less frequent aortic arch anomaly, with a reported prevalence of less than 0.1% [4]. The coexistence of an arteria lusoria with a truncus bicaroticus represents an extremely rare combined anomaly of the aortic arch. Very few cases were reported in English literature.

TEVAR is recognized as an attractive option for complicated Type B aortic dissections [5]. Nevertheless TEVAR is not always technically feasible. When the anatomy of the dissection is not favorable for TEVAR, for example in cases with an acute angled aortic arch, entry tear close to the left subclavian
artery, and entry tear in the concavity of the distal arch, the risk of periprocedural failure is elevated [6]. In these cases, open surgical treatment might be considered as a better approach. In our patient endografting was contraindicated, because there was not enough proximal landing zone between the port of entry, the left subclavian artery and the arteria lusoria.

In 1983, Borst [7] introduced the elephant trunk procedure as a new technique for aortic arch surgery. It was divided into two stages. The first stage consists of the prosthetic replacement of the ascending aorta and the aortic arch with an additional elephant trunk-like extension of the arch graft into the descending aorta. The second stage consists of using this elephant trunk-like extension to replace the descending aorta through a lateral thoracic or thoraco-abdominal approach [8]. This two-stage surgery was associated with a high morbidity and a significant mortality, with substantial cumulative risk of the two major surgical procedures and frequent failure to complete the second stage.

In 1996, the frozen elephant trunk (FET) technique, a hybrid repair combining endovascular treatment with conventional surgery, was introduced to simplify aortic arch surgery. It allows concomitant repair of the aortic arch and the proximal descending aortic aneurysms in a single stage approach. FET is considered an interesting approach for complicated Type B aortic dissections when TEVAR is not possible and in patients who are good candidates for open surgery [6]. This technique can offer as well a better landing zone for a secondary TEVAR procedure later on, in the descending aorta if necessary [9].

At the present time, multiple FET prostheses have been developed, such as the custom-made Chavan-Haverich (Curative GmbH, Dresden, Germany), the Jotec E-vita (Jotec GmbH, Hechingen, Germany) and the Thoraflex (Vascutek, Terumo, Inchinnan, Scotland, United Kingdom) prosthesis.

In March 2014, Leone et al. [10] published a case report of two patients with similar complex aortic arch disease (aberrant right subclavian artery) treated with the frozen elephant trunk technique using the Jotec E-vita prosthesis. The first patient had an ascending aortic aneurysm extending to his distal arch while the second one was diagnosed with a chronic Type B dissection.

To our knowledge, this is the first case report of Type B aortic dissection with an arteria lusoria and a truncus bicaroticus treated with the Thoraflex hybrid prosthesis.

In conclusion, we can say that hybrid repair (ascending and arch replacement combined with stenting of the descending aorta) represents a valuable tool for the treatment and simultaneous reconstruction of the aortic arch and the proximal descending aorta. Such an approach permits one-stage treatment of complex aortic pathologies.

Despite the significant morbidity and mortality (especially paraplegia), FET is becoming an indispensable tool. Studies and follow up will be needed to evaluate the medium and long term results of this procedure as well as to refine the indications and the limitations.

Conflict of Interest

The authors have no conflicts of interest relevant to this publication.

References


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Chronic Type A Aortic Dissection
Two Cases and a Review of Current Management Strategies

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Abstract
Stanford Type A aortic dissection is a rapidly progressing disease process that is often fatal without emergent surgical repair. A small proportion of Type A dissections go undiagnosed in the acute phase and are found upon delayed presentation of symptoms or incidentally. These chronic lesions may have a distinct natural history that may have a better prognosis and could potentially be managed differently than those presenting acutely. The method of repair depends on location and extent of the false lumen, as well as involvement of critical structures and branch arteries. Surgical repair techniques similar to those employed for acute dissection management are currently first-line therapy for chronic cases that involve the aortic valve, sinuses of Valsalva, coronary arteries, and supra-aortic branch arteries. In patients with high-risk for surgery, endovascular repairs have been successful, and active development of delivery systems and grafts will continue to enhance outcomes. We present two cases of chronic Type A aortic dissection and review the current literature.

