Postoperative Fever, Bowel Ischaemia and Cytokine Response to Abdominal Aortic Aneurysm Repair – a Comparison Between Endovascular and Open Surgery

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Objectives: To study bowel ischaemia in transfemorally placed endoluminal grafting (TPEG) for abdominal aortic aneurysms, and any relation to cytokine response or postoperative fever.

Design: Prospective not randomised. University hospital setting.

Material: Fourteen cases of conventional surgery and 23 cases of endovascular technique for infrarenal abdominal aortic aneurysm repair.

Methods: Tonometry was used for sigmoid colon pH, and ELISAs for serum IL-6.

Results: Mucosal pH in the sigmoid colon fell significantly during clamping and reperfusion in both groups. Lowest measured sigmoid colon pH was 7.10 in the open group, compared to 7.22 in the TPEG group (p<0.05). The IL-6 levels in serum peaked after 4h of reperfusion; 249 pg/ml in the open group, compared to 89 pg/ml in the TPEG group (p<0.05). High levels of IL-6 in the postoperative period and persisting low sigmoidal pH were associated with serious complications.

Postoperative temperature did not differ significantly between the groups, and no significant correlation could be found with sigmoid colon pH or IL-6 levels.

Conclusions: The less pronounced perioperative bowel ischaemia in TPEG patients indicates an advantage of the TPEG technique. Splanchnic ischaemia was not related to postoperative fever, nor the IL-6 or TNF response.

Key Words: Vascular surgery; Endoluminal grafts; Cytokines; Ischaemia; Fever.

Introduction

Non-infectious fevers after major surgery and trauma are well recognised. When endovascular techniques for abdominal aortic aneurysm repair were introduced, a postoperative fever of uncertain origin was noted, despite a minimally invasive approach. It is reported that splanchnic ischaemia promotes bacterial translocation, and endotoxaemia is a stimulus for the release of cytokines such as interleukin-6 (IL-6) and tumour necrosis factor (TNF), which are capable of producing fever. Hence, splanchnic ischaemia could be a source of the reported postoperative fever.

Cytokines are important mediators of the local inflammatory response, triggering a cascade of reactions including chemotaxis and activation of leukocytes, T cells and NK cells. Moreover, IL-6 is reported to induce the production and release of C-reactive protein (CRP). Circulating IL-6 has been reported after major surgery and trauma, the serum levels correlating to the magnitude of trauma. TNF has been found sporadically in aortic or other major surgery, but frequently in cases of a bacterial challenge or post-traumatic infectious complications. Endotoxaemia has been reported in aortic surgery and septic conditions, and is a stimulus for TNF and IL-6 release. A prolonged or enhanced IL-6 or TNF response in the postoperative/post-traumatic period is a bad prognostic sign.

Open surgery for aortic aneurysms requires clamping of the aorta, which implies a risk of splanchnic ischaemia. With transfemorally placed endoluminal grafts (TPEG), clamping of the aorta is not required. Hence, this technique might lead to less intraoperative...
Table 1. Perioperative white blood cell count and blood platelet concentration as median with range.

<table>
<thead>
<tr>
<th></th>
<th>White blood cell count, (10^9/1)</th>
<th>Platelet concentration ((10^9/1))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperatively</td>
<td>4 h of reperfusion</td>
</tr>
<tr>
<td>TPEG</td>
<td>7.3 (5.9-9.4)</td>
<td>11.6 (6.6-19.1)</td>
</tr>
<tr>
<td>Open</td>
<td>7.9 (5.8-12.2)</td>
<td>11.4 (6.1-20.9)</td>
</tr>
<tr>
<td>Statistical significance</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>All</td>
<td>7.5 (5.1-12.2)</td>
<td>11.5 (6.1-20.9)</td>
</tr>
</tbody>
</table>

Splanchnic ischaemia, but this has not been studied before. Irrespective of what method is used, occlusion of a patent inferior mesenteric artery increases the risk of postoperative ischaemia in the sigmoid colon – especially when flow through the internal iliacs is compromised.

Severe ischaemia with development of bowel gangrene is reported in 1–3% of cases following open aortic surgery, and the rate of less pronounced ischaemia is unknown. Ischaemia reperfusion injury triggers complex reactions, which may lead to adult respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS). A threshold for pH in the sigmoid colon around 7.00 has been reported, below which postoperative morbidity and mortality increases after aortic surgery.

By measuring intraluminal pCO₂ which is in equilibrium with mucosal pCO₂, pH in the sigmoid mucosa can be calculated by a well-established method. This gives a good indication of hypoxia.

