Polyester Grafts Are a Risk Factor for Postimplantation Syndrome after Abdominal Endovascular Aneurysm Repair: Retrospective Analysis for Polyester Graft, Excluder®, and Endologix Powerlink®/AFX®

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Objective: Postimplantation syndrome (PIS) is a postoperative syndrome that occurs after endovascular aneurysm repair (EVAR), accompanied by high fever, leukocytosis, and high serum C-reactive protein (CRP). Its pathogenesis and clinical meaning are still under discussion. Here, we evaluate the relationship between postoperative fever after EVAR and graft fabric focusing on Endologix Powerlink® and AFX® (EPL/AFX).

Materials and Methods: From January 2015 to July 2017, data on elective EVAR for abdominal aortic aneurysm (AAA) using mainbody were retrospectively collected. The primary endpoint was maximal postoperative fever.

Results: We identified 128 patients who underwent elective EVAR for AAA (105 males, 82%; aged 57–90, median: 74 years). The median maximal postoperative fever was 37.8°C (36.6–39.7°C): polyester graft, 38.2°C (37.1–39.7°C); Excluder®, 37.8°C (36.6–39.2°C); and EPL/AFX, 37.7°C (37–38.7°C). The maximal postoperative fever with a polyester graft was significantly higher than that with an expanded polytetrafluoroethylene (ePTFE) graft (p<0.001). However, there was no difference between Excluder® and EPL/AFX (p=0.214).

Conclusion: In this study, it was found that polyester grafts are significantly associated with PIS after elective EVAR for AAA. If patient anatomy is permitted, it may be better to choose the ePTFE graft, especially for patients with a poor general condition.

Keywords: endovascular aneurysm repair, abdominal aortic aneurysm, postimplantation syndrome

Introduction

Endovascular aneurysm repair (EVAR) for abdominal aortic aneurysms (AAAs) is less invasive and is associated with a significant reduction in operative mortality and morbidity compared with conventional open surgery.1–3 Postimplantation syndrome (PIS) is a postoperative syndrome characterized by high fever, leukocytosis, and high serum C-reactive protein (CRP) following EVAR.4–7 There are some reports on PIS associated with acute hepatic dysfunction and multiple-organ failure.8,9 However, the pathogenesis and clinical meaning of PIS are still under discussion.4,8,9 Compared with expanded polytetrafluoroethylene (ePTFE) grafts, polyester grafts have been reported to be a risk factor for PIS. However, there are many reports on PIS associated with Gore Excluder® (Excluder®, W. L. Gore & Associates, Flagstaff, AZ, USA), which is one of the most famous ePTFE grafts, but there is no report on PIS associated with Endologix Powerlink® (Endologix Inc., Irvine, CA, USA) and AFX® (Endologix Inc., Irvine, CA, USA) (EPL/AFX), which is an ePTFE graft. Here, we evaluated the relationship between postoperative fever after EVAR and graft fabric focusing on EPL/AFX.

Methods

Study design

We performed a retrospective review of patients who
underwent EVAR using a Zenith Flex® stent graft (Cook Medical, Bloomington, IN, USA), an Excluder® stent graft, an Endurant® stent graft (Medtronic, Minneapolis, MN, USA), an Aorfix® stent graft (Lombard Medical Technologies, Didcot, UK), or a Powerlink® and AFX® stent graft at The Jikei University Kashiwa Hospital, Chiba, Japan, between January 2015 and July 2017. The patients included in this study underwent elective EVAR for AAA using a bifurcated mainbody stent graft. Patients with ruptured AAAs were excluded. The primary endpoint was maximal postoperative fever.

The Jikei University Kashiwa Hospital’s Institutional Review Board approved this study, and informed consent was waived because it is a retrospective observational study using a deidentified database, 29-205(8821).

**Patients**

Patients with AAAs and a minimum external diameter of 5.5 cm (short axis) or saccular morphology were deemed eligible for EVAR. The exclusion criteria for elective EVAR included acute myocardial or cerebral infarction within three months before the surgery and/or a recent symptomatic blue toe syndrome. All patients were classified according to the American Society of Anesthesiologists system (grades 1–4). EVAR was performed under local or epidural anesthesia in patients with severe and extremely severe chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in one second (FEV1) of 50% [stage III or IV according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification]. Patients with end-stage renal disease were considered eligible for EVAR.

