Factors Predisposing to Endograft Limb Occlusion after Endovascular Aortic Repair


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WHAT THIS PAPER ADDS
This study demonstrates that the presence of significant angulation and calcification of the iliac arteries as well as excessive limb oversizing appear to be independent predictors for endograft limb occlusion after endovascular aortic repair. For the first time the lack of clearly defined predisposing factors for endograft limb thrombosis led to the design of a case control study, which is ideal for studying multiple potential causes of a disease.

INTRODUCTION
Endovascular abdominal aneurysm repair (EVAR) has been widely used for the treatment of patients with infrarenal abdominal aortic aneurysms (AAAs). EVAR is considered to have fewer short term complications than open reconstruction of AAAs. However, long term durability of the technique is probably limited by the high incidence of late complications requiring re-intervention. A well known risk after EVAR is endograft limb occlusion, especially in complex iliac anatomy. It occurs in 2.6 – 7.4% of patients during follow up and it usually requires intervention to restore limb perfusion. Several anatomical risk factors predisposing to limb thrombosis have been proposed, including common iliac artery diameter, calcification, angulation, and the presence of thrombus, whereas procedure related risk factors for limb thrombosis include endograft oversizing and extension to the external iliac artery. However, no study has yet compared these characteristics between patients with endograft limb occlusion and EVAR controls without limb occlusion.

The aim of this study was to present the experience with endograft limb thrombosis in order to identify potential anatomical and procedure related risk factors using a case control design; each patient with endograft limb occlusion was matched for sex, age, and commercial type of endograft used to three patients having EVAR without limb thrombosis.

MATERIALS AND METHODS

Patients
Between January 2010 and June 2013, 439 patients underwent elective EVAR for AAA using bifurcated endografts.
All patients were treated with commercially available bifurcated endografts \( (n = 439) \): Gore Excluder \( (n = 139) \), Cook Zenith \( (n = 155) \), Vascutek Anaconda \( (n = 111) \), and Medtronic Endurant \( (n = 34) \). All four types of these commercially available endografts were used according to their instructions for use, based on anatomical criteria and the surgeon’s preference. A review of prospectively collected data for all consecutive patients presenting with endograft limb occlusion after elective EVAR for infra-renal AAA repair was performed. Patients presenting with ruptured or isolated iliac aneurysms or with a history of previous aortic surgery were excluded. Each patient with endograft limb occlusion (case) was matched for sex, age, and commercial type of endograft used to three patients having EVAR and no endograft limb occlusion (controls). Cumulative random sampling of controls was carried out, in which the controls were automatically matched on age (within 3 years), gender, and type of endograft with cases in the entire cohort of patients. In the next step, the fixed number (3) of control subjects for each case was randomly selected. Increasing the number of controls above the number of cases may be a cost effective way of improving the study. The number of controls for each case was increased to three in order to improve the chance of detecting important differences.\(^{10}\) For this research, approval of the Ethical Committee of the institution was obtained and informed consent from each recruited patient was mandatory.

**Surgical approach and technique**

All procedures were performed in the operating theater using a C-arm with angiographic and road mapping capabilities (Philips BV Pulsera). Patients were administered general or epidural anesthesia based on their comorbidities, and access to the femoral arteries was obtained by surgical dissection. Peri-operative antibiotic prophylaxis with intravenous vancomycin (1 g) and piperacillin plus tazobactam (4.5 g) was administered 1 h before and 12 h after the operation. Systemic heparinization was achieved with 5000 IU of heparin. All endovascular grafts were deployed below the renal arteries, whereas endograft limbs were deployed with a distal sealing zone in the common or external iliac artery, depending on the extent of the aneurysm. Balloon dilatation of the entire length of the endograft, and completion angiography assessing graft position and function was performed routinely without stiff wires in place in order to detect limb kinking that might predispose to thrombosis. At discharge, antiplatelet therapy was prescribed to all patients. The follow up protocol included history, physical examination and 1 mm slice computed tomographic angiography (CTA) scan with intravenous contrast at 30 days and 12 months post procedure and color duplex ultrasound yearly thereafter. In cases with an endoleak or hostile neck, CTA was also performed 6 months post-operatively. On clinical suspicion of endograft limb thrombosis, the diagnosis was confirmed by CTA. Morphologic analysis and measurement of aneurysm characteristics based on CTA scan were performed pre-operatively using commercially available image processing software with center lumen line reconstruction (Osirix MD, v3.8.1 32 bit). Commonly used cut off values for the variable of interest were implemented.\(^{12}\) Angulation of the iliac artery was estimated from the maximum iliac angulation measured from the Osirix MD software centerline taking into account the entire length between the aortic and the iliac bifurcation. In addition, calcification of the iliac artery was classified as distributed around more or less than 50% of the circumference of the vessel. With respect to the oversizing, the diameter at the end of the graft limb (seal zone diameter) was used. Two independent observers (G.M., C.A.) performed all image analyses, blinded to patient data and inter observer agreement was determined using the \( \kappa \) statistic.