Ischaemia reperfusion injury in the splanchnic region and in the lower extremities triggers the release of IL-6 and TNF. High levels of IL-6 and TNF in the systemic blood stream induce severe systemic adverse reactions. TNF induces a shock response, with a dramatic fall in blood pressure and peripheral perfusion. In the pulmonary vascular bed, IL-6 and TNF upregulate the endothelial expression of adhesion molecules (ICAM and LECAM), leading to a sequestration of leukocytes in the lungs, and an increased permeability for macromolecules. Migration of leukocytes through the endothelium occurs, and a flow of macromolecules follows, leading to ARDS. Similar changes occur in the kidneys and myocardium, leading to MODS.

Pretreatment with antibodies to TNF-a and IL-6 in experimental models prevents remote organ injury indicating the pathogenic role of cytokines.

The aim of the present study was to compare the degree of bowel ischaemia in conventional surgery and TPEG procedure for AAA, and to study any correlation between postoperative fever or bowel ischaemia and cytokine release.

Material

Thirty-seven patients treated for an infrarenal abdominal aortic aneurysm (AAA) were included in the study; 23 with the TPEG technique (14 aortoiliacal + fem–fem cross-over; eight aortobifemoral; one tube graft) and 14 by conventional open technique (seven straight; seven bifurcated grafts), in seven cases via a standard transperitoneal approach and in six cases via an extraperitoneal approach. All patients with a proximal neck (distance from renal arteries to the start of the aneurysm) of 10 mm or more were considered for TPEG procedure, whereas patients with a neck shorter than 10 mm were treated by conventional open surgery. The groups did not differ in age or gender distribution. Median age was 71 in both groups (range 55–84 in the TPEG group; 59–81 in the open surgery group); female:male ratio was 1:22 and 2:1 respectively in the groups (Table 2). The median size of aneurysm on preoperative CT scan was 55 cm in both groups, ranging between 45–79 mm in the TPEG group and 45–85 mm in the open surgery group. Irrespective of surgical technique, infrarenal repair with Woven Dacron, Cooley Very Soft grafts (Meadox, Boston Scientific; Boston, U.S.A.) were used. In the TPEG cases, stainless steel Gianturco stents (Cook; Baesgsved, Denmark) and stainless steel Wallstents (Schneider; Bülach, Switzerland) were used.

Both groups had a combination of general anaesthesia (thiopental, fentanyl, atracurium, N₂O) and...
epidural anaesthesia (Thl0–L1 with bupivacain or me-
pivacain). Low molecular weight heparin (40 mg Klex-
ane®) was given routinely as thrombosis prophylactics
in both groups, and intravenous infusion of kloxacinill
(three doses of 2 g) was given as infection pro-
phylactics. There were no differences in paracetamol
or NSAID consumption between the groups in the
postoperative period, and no patient was given cortico
steroids.

Methods

The night before surgery an enema was given, and
prior to surgery a tonometer catheter from Ton-
ometrics® inc, Worcester, MA, U.S.A., was placed in
the sigmoid colon by rigid sigmoidoscopy, and in the
stomach as a nasogastric tube and left in place for
24–48 h postoperatively. Tonometers have a semi-per-
amable balloon, allowing CO₂ to pass freely over the
membrane – thus making it possible to measure pCO₂
in the lumen of the gastrointestinal tract. Mucosal
pCO₂ is in equilibrium with intraluminal pCO₂, and
knowing the arterial HCO₃⁻, mucosal pH can be cal-
culated by the Hasselbach–Hendersson equation.
Blood samples were taken peripherally for analysis of
systemic serum levels of IL-6, TNF-a and C-reactive
protein (CRP) at the following intervals: before sur-
gery; at surgery but before clamping or placement of
the proximal stent; 1 h after clamping or placement of
stent; at maximal ischaemia (i.e. just before distal
declamping); after 4h and 24 h of reperfusion and
then daily for 6 days in the postoperative period.
Splanchnic pH measurements were done at the same
intervals, but were aborted after 48 h, unless there was
persisting sigmoid colon ischaemia, in which case a
72 h measurement was performed. Commercial ELISAs
(Endogen/Electrabox; Tyresö, Sweden) were utilised
for analysis of cytokines. Several samples were double
checked for TNF with ELISAs from Innogenetics;
Zwijndrecht, Belgium and R&D systems; Minneapolis
U.S.A. One batch of samples was checked in an in-
dependent laboratory with R&D ELISA. CRP analysis
were done by turbidometry, as routine in the hospital
chemical laboratory.

Peripheral blood samples were taken for white blood
cell count (WBC); haemoglobin concentration (Hb);
platelet concentration; serum levels of sodium (S-Na),
potassium (S-K) and creatinin (S-Crea) on a daily
basis. Blood-cultures were taken after 24 and 48 h of
reperfusion and in the case of shivering or high fever.
Temperature and clinical signs of ischaemia were re-
corded repeatedly in the postoperative period.