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Key Words
Chronic aortic dissection • Stanford Type A dissection • Thoracic endovascular aortic repair

Introduction
Stanford Type A aortic dissections are life-threatening emergencies in the acute phase that require immediate surgical repair, in contradistinction to dissections limited to the descending aorta, which can be managed medically in most cases. The emergency of acute Type A dissections (ATAD) is defined by the high propensity to quickly develop severe complications including aortic rupture, severe aortic regurgitation, pericardial tamponade, and cerebral and coronary malperfusion. Mortality estimates suggest 40% are fatal prior to reaching a hospital, 1% die per hour upon arrival, and perioperative mortality of repair is 5–20% [1]. These statistics do not account for cases that are incorrectly diagnosed, due to prehospital mortality or failure to recognize dissection as the cause of a complication.

Chronic Type A dissections (CTAD) of the native aorta represent a subset of patients who were not diagnosed at the time of onset due to absent or atypical symptoms and remained stable, in contrast to the majority of symptomatic ATAD. Chronic aortic dissections are traditionally defined as those older than 14 days. A designation of subacute has also been proposed for dissections at 14–90 days, placing chronic at more than 90 days, though these definitions are less commonly utilized [2]. Few Type
A dissections advance to the chronic phase, and thus the natural progression of CTAD is not well understood. The current standard management of CTAD is also open surgical aortic repair; however, a range of disease characteristics and associated pathologies may have implications for prognosis and repair. Moreover, new successes with endovascular techniques are providing credence for alternative repair approaches.

**Case Presentation**

The first case is that of a 57-year-old male with a history of hypertension and alcohol abuse who presented with dizziness and chest pain and reported having similar though milder bouts of chest pain over the preceding 2 years. Transesophageal echocardiogram (TEE) showed moderate aortic insufficiency (AI) and aortic root dilatation. Contrast-enhanced computed tomography (CECT) revealed a dissection of the ascending aorta and 5.5 cm fusiform dilatation limited to the ascending aorta (Figure 1). The patient was taken to the operating room for open repair. Intraoperatively the intimal tear was identified 2 cm distal to the sinotubular junction on the anterolateral aspect of the aorta, and exhibited evidence of chronicity based on thickening of the septum and fibrotic changes. The false lumen was confined to the ascending aorta; however, it extended into the right coronary sinus. The patient, therefore, underwent a repair of the ascending aorta with Dacron interposition graft and resuspension of the aortic valve. TEE at the end of the procedure showed trace AI. His postoperative course was uncomplicated. He survived without recurrence of symptoms or AI until 8 years later when he died of complications of pancreatic cancer.

The second case is a 76-year-old male with a history of hypertension and a known abdominal aortic dissection previously diagnosed incidentally. He had delayed follow up imaging of the thoracic aorta for several months, but ultimately presented with complaints of recurrent chest pain. CECT found a dissection extending from ascending aorta down to infrarenal abdominal aorta (Figure 2). The ascending aorta and root were dilated to 5.5 cm and contained thrombus in the false lumen, which extended into the left coronary sinus as well as the innominate artery. Magnetic resonance imaging revealed signals consistent with chronic thrombus of the false lumen (Figure 3). The patient underwent aortic repair with composite mechanical valve graft and hemi-arch replacement. Cannulations of the left femoral artery and right atrium were made for cardiopulmonary bypass. Hypothermic circulatory arrest at 18°C was instituted for distal anastomosis of the hemi-arch repair. This was complicated by postoperative complete heart block managed by placement of a permanent transvenous pacemaker. He had no further aortic disease complications and died 2.5 years later of cardiac arrest during an admission for non-obstructive bowel ileus.
Natural History

Given that ATAD is often rapidly fatal without surgical management, patients with CTAD likely have pathologic or physiologic differences that allow for stabilization of the disease process. A recent review of 696 Type A dissection (TAD) repairs found that CTADs were significantly more likely to have bicuspid aortic valve morphology and less likely to extend beyond the arch, compared with ATAD [3]. Somewhat intuitively, a greater proportion of CTAD had undergone previous cardiac surgery; however, postoperative dissections are likely a separate disease process from spontaneous CTAD. Chronic cases were reported as asymptomatic 69% of the time, with a median of 10 weeks until symptom onset in patients who became symptomatic. Following open repair, the same study found in-hospital mortality for CTAD to be 1/3 of the rate for ATAD (4.5% vs. 13.2%), corroborating previous reports [4], and survival to be longer (80% vs. 68%) at 5 years and at 10 years (64% vs. 49%).