**Data analysis**

The body temperature of all patients was evaluated every eight hours after EVAR, and it was confirmed that their serum CRP levels normalized before discharge. If the body temperature was higher than 38.5°C, the patient received ice cooling and oral acetaminophens (400 mg/8 h). Postoperative hepatic failure was defined when the level of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) rose to more than double compared with preoperative data.

**Statistical analysis**

Patient characteristics and operative variables were analyzed using the Chi-square test, analysis of variance (ANOVA), and the Kruskal–Wallis test. Univariate analyses were performed in order to identify patient- and procedure-related risk factors for postoperative fever using linear progression models. ANOVA was used when continuous data exhibited a normal distribution. For comparison of nonparametric data, the Kruskal–Wallis test was used. Categorical data were evaluated using the Chi-square or Fisher’s exact test. Then, only factors that achieved a level of p<0.05 after univariate testing were entered in the logistic regression analysis. All statistical analyses were performed using Stata/IC (STATA statisti-

| Variables                          | Polyester graft (n=59) | Excluder (n=33) | EPL/AFX (n=36) | p value |
|------------------------------------|------------------------|-----------------|----------------|---------|
| **Preoperative factors**           |                        |                 |                |         |
| Age (years)                        | 74 (57–89)             | 77 (58–89)      | 74 (59–90)     | 0.233*  |
| Male                               | 49 (83.1%)             | 24 (72.7%)      | 32 (88.9%)     | 0.209†  |
| Hypertension                       | 39 (66.1%)             | 23 (69.7%)      | 18 (51.4%)     | 0.236†  |
| Coronary artery disease            | 11 (18.6%)             | 7 (21.2%)       | 6 (17.1%)      | 0.910†  |
| Dysplasia                          | 19 (32.2%)             | 11 (33.3%)      | 6 (17.1%)      | 0.223†  |
| Stroke                             | 8 (13.6%)              | 3 (9.1%)        | 6 (17.1%)      | 0.745†  |
| Diabetes                           | 7 (11.9%)              | 4 (12.1%)       | 6 (17.1%)      | 0.520†  |
| COPD                               | 3 (5.1%)               | 3 (9.1%)        | 4 (11.4%)      | 0.324†  |
| Chronic renal failure              | 20 (33.9%)             | 13 (39.4%)      | 8 (22.9%)      | 0.002** |
| Aneurysm size (mm)                 | 50 (34–67)             | 48.5 (33–100)   | 43 (28–79)     | 0.015†  |
| Saccular aneurysm                  | 9 (15.3%)              | 4 (12.1%)       | 13 (37.1%)     |         |
| **Operative factors**              |                        |                 |                |         |
| Internal iliac artery embolization | 21 (35.6%)             | 8 (24.2%)       | 16 (44.4%)     | 0.213†  |
| Surgery duration (min)             | 132 (80–276)           | 131(81–306)     | 126 (63–264)   | 0.420** |
| Blood loss (mL)                    | 40 (10–1000)           | 40 (0–6800)     | 50 (10–800)    | 0.328** |
| Fluoroscopy time (min)             | 25 (12–147)            | 25.5 (10–65)    | 21.5 (9–104)   | 0.230** |
| Contrast media (mL)                | 140 (37–320)           | 130 (82–395)    | 98 (46–239)    | <0.004**|

† Chi-square test; * ANOVA; ** Kruskal–Wallis test
EPL: Endologix Powerlink; COPD: chronic obstructive pulmonary disease

Table 1 Patient characteristics and operative details (univariate analysis)
Results

Baseline characteristics and operative details (Table 1)
We identified 128 patients who underwent elective EVAR for AAA using mainbody (105 males, 82%; aged 57–90, median: 74 years). Excluder® was used on 33 patients (25.8%), EPL/AFX was used on 36 patients (28.1%), Aor-fix® was used on 32 patients (25%), Endurant® was used on 26 patients (20.3%), and Zenith Flex® was used on one patient (0.8%). There were no hospital deaths, major adverse effects, multiple-organ failure, or hepatic failure. The rate of saccular aneurysm with EPL/AFX was significantly higher than with the other devices (p = 0.002), and lower-contrast media were significantly associated with maximal postoperative fever (p = 0.010, p = 0.001).