**Variables of interest: exclusion criteria**

Pre-operative factors extracted from patients’ medical records included age, gender, commercial endograft type (Gore Excluder, Cook Zenith, Vascutek Anaconda, Medtronic Endurant), atherosclerotic risk factors (coronary artery disease; CAD, hyperlipidemia, hypertension, diabetes mellitus; DM, smoking), antiplatelet therapy at discharge (single, dual or other), pre-operative maximum aneurysm diameter (cm), vascular access during EVAR indicating the side used to deliver the main body of bifurcated prostheses (right, left), pre-operative neck characteristics (length; cm, diameter; cm, angle \( \geq 45^\circ \)), calcification \( \geq 50\%\) of the circumference, presence of luminal thrombus \( \geq 50\%\) and pre-operative characteristics of common iliac artery, ipsilateral to endograft limb occlusion (diameter; cm, length; cm, angle \( \geq 60^\circ \)), calcification \( \geq 50\%\), endograft limb oversizing \( \geq 15\%\), extension to the external iliac artery). Post-operative follow up time was also considered as a potential confounder and an additional multivariate analysis was also performed.

**Statistical analysis**

Continuous data were reported as mean \( \pm \) SD. Distribution of categorical study characteristics was reported as percentage among cases and controls. Standard statistical procedures (non-parametric chi-square distribution and Student’s t-test with corresponding \( p \) values) were used to assess differences in categorical and continuous study variables among cases and controls, respectively. Univariate logistic regression analysis was performed to derive crude odds ratios (ORs) and 95% confidence intervals (95% CIs) for study variables among cases and controls from 2 \( \times \) 2 tables. Furthermore, multivariate logistic regression analysis and conditional logistic regression analysis for 1:3 matched pairs were modeled, to derive adjusted ORs with 95% CIs using patients with endograft limb occlusion as cases and patients with EVAR and patent endograft limbs as controls (dependent variable) and significant co-variates in univariate analysis as predictor variables. All analyses were performed using STATA version 11 (STATA Corp., TX, USA).
RESULTS

A total of 18 patients (4%) with a mean age of 71.3 ± 5.8 years presented with endograft limb occlusion. The occlusion rate per commercially available endograft used was 2.2% (3/139) for Gore Excluder, 5.8% (9/155) for Cook Zenith, 2.7% (3/111) for Vascutek Anaconda, and 8.8% (3/34) for Medtronic Endurant. No statistical significance for occlusion rate was observed after all possible comparisons among the different types of endografts (all \( p > .05 \)). The 18 patients with endograft limb occlusion and 54 age, sex, and type of endograft matched controls were included in the study. There was one case of limb occlusion during the first post-operative week, two cases of endograft limb occlusion between the first and the fourth post-operative week, while in the remaining 15 cases (83%) limb occlusion occurred after 2–34 months. Diagnosis was based on clinical examination and imaging findings from color duplex ultrasound and CTA. Seven of the 18 patients (39%) with endograft limb occlusion presented with symptoms of acute limb ischemia and were treated as an emergency, whereas the remaining 11 patients presented with symptoms of buttock or leg claudication and were treated electively by femoral–femoral bypass. Thrombectomy was attempted in all seven patients who presented with acute limb occlusion. However, in three it was impossible to advance the catheter into the thrombosed endograft limb so they were treated by femoral–femoral bypass. As a result, in 14 cases (78%) limb reperfusion was achieved with a femoral–femoral bypass. In the remaining four patients, limb thrombectomy and stenting with balloon angioplasty was successful. Lower limb perfusion was restored in all cases. During the 2–30 month follow up period after re-operation, one patient died from thoracic aortic aneurysm rupture, two patients with a previous femoral–femoral bypass required re-intervention with axillo-femoral bypass, and the rest remained free of symptoms. Statistically significant agreement was recorded between the two independent observers \( (k = 0.65, p < .01) \) regarding the morphologic analysis and the pre-operative AAA measurements.

Table 1 presents differences among cases and controls with respect to the variables studied. No statistically significant differences were observed regarding demographic characteristics (matched variables), atherosclerotic risk factors, antiplatelet therapy, access side, pre-operative AAAs, and characteristics of common iliac artery, ipsilateral to endograft limb occlusion.
maximum aneurysm diameter and pre-operative neck characteristics. In only two patients (1 case and 1 control) was there significant thrombus in the common iliac arteries. Statistically significant differences were observed in the pre-operative characteristics of the common iliac artery ipsilateral to the occluded endograft limb, including angle $\geq 60^\circ$ (50% vs. 14.8%; $p = .002$), calcification $\geq 50\%$ (44.4% vs. 13%; $p = .004$) and endograft limb oversizing $\geq 15\%$ (83.3% vs. 48.1%; $p = .01$), respectively. Common iliac artery angulation was evident in the post-operative CTA, but not in the intra-operative final digital subtraction angiogram (DSA) in one patient.