The relative stability of CTAD provides logical support for medical management of uncomplicated asymptomatic lesions. Furthermore, histologic evaluations suggest a remodeling process that may stabilize the false lumen through development of a new endothelial lining and thickening of the media by production of new smooth muscle cells [5]. However, there is no significant body of data to adequately define the outcomes of nonoperative management for this subset of patients. In fact, many cases reportedly have been associated with sudden onset of delayed symptoms, false lumen expansion, and progressive aneurysmal dilatation.

Classification

The type of intimal lesion may influence disease progression in CTAD though, in general, Type A lesions tend to be more progressive and do not mirror the natural history of Type B lesions [6]. Intimal tears of the aorta are stratified into five classes based on imaging characteristics according to the European Society of Cardiology [7]. Class I tears have the standard pairing of true and false lumina, involving variable length of aorta that determine associated symptoms and type of necessary repair. Class II, also known as intramural hematomas (IMH), do not have an intimal tear visible on imaging, though a majority have a tear seen at the time of surgery or autopsy [1]. Stable IMH of the ascending aorta is believed to portend slightly better outcomes than Class I tears, and
have been reported to resorb in some cases. However, 1-year mortality with medical management of these lesions is approximately 60%, whereas open ascending aortic repair decreases 1-year mortality to 5–26% depending on patient characteristics and center experience [8]. Class III tears do not have separation of the medial layers, and thus create an eccentric mural bulge that undermines a small area of intima and are difficult to detect on imaging. Class IV, commonly referred to as penetrating atheromatous ulcerations (PAU), are tears down to the adventitia that form adjacent to atheromatous plaques. Although rarely found in the ascending aorta, PAU in this region are associated with increased rate of aneurysmal dilatation, and therefore should be repaired upon diagnosis [2]. Class V lesions are iatrogenic tears associated with endovascular procedures or previous aortic surgery [1].

Surgical Technique

Though surgical guidelines for the management of CTAD are limited by the paucity of data, generally accepted indications for aortic repair include onset of severe AI, enlarging ascending aortic diameter or onset of symptoms. Management of uncomplicated asymptomatic CTAD must be individualized considering patient comorbidities, and those patients unfit for open surgical repair may be candidates for emerging hybrid and endovascular therapies.

Depending on the extent of dissection, open repair may include simple tube graft replacement of the ascending aorta, aortic valve replacement when one or more leaflets is damaged, valve repair or resuspension when the valve is salvageable, and hemiarch or total arch replacement techniques. Perioperative mortality of ascending aorta or arch repairs ranges from 1–15% [8].

Endovascular Repair

Chronic lesions restricted to the ascending aorta that do not involve the arch, aortic valve or coronary arteries, have been successfully managed with endovascular stent grafts, as a variation on thoracic endovascular aortic repair (TEVAR). Experience is limited to cases performed in patients at prohibitive risk for open aortic repair and patients refusing surgery. Current challenges include the lack of endovascular delivery systems and stents designed for the ascending aorta [9] at most centers, though new devices have been developed and utilized in cases approved on compassionate grounds [10]. The curvature of the aorta also makes measurement of graft size difficult to estimate, which may be associated with early graft migration at or near the time of deployment [11]. In addition, lack of vascular suitability can preclude Type A TEVAR (aTEVAR); imaging studies estimate that a minority of patients undergoing open repair of Type A dissections meet criteria for endovascular repair of the ascending aorta [12, 13]. In this regard, suitability criteria have largely been extrapolated from success with Type B TEVAR. Proposed tenets of aTEVAR include 2 cm distance from sinotubular junction to the intimal tear, 0.5 cm from tear to brachiocephalic artery, absence of pericardial tamponade or severe aortic regurgitation, absence of ischemia to aortic branches, and no prior coronary revascularization from ascending aorta [13]. Patients with connective tissue diseases are not regularly considered for aTEVAR due to likelihood of requiring further surgery [11].