Outcomes
The median maximal postoperative fever was 37.8°C (36.6–39.7°C): polyester graft, 38.2°C (37.1–39.7°C); Excluder®, 37.8°C (36.6–39.2°C); and EPL/AFX, 37.7°C (37–38.7°C).

Univariate analysis for postoperative fever (logistic regression analysis) (Table 2)
Univariate analyses were performed using logistic regression analysis for postoperative fever. The cut-off of fever was 38°C. The contrast media and polyester graft were significantly associated with maximal postoperative fever (p = 0.010, p = 0.001).

Table 2 Univariate analysis for postoperative fever (≥38°C) (logistic regression analysis)

| Variables                  | OR     | (95%CI) | p value |
|----------------------------|--------|---------|---------|
| Preoperative factors       |        |         |         |
| Age (years)                | 0.983  | (0.938–1.030) | 0.480   |
| Male                       | 1.469  | (0.585–3.689) | 0.413   |
| Hypertension               | 0.898  | (0.436–1.847) | 0.770   |
| Coronary artery disease    | 1.408  | (0.577–3.435) | 0.452   |
| Dyslipidemia               | 1.594  | (0.733–3.466) | 0.240   |
| Stroke                     | 0.399  | (0.078–1.147) | 0.079   |
| Diabetes                   | 0.991  | (0.356–2.759) | 0.987   |
| COPD                       | 1.750  | (0.469–6.527) | 0.405   |
| Chronic renal failure      | 0.708  | (0.334–1.502) | 0.368   |
| Aneurysm size (mm)         | 1.001  | (0.975–1.045) | 0.593   |
| Saccular aneurysm          | 0.551  | (0.223–1.363) | 0.197   |
| Operative factors          |        |         |         |
| Internal iliac artery embo-| 1.133  | (0.548–2.343) | 0.737   |
| lization                   |        |         |         |
| Surgery duration (min)     | 1.003  | (0.995–1.011) | 0.480   |
| Blood loss (mL)            | 0.999  | (0.997–1.001) | 0.445   |
| Fluoroscopy time (min)     | 1.017  | (0.996–1.038) | 0.115   |
| Contrast media (mL)        | 1.010  | (1.002–1.016) | 0.010   |
| Polyester graft            | 3.364  | (1.625–6.961) | 0.001   |

OR: odds ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease

Table 3 Subgroup analysis for postoperative fever in each graft (linear regression analysis)

| Variables                  | Polyester graft* (n=59) | ePTFE graft** (n=69) | Excluder® (n=33) | EPL/AFX (n=36) | P1  | P2  | P3  | P4  |
|----------------------------|-------------------------|----------------------|------------------|----------------|-----|-----|-----|-----|
| Post-operative maximal fever (°C) | 38.2 (37.1–39.7)        | 37.7 (36.6–39.2)     | 37.8 (36.6–39.2) | 37.7 (37.0–38.7) | <0.001 | 0.027 | <0.001 | 0.214 |
| Serum CRP (mg/dL)           |                         |                      |                  |                |     |     |     |     |
| POD1                       | 2.9 (0.3–9.2)           | 1.1 (0.1–27.7)       | 1.3 (0.1–27.7)   | 1.1 (0.1–3.9)  | 0.038 | 0.404 | <0.001 | 0.148 |
| POD3                       | 11.9 (0.8–24.7)         | 5.6 (0.1–26.1)       | 5.7 (0.1–26.1)   | 4.9 (0.2–12.9) | <0.001 | <0.001 | <0.001 | 0.110 |
| White blood cell count (/µL)|                         |                      |                  |                |     |     |     |     |
| POD1                       | 11000 (4700–28700)      | 7900 (1200–15900)    | 8100 (1200–15900)| 7550 (4700–14200)| <0.001 | <0.001 | <0.001 | 0.600 |
| POD3                       | 8500 (4100–18600)       | 7400 (3000–14100)    | 8350 (4100–14100)| 7000 (3000–11000)| 0.009 | 0.378 | 0.001 | 0.019 |
| Postoperative hepatic failure | 8 (13.6%)              | 6 (8.7%)             | 4 (12.1%)        | 2 (5.6%)       | 0.740 | 0.836 | 0.445 | 0.384 |
| Admission duration after EVAR (days) | 6 (2–17)              | 5 (2–34)             | 4.5 (2–19)       | 5 (3–34)       | 0.959 | 0.934 | 0.986 | 0.970 |

*Polyester grafts included Zenith Flex®, Endurant®, and Aorfix®. **ePTFE grafts included Excluder® and EPL/AFX.