Results of univariate analysis for endograft limb occlusion by study covariates are presented in Table 2. An angle $\geq 60^\circ$ (OR $= 5.75$, 95% CI = 1.75–18.91; $p = 0.004$), calcification $\geq 50\%$ (OR $= 5.37$, 95% CI = 1.58–18.24; $p = .007$) and endograft limb oversizing $\geq 15\%$ (OR $= 5.38$, 95% CI = 1.39–20.76; $p = .01$) of the ipsilateral common iliac artery increased the risk for endograft limb occlusion. The significance of the findings remained robust in the conditional (matched pair case control) regression analysis (Table 3). More specifically, endograft limb occlusion was associated with angle $\geq 60^\circ$ (OR $= 5.76$, 95% CI = 1.24–26.74; $p = .03$), calcification $\geq 50\%$ (OR $= 5.87$, 95% CI = 1.10–31.32; $p = .04$) and endograft limb oversizing $\geq 15\%$ (OR $= 5.54$, 95% CI = 1.11–27.60; $p = .04$) of the common iliac artery, ipsilateral to endograft limb occlusion. Time since operation did not prove to be a significant covariate (OR $= 1.04$, 95% CI = 0.96–1.09).

**DISCUSSION**

A case control design has been used for the first time to investigate AAA characteristics which can be easily detected in the pre-operative CTA and which may predispose to post-operative endograft limb occlusion. The results suggest that angle $\geq 60^\circ$, calcification $\geq 50\%$ and endograft limb oversizing $\geq 15\%$ of the ipsilateral common iliac artery may present a more than fivefold increase in risk for endograft limb occlusion. In contrast, extension of the endograft into the external iliac artery did not prove to be a significant factor. This is not in line with some of the previous studies, identifying endograft extension to the external iliac artery as a risk factor for limb thrombosis. The study by Wyss et al. found that increased neck thrombus and common iliac calcification appear to protect against complications. It is possible that softer thrombus acts as a plaster like texture resulting in a more snug apposition of the stent graft to the vessel wall, whereas uneven calcifications may impede close apposition. However, quality of thrombus was not measured in either Wyss et al.’s study or the current study, and, as a result, findings may not be comparable. All the other factors investigated in the study, including medical history, pre-operative maximum aneurysm diameter (cm), pre-operative neck characteristics, access site, and anti-platelet therapy did not seem to have any impact on endograft limb thrombosis.

The anatomic characteristics of the aorta and iliac arteries must be carefully assessed when planning EVAR. The aortic bifurcation must accommodate both limbs of the endograft. Mural thrombus or atherosclerotic disease can cause a narrow distal aortic lumen. EVAR in patients with common iliac artery anatomy outside the instructions for use (IFU) may be an important risk factor for endograft limb compression and/or kinking and thrombosis. Among these characteristics, severe iliac artery angulation and/or tortuosity have been linked with early kink development. Kinking of the endograft limb may not be visualized when