Long-term outcome data for aTEVAR are lacking due to small number of cases. Reported peri-procedural complications with aTEVAR include endoleaks, stent buckling [14], stent migration [15], delivery device retention [9], and stroke. Further, the optimal degree of oversizing has not been delineated, although excess oversizing has been associated with aortic insufficiency. Broader experience and improvement of endovascular device design to conform to the ascending aortic environment will address many of these issues.

Conclusions

The small number of cases continues to limit our understanding of CTAD. Open surgical repair remains the first-line management when any complications or symptoms are present. The current body of evidence suggests most chronic Type A lesions should also be considered progressive, despite poor understanding of factors affecting prognosis. Endovascular repair of Type A dissections have met some success; and despite significant challenges, hold potential for improvement with further device innovations.
Conflict of Interest

The authors have no conflicts of interest relevant to this publication.

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EDITOR’S QUESTIONS

1. What do you feel would be the outlook for your two chronic ascending aortic dissection patients without an operation? Why do you think so?

The lack of strong evidence in the current literature defining the natural history of chronic Type A dissections creates uncertainty in predicting the outcomes of these patients. However, given that dissections of this type have been found to become rapidly progressive, in combination with onset of symptoms in these patients, we believe both cases were high risk for becoming rapidly fatal.

2. Is there any literature evidence that chronic ascending dissections rupture?

Chronic Type A dissections have been reported to quickly develop expansion of the false lumen, as well be associated with progressive aortic dilatation. The relationship between chronic dissections and rupture has not been clearly established; however, the risk of rupture exists in cases of sudden progression or cases with extensive dilatation. Whether this risk is attenuated by chronic fibrosis surrounding the dissection is unknown.
3. Is not the key to development of chronic ascending dissections that early rupture has not occurred in these cases?

Correct. Unlike cases of rapidly fatal acute Type A dissections, chronic dissections have somehow been able to stabilize and are associated with a reactive fibrotic process at the site of intimal tear. This suggests therapy of these lesions could be aimed at supporting the stabilizing process rather than replacing the tissue. Cases of prohibitive operative risk give us a limited ability to evaluate this pathway.

4. Are you not concerned about the cardiac arrest at 2.5 years follow-up in patient # 2? Do you think this was aortic related? Valve related (anti-coagulation held)? Coronary related? Pacemaker related? Is there any autopsy data or first hand hospital data?

Unfortunately, we do not have complete data surrounding this patient's death, which did not occur at our institution. We are indeed suspicious that this mortality could have been related to the mechanical valve, coronary arteries or aortic repair. The 2.5-year survival is positive, given the initial presentation of symptomatic progression of Type A dissection; however, the cardiac arrest raises serious concerns.
Abstract
A 75-year-old man who had undergone ascending aorta replacement for acute Type A aortic dissection presented with a recurring high fever. Transesophageal echocardiography revealed that a vegetation had formed on the re-dissected intimal flap of the noncoronary sinus of Valsalva. This didactic case suggests that antibiotic prophylactic measures be considered for aortic dissection flaps as for irregular valves susceptible to infective endocarditis.

Key Words
Aortic root reoperation • Aortic dissection • Vegetation

Introduction
Aortic root reoperation after aortic dissection repair, still challenging to perform, has a reported mortality rate of nearly 20% [1, 2]. Risk may be much higher when the patient's condition is complicated by infection.

Case Presentation
A 75-year-old man presented with a recurring high fever after teeth cleaning. He had undergone ascending aorta replacement for acute Type A aortic dissection 8 years previously. The proximal and distal ascending aorta had been reconstructed with gelatin-resorcin-formalin glue. The patient had been observed closely because he had developed aortic root re-dissection and mild aortic regurgitation during the most recent 6 years.