CRP: C-reactive protein; POD: postoperative day; EVAR: endovascular aneurysm repair; ePTFE: expanded polytetrafluoroethylene; EPL/AFX: Endologix Powerlink™ and AFX®.

P1: polyester graft versus ePTFE graft; P2: polyester graft versus Excluder®; P3: polyester graft versus EPL/AFX; P4: Excluder® versus EPL/AFX.
Polyester Grafts Are a Risk for PIS after EVAR

Subgroup analysis for postoperative fever in each grafts (liner regression analysis) (Table 3)
Subgroup analysis was performed using linear regression analysis for fever in each graft. It was found that the maximal postoperative fever with polyester grafts was significantly higher than that with ePTFE grafts \((p<0.001)\). However, there was no difference between Excluder® and EPL/AFX \((p=0.214)\). There were 14 patients with post-operative hepatic failure. However, there was no significant difference between polyester grafts and ePTFE grafts. ePTFE grafts tended to reduce postoperative hepatic failure \((13.6\%\text{ versus } 8.7\%, \ p=0.740)\).

Discussion
Although the inflammatory responses after EVAR are defined in PIS, the diagnostic criteria are not confirmed. High fever, leukocytosis, and elevated serum CRP and interleukin (IL)-6 are known to be symptoms and signs for PIS. The rate of PIS was reported to be 14%–60%\(^{4,6-7}\). Although PIS is usually treated conservatively, it occasionally induces acute hepatic failure and multiple-organ failure\(^{4,6-9}\). Moreover, it was reported that PIS is associated with a 30-day cardiovascular event after EVAR\(^{4,6}\). Therefore, postoperative surveillance is thought to be necessary\(^{4,6,7}\).

The pathogenesis of PIS is unknown\(^{4,8,9}\). Compared with ePTFE grafts, polyester grafts have been reported to be a risk factor for PIS\(^7\). In general, after enhanced computerized tomography scans, percutaneous coronary angioplasty, or endovascular therapy for limb revascularization, inflammatory responses are uncommon. Therefore, contrast media and stent structure are not related to postoperative fevers\(^{41}\). In this study, it was shown that polyester grafts are associated with postoperative fevers. This phenomenon is known to occur after open graft repair using a polyester graft. Polyester grafts are comprised of gelatin, and gelatin is thought to be associated with postoperative fevers\(^{10-12}\). However, polyester grafts used as stent grafts do not contain sealed gelatin. It is thought that the pathogenesis of PIS differs between EVAR and open surgeries. There are some reports proposing that polyester triggers higher release of inflammatory biomarkers (tumor necrosis factor-α, IL-6, IL-10, and CRP) than ePTFE in vitro\(^{7,13,14}\). We hypothesize that these inflammatory biomarkers promote PIS.

Limitations
Our study had several limitations. First, in this study, due to the fact that EPL/AFX tended to be chosen for saccular and smaller aneurysms, there might be some biases. Second, we were not able to perform multivariate analyses because of the sample size. Finally, this study was retrospective in nature and had a relatively small number of patients from a single center. A prospective, blinded clinical trial is required in order to establish the mechanism and physiology of PIS and aneurysm prognosis.

Conclusion
In this study, it was shown that ePTFE grafts (Excluder® and EPL/AFX) are associated with a lower probability of postoperative fever. If patient anatomy is permitted, it may be better to choose ePTFE grafts, especially for patients with a poor general condition.

Disclosure Statement
Takao Ohki is a paid consultant of W. L. Gore & Associates. The other authors do not have any conflicts of interest or financial ties to disclose.

Author Contributions
Study conception: EI
Data collection: EI, NT, SF, RN
Analysis: EI, NT
Investigation: EI, NT, SF, RN
Writing: EI
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

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