**Table 2. Univariate logistic regression derived ORs and 95% CIs for endograft limb occlusion controlling by study covariates.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category or increment</th>
<th>Univariate logistic regression analysis OR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access</td>
<td>Right vs. Left</td>
<td>0.26 (0.31–2.18)</td>
<td>.21</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Yes vs. No</td>
<td>0.56 (0.17–1.79)</td>
<td>.33</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Yes vs. No</td>
<td>1.86 (0.61–5.67)</td>
<td>.28</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes vs. No</td>
<td>0.52 (0.13–2.04)</td>
<td>.35</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes vs. No</td>
<td>0.88 (0.21–3.63)</td>
<td>.86</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes vs. No</td>
<td>1.39 (0.46–4.20)</td>
<td>.56</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>1 Level more</td>
<td>1.06 (0.49–2.30)</td>
<td>.88</td>
</tr>
<tr>
<td>Pre-operative maximum aneurysm diameter (cm)</td>
<td>1 SD among controls</td>
<td>1.04 (0.57–1.90)</td>
<td>.89</td>
</tr>
<tr>
<td>Pre-operative neck characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angle</td>
<td>$\geq 45^\circ$ vs. $&lt; 45^\circ$</td>
<td>1.00 (0.24–4.18)</td>
<td>.99</td>
</tr>
<tr>
<td>Calcification</td>
<td>$\geq 50%$ vs. $&lt; 50%$</td>
<td>0.58 (0.06–5.29)</td>
<td>.63</td>
</tr>
<tr>
<td>Thrombus</td>
<td>$\geq 50%$ vs. $&lt; 50%$</td>
<td>0.31 (0.08–1.21)</td>
<td>.10</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>1 SD among controls</td>
<td>1.01 (0.64–1.61)</td>
<td>.96</td>
</tr>
<tr>
<td>Diameter (cm)</td>
<td>1 SD among controls</td>
<td>0.66 (0.20–2.17)</td>
<td>.50</td>
</tr>
<tr>
<td>Characteristics of common iliac artery, ipsilateral to endograft limb occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter (cm)</td>
<td>1 SD among controls</td>
<td>0.88 (0.34–2.27)</td>
<td>.80</td>
</tr>
<tr>
<td>Angle</td>
<td>$&gt; 60^\circ$ vs. $&lt; 60^\circ$</td>
<td>5.75 (1.75–18.91)</td>
<td>.004</td>
</tr>
<tr>
<td>Calcification</td>
<td>$\geq 50%$ vs. $&lt; 50%$</td>
<td>5.37 (1.58–18.24)</td>
<td>.007</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>1 SD among controls</td>
<td>0.90 (0.58–1.40)</td>
<td>.63</td>
</tr>
<tr>
<td>Endograft limb oversizing</td>
<td>$\geq 15%$ vs. $&lt; 15%$</td>
<td>5.38 (1.39–20.76)</td>
<td>.01</td>
</tr>
<tr>
<td>Extension to external iliac artery</td>
<td>Yes vs. No</td>
<td>1.91 (0.49–7.52)</td>
<td>.35</td>
</tr>
</tbody>
</table>
the completion angiography is performed with the stiff wire in place. Therefore, it is recommended that the completion angiogram should be performed without stiff wires present. In this series, no severe limb kinking was recognized on the final angiogram.

Patients included in this study were treated using four types of endograft. There was no statistically significant difference in the incidence of limb thrombosis between the different types of endografts (p = .20), but this may be attributed to the small sample size. However, some characteristics of the endograft may be associated with limb thrombosis. The main graft related cause of limb occlusion is lack of support within the structure of the endograft. Limb occlusion in the Guidant Ancure graft had been described several times. During the short term follow up, excessive iliac oversizing has been recognized as a predisposing factor for limb thrombosis in this study. Excessive oversizing of the endograft may lead to inolding of the endograft limb into the vessel lumen. This is also supported by the fact that oversizing of an iliac limb by 4 mm led to a 12-fold increase in graft limb dysfunction.

Limited experience and lack of long term follow up makes decisions for the optimal treatment of endograft limb thrombosis difficult. Both surgical and endovascular options are available. Surgical options include thrombectomy and extra-anatomic bypass graft. There are however concerns about the possibility of graft damage or dislodgement and endoleak during thrombectomy. On the other hand, this argument was not validated by a series in which no endoleak or graft dislodgement occurred despite using thrombectomy in modular graft designs. Early experience tended towards extra-anatomic bypass, mainly femoral–femoral bypass. Endovascular options include thrombolysis and balloon angioplasty or stenting and recent reports have encouraged an endovascular approach with or without thrombolysis. The majority of patients presenting with a delayed (more than 15 days) limb thrombosis were treated with a femoral–femoral bypass. In four cases of early occlusion, endograft limb thrombectomy was successfully performed and thereafter a stent was placed to correct the cause of thrombosis. During the follow up period two patients with a previous femoral–femoral bypass due to limb thrombosis required re-intervention and were treated with an axillo-femoral bypass graft.

Among the strengths of a case control design is the simultaneous exploration of multiple risk factors and its power to investigate potential associations that are difficult to be identified in case series. Furthermore, the number of controls was increased to three for each case in order to improve the ability to find important differences. Limitations of the current study may include a small study sample, however, the case control design allowed for robust findings. A non-statistically significant difference in the incidence of endograft limb occlusion was noted between the different types of endografts. However, this could be due to the small sample size. Furthermore, a difference in follow up time, although not statistical significant was recorded between cases and controls. In addition, in the multivariate analysis time was not controlled, and a significant effect of time was not recorded. As a result, the findings remained robust. On the other hand, in order to fully take into consideration the effect of time on the probability of limb occlusion, future studies should incorporate a prospective cohort design.

CONCLUSION
Endograft limb thrombosis occurred in 4% of the patients who underwent EVAR. The presence of significant angulation and calcification of the iliac arteries, as well as excessive endograft limb oversizing appear to be independent predictors of endograft limb occlusion.

CONFLICT OF INTEREST
None.

FUNDING
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REFERENCES
5. Sivamurthy N, Schneider DB, Reilly LM, Rapp JH, Skovobogaty H, Chuter TA. Adjunctive primary stenting of