Blood cultures were positive for Streptococcus sanguinis. Transesophageal echocardiography revealed mild aortic regurgitation and a 3.46-cm-long mobile vegetation that was blown back and forth with the bloodstream at the aortic root (Figure 1; see supplemental Video 1 at http://dx.doi.org/10.12945/j.aorta.2015.15.012.vid.01).

To prevent embolism due to the vegetation, urgent aortic root replacement (Bentall procedure) with a valved conduit (with a 24-mm Gelweave Valsalva graft; TERUMO, Tokyo, Japan and 21-mm bovine pericardial bioprosthesis Magna EASE; Edwards Lifesciences, Irvine, California, USA) was performed under cardiopulmonary bypass with femoral artery and bicaval venous cannulation. The vegetation was stuck on the intimal flap of the noncoronary sinus of Valsalva. The aortic valve leaflets were intact without vegetations. Postoperative histopathology of vegetation tissue, aortic valve, and aortic wall revealed no evidence of bacterial clusters, acute inflammation or cultures taken intraoperatively.

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Although cardiopulmonary bypass was smoothly weaned, the patient developed acute respiratory distress syndrome on postoperative day 5 because of ventilator-associated pneumonia and died on postoperative day 26.

**Discussion**

Infective endoarteritis is a relatively rare but devastating condition. A few reports have been published about infection on an aortic dissection flap [3]. Although prophylactic procedures for native or prosthetic valve endocarditis are well established by American Heart Association and European Society of Cardiology guidelines [4, 5], these guidelines do not mention prevention of infection for chronic aortic dissection patients. This didactic case suggests that antibotic prophylactic measures be considered for chronic aortic dissection as for valvular infective endocarditis.

**Conflict of Interest**

The authors have no conflict of interest relevant to this publication.

**References**


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Case Report

Complete Resolution of Wegener’s Granulomatosis Lung Granuloma After Aortic Root Replacement

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Abstract

Wegener’s granulomatosis (WG) is an autoimmune systemic vasculitis that results in necrotizing granulomas. We report a WG patient with a lung granuloma and aortic root dilatation, who underwent aortic root replacement on cardiopulmonary bypass (CPB). Intraoperatively, the patient suffered an aortic dissection, which was repaired immediately under deep hypothermic circulatory arrest (DHCA). Follow-up imaging showed complete granuloma resolution, despite absence of immunosuppressive therapy. Immune stimulation following CPB is well described; here, the opposite was observed and DHCA effects are discussed.

Key Words:
Aortic root • Dissection • Inflammation • Wegener’s granulomatosis

Introduction

Wegener’s granulomatosis (WG) is an autoimmune systemic vasculitis, of unknown etiology, classical affecting small-to-medium-sized vessels and characterized by necrotizing granulomas. It most commonly affects the respiratory and renal systems; however, cardiac involvement is not uncommon (up to 44% of cases), with the most common clinical presentations being pericarditis, supraventricular arrhythmias, and heart block [1]. Although the exact etiology of inflammation in WG is unclear, lesions are thought to be initiated by T-cells, which cross-react with auto-antigens in vessel walls, overproducing factors such as tumor necrosis factor alpha (TNFα) [2]. These cells then activate macrophages and upregulate the production of pro-inflammatory cytokines [2], advancing WG inflammation. Treatment is therefore focused on inhibiting pro-inflammatory pathways with cyclophosphamide (which acts through its metabolite, phosphoramide mustard, forming irreversible DNA crosslinks both between and within DNA strands at guanine N-7 positions and leading to enhanced cell apoptosis and depletion of T-lymphocytes); or, in resistant cases, monoclonal antibodies (causing TNFα blockade) [3].

We report a case of a patient with WG requiring cardiac surgery who had a surprising response to the effects of cardiopulmonary bypass (CPB), which is well known to cause a significantly augmented increase of most humoral parameters of inflammation [4].

Case Presentation

A 63-year-old female was diagnosed with WG following an investigation of hemoptysis, revealing three respiratory necrotising granulomas in her left lower lobe. Despite immunosuppressant and steroid treatment (pulsed Intravenous cyclophosphamide (15 mg/kg) and prednisolone (1 mg/kg/day), respectively), the lesions increased in size, necessitating granuloma and, hence, left lower lobe resection. Histology showed features
characteristic of Wegener’s disease, including a pauci-immune leukocytoclastic vasculitis with necrotizing granulomatous inflammation. Remission was achieved. Following cessation of maintenance immunosuppressive therapy, 20 months following her initial diagnosis, she remained under regular review.

Three years after her initial diagnosis, a surveillance computed tomography (CT) scan of her chest showed a cavitating mass (29 mm × 39 mm) in the mid-zone of the left lung (Figure 1A), highly suspicious of a new granulomatous lesion. Differential diagnosis of infective or neoplastic causes were actively excluded, and serology (ANCA), imaging, and clinical features confirmed WG. Incidentally, a significantly dilated aortic root was also noted, with the following measurements: sinus of Valsalva, 56 mm; sinotubular junction, 51 mm; and, ascending aorta, 41 mm (Figure 1B).

The patient was referred to our department for aortic root replacement. Following a multidisciplinary team discussion, it was determined that surgery should be expedited prior to commencing immunosuppressive treatment, as the anticipated, and well described, significantly increased immune response seen during CPB in combination with immunosuppressive therapy would have put the patient at a greater risk of an adverse outcome and rapid disease progression. In view of her significant family history of two sisters who also suffered from aortic dilatations and, in one case, rupture, the patient was additionally referred for genetic testing. No mutations were identified in the fibrillin-1 gene, excluding Marfan’s as a possible factor in dilatation.

After median sternotomy and heparinization, CPB was initiated. While cannulating the aorta, the patient suffered an acute Type A aortic dissection (DeBakey I). This was noted immediately, and the ascending aorta was replaced with a 30-mm Hemashield vascular graft (Atrium, USA) under deep hypothermic circulatory arrest (DHCA) (22°C body temperature). The aortic root was replaced with a 29-mm stentless bioprosthetic root (Freestyle, Medtronic, Minneapolis, Minnesota, USA) with coronary reimplantation.

The patient made a full recovery postoperatively. Histology of the ascending aorta showed intimal fibrosis but no cystic medial degeneration or arteritis. CT of the chest 1 week postoperatively revealed an almost complete resolution of the lung granuloma despite no interim immunosuppressive therapy (Figure 2). Serial CT scans up to 6 months postoperatively demonstrated no ressurgence of the lung granuloma. We also noted that besides a residual epiaortic hematoma, there was no evidence of previous dissection, with no persisting false lumen.

Discussion

The significantly increased immune response during CPB is thought to be due to systemic endotoxemia, following exposure to the bypass circuit, stimulating pro-inflammatory cytokines and TNFα release, and causing T-cell activation [4]. As previously discussed, such T-cells are thought to be the

Figure 1. Panel A. Computerized tomography (CT) confirming new lung granuloma with the typical vascularized necrotic core seen in Wegener’s granulomatosis lesions. Panel B. CT showing dilated aortic root.
main initiators and propagators of WG [2]. Therefore, deterioration of WG, and other auto-immune conditions, is anticipated in patients undergoing CPB due to this increased immune response. However, in this case, the opposite occurred, and, to our knowledge, this is the first time such a case has been reported in the literature.

Studies have now shown, however, that a physiologically balanced anti-inflammatory response also occurs during CPB, through parallel increases in IL-10: a potent anti-inflammatory cytokine that suppresses T-cell activity by downregulating certain immune pathways [4]. A degree of balance in immune response to CPB may imply that WG lesions should, if not deteriorate, remain unchanged. However, IL-10 has also been found in increased circulating levels in patients during DHCA [5], which has been suggested to be the reason for significant, post-DHCA immunosuppression [5]. Studies into novel WG treatments have suggested that IL-10 may be effective in achieving WG resolution [2]. Therefore, an explanation for granuloma resolution in this case could be that the CPB pro-/anti-inflammatory balance was tipped toward immunosuppression via increased IL-10 levels during, and post, DHCA. The resolution may also have been aided by decreased TNFα levels, as another study has shown diminished mRNA levels for TNFα post-CPB [6]. This finding suggests a highly significant reduction in pro-inflammatory cytokine biosynthesis and TNFα synthesis in the immediate post-CPB period [6]. We speculate from our observations that there is a possibility that if DHCA stimulates granuloma remission, there is a possibility that it could also promote malignant tumor remission; however, no studies to date have confirmed this.

Aside from granuloma resolution, the cause of aortic dilatation is unclear. Although WG primarily affects small-to-medium-sized vessels, there are reports of large-vessel, such as subclavian artery, aneurysms occurring [7]. Histology from the ascending aorta did not show WG pathognomonic changes; however, it did show intimal fibrosis, which is seen initially as part of WG changes. We wonder if the findings represent early WG cardiovascular changes, which, when combined with an unaccounted genetic predisposition, may lead to the development of a dilated root.

In addition, this case emphasises that immediate/very early recognition and repair of intraoperative, retrograde acute aortic dissection can result in the complete restoration of the aortic wall without a residual false lumen, which usually persists after Type A repair. A patent false lumen is associated with increased late mortality and morbidity due to progressive aneurysmal false-lumen dilatation, occurring in approximately one-fifth of cases. The thinner outer wall confers an increased rupture and hence mortality risk [8]. Therefore, in this patient with an unexplained genetic predisposition to large-vessel aneurysms, we predict that repair will provide a reduced risk of further aneurysmal development and/or rupture.

In conclusion, this case demonstrates the need for further investigations into the pathophysiology of tumor tissue and the immune system under the circumstances of CPB and DHCA. The immediate complete resolution of a WG lesion after CPB with DHCA suggests a cause-effect relationship—and ample potential molecular pathways for such an effect can be called to bear.

**Conflict of Interest**

The authors have no conflicts of interest relevant to this publication.
References


Abstract

A 78-year-old man with a Kommerell diverticulum and aberrant right subclavian artery was admitted for thoracic pain and severe malnutrition due to esophageal compression. We performed an atypical surgical procedure including extra-anatomical debranching and direct aortic repair, trying to avoid deep hypothermic circulatory arrest and shorten the cardiopulmonary bypass time.

Key Words
Kommerell diverticulum • Arch aneurysm repair

Introduction

Aortic arch replacement under deep hypothermic circulatory arrest (DHCA) is a complex operation, associated with significant mortality and morbidity. The elderly and patients with poor physiologic reserve are often not candidates for these procedures. We describe a proposed technique for aortic arch replacement and the resection of a Kommerell diverticulum (KD) without DHCA in a frail and malnourished patient.

Case Presentation

A 78-year-old man with history of hypertension and renal insufficiency presented with back pain and severe dysphagia, which rendered the patient severely malnourished. The patient's body mass index was 15.7. The creatinine level was 1.3 mg/dl, and the urea level was 108 mg/dl. Computed tomography demonstrated an arch and proximal descending aortic aneurysm, measuring up to 12 cm in diameter. The left subclavian artery (LSA) and an aberrant right subclavian artery (ARSA) both arose from the distal aspect of the aneurysm. The proximal ARSA measured 70 mm in diameter, compressing the esophagus and displacing the trachea. Coronary angiography was normal; echocardiography showed normal ventricular function, the aortic valve was mildly calcified without gradient or insufficiency. There was no mitral regurgitation.

Not only was the intervention necessary to prevent rupture, but correction of the esophageal compression was also critical. Due to patient's debilitated state and co-morbidities we conceived this alternative surgical approach, which would avoid DHCA and shorten cardiopulmonary bypass (CPB) time while resolving the problem.

Surgical Technique

Access to the chest was obtained via a four intercostal space-left anterolateral thoracotomy extending into the right chest across the sternum (clam shell).

First step (de-branching). This step included a right carotid to right axillary artery bypass and a left

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How I Do It

Single Stage Aortic Arch Replacement without Circulatory Arrest

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Figure 1. First Step (de-branching): Carotid-subclavian artery bypass on the left side and carotid-axillary artery bypass on the right side.

Carotid to left subclavian artery bypass, using 8-mm polytetrafluoroethylene grafts (Figure 1). Then, using a thoracotomy approach, both carotid arteries were sequentially transected and anastomosed in an end-to-end fashion to the two arms of a 10 × 20 Y graft (Figure 2).

Second step (resection of aneurysm including KD). CPB was established via the LSA, left femoral artery, and right atrium, and moderate hypothermia was implemented (28 °C). By clamping the single arm of the Y graft, the head vessels and the upper body were perfused via the LSA cannula. The ascending aorta was clamped and heart was arrested. Then, the descending aorta was clamped while the abdomen was perfused via the femoral artery cannula (Figure 3). We resected the KD and proximal ARSA in order to resolve the esophageal compression. The ostium of LSA was oversewn.

Third step (reconstruction). The reconstruction of the aorta was performed with a #28 Dacron graft bypass from distal ascending aorta down to the proximal descending aorta. Then, we anastomosed the single arm of the Y graft in this aortic graft in an end-to-side fashion (Figure 4).

Total CPB time was 90 minutes. There were no intervals between the steps.

The patient recovered very well. He was neurologically intact. His dysphagia resolved completely, and he was discharged from the hospital 3 weeks after surgery with an improving nutritional state.

Discussion

This case combines an ARSA with KD associated with a distal arch and descending thoracic aortic aneurysm in a very frail patient. The sizes of the aneurysm as well as dysphagia were both clear indications for surgery.

Considering the patient’s debilitated state, a hybrid de-branching/endovascular repair was considered as an initial approach in terms of being a less traumatic intervention. However, it was ruled out for two reasons: 1) the lack of an adequate proximal landing zone for the deployment of the endovascular graft, and 2) the need for surgical resection of the diverticulum in order to resolve the dysphagia.

Although some authors have described aortic arch replacement without DHCA [1, 2], the traditional surgical approach for the treatment of this pathology requires CPB and DHCA and is associated with mortality and morbidity [3, 4]. We ruled out this option in view of our patient’s malnourishment and frail condition.

We chose a procedure that was entirely surgical but avoided prolonged CPB times and DHCA. Proceeding with the de-branching component...
described in step 1 permitted perfusion of the brain and upper body via a cannula in LSA, avoiding the need for DHCA. CPB time was reduced considering that this step was performed off pump. Steps 2 and 3 describe a combination of standard aortic arch replacement and debranching techniques. In this case, the esophageal compression caused by the KD was significant, leading dysphagia and malnourishment. The resolution of this problem could have not been resolved with an endovascular procedure [5].

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List of Upcoming Meetings

**June**

1. Minimally Invasive Techniques in Adult Cardiac Surgery  
   June 7-9, 2016  
   Berlin, Germany  
   Meeting information available at: www.eacts.org

2. Complex Cardiovascular Catheter Therapeutics  
   June 28-July 1, 2016  
   Orlando, FL, USA  
   Meeting information available at: www.C3conference.net

**July**

1. Annual Conference on Atherosclerosis  
   July 11-12, 2016  
   Philadelphia, PA, USA  
   Meeting information available at: atherosclerosis.conferenceseries.com

2. 4th Singapore VALVE 2016  
   July 14-16, 2016  
   Outram, Singapore  
   www.nhcs.sg/educationandtraining/events/ Pages/Home.aspx

3. Heart Valve-Related Disorders Conference  
   July 23-26, 2016  
   Cambridge, UK  
   Meeting information available at: www.zingconferences.com/conferences/heart-valve-related-disorders

**August**

1. AATS Cardiovascular Valve Symposium  
   August 11-12, 2016  
   Beijing, China  
   Meeting information available at: aats.org/valvebeijing/

**September**

1. 2nd North American Aortic Valve Repair Symposium  
   September 9-10, 2016  
   Philadelphia, PA, USA  
   Meeting information available at: penncmeonline.com/cv_surgery/node/59142