Blood loss was estimated by the anaesthetist, by
measuring the content of the suction bottles and the
number of towels used. Bloodsavers were used in 12
of the 14 conventionally operated patients, giving back
400–2800 ml of blood. In no case was preoperative
blood donation for later autotransfusion used.

For statistical analysis the Mann–Whitney U-test
was used for non-paired data and the Wilcoxon signed
rank test for paired data, for which p<0.05 was con-
sidered as statistically significant. For correlation tests,
the Pearson test was used when measured values
showed a narrow range; in all other cases the Spearman
test was used. A strong correlation was considered
when R/Rho ≥ 0.8; a moderate correlation when
0.8>R/Rho > 0.4; and a weak correlation when 0.4>R/
Rho ≥ 0.2. All data are presented as median with range.

Results

Ischaemic time in the lower extremities (time until
declamping of the last leg) was significantly longer in
the TPEG group; 121 min (27–315 min) compared to
59 min (24–115 min) in the conventionally operated
group, but total time of operation did not differ be-
tween the groups (220 and 235 min, respectively). Me-
dian peroperative blood loss was 300 ml (100–2500 ml)
in the TPEG group, which was significantly less than
the 1500 ml (400–5300 ml) in the conventional surgery
group. A drop in haemoglobin concentration of 25
and 24 g/l in the two groups, respectively, was noted
after the end of the operation. A significant fall in
platelet concentrations at the time of maximal isch-
aemia was noted in both groups. The decrease re-
mained through the postoperative period and was
significantly less pronounced in the TPEG group, with
a maximal decrease from base line from 207 to 103,
compared to 209–103 in the open group. A moderate,
but significant (p = 0.0001), rise in the white blood cell
count from 7.9 to 11.6 and 7.4 to 11.4 x 10⁹ c/l after 4 h
of reperfusion, was noted in the TPEG and open group
respectively – a non-significant difference between the
groups (see Table 1).

Three perioperative deaths occurred, all in the TPEG
group. Two patients died of MODS in the postoperative
period; in one case following a large myocardial in-
farction at operation, with subsequent severe cardiac
failure, leading to uraemia, liver failure and death at
day 17. No autopsy was performed at the request of
the relatives. The second case of MODS developed
following ventricular fibrillation at operation, which
was corrected, but postoperatively he remained in
coma and developed pronounced hepatic failure and
died in progressive multiple organ failure. Autopsy showed disseminated intravascular coagulation, hepatic necrosis and congestion in lungs and splanchnic organs. Both patients had previously been judged unfit for conventional aortic surgery, due to their cardiac disease. The third patient died at home 3 weeks after surgery. No autopsy was done in this case. No diarrhoea, rectal bleeding or abdominal pain, indicating bowel ischaemia, was recorded in any of these cases.

Two patients in the conventional surgery group developed severe intestinal ischaemia requiring resection of the sigmoid colon and small intestine, respectively. Both patients had an uneventful recovery, but one of them died after 12 months from complete intestinal gangrene. None of them had a patent inferior mesenteric artery, and the patient who developed sigmoid colon gangrene had an occluded internal iliac artery on the left side as well. No reconstruction was made at operation. Two patients in the conventional surgery group developed postoperative ischaemia in the lower extremities, requiring acute unilateral femoropopliteal grafting.

All blood cultures were negative at all measure points.

**Mucosal pH**

A non-significant decrease in mucosal pH in the sigmoid colon was noted during surgery, with the lowest levels just before reperfusion: 7.28 (7.00-7.43) in the TPEG group and 7.16 (6.95-7.43) in the conventionally operated group – a statistically non-significant difference. After 4 h of reperfusion a significant decrease in the pH of the sigmoid colon was noted in the open group; 7.25 (6.85-7.39), but not in the TPEG group; 7.29 (7.00-7.50) (Fig. 1). The lowest perioperative sigmoid colon pH noted in each patient was significantly lower in the open group compared to the TPEG group; 7.10 (6.82-7.37) vs. 7.22 (6.96-7.38).

Patients with a bad outcome (perioperative death or bowel gangrene) had significantly lower sigmoidal pH after 4 h of reperfusion; 7.18 (6.85-7.22) compared to 7.29 (7.00-7.50) in patients without these complications (p<0.05).

A non-significant decrease in gastric mucosal pH from 7.40 and 7.42 before surgery to 7.34 and 7.39 at maximum ischaemia was noted, in the open and TPEG groups, respectively. After 4 h of reperfusion there was a moderate but statistically significant decrease in pH to 7.35 in both groups (Fig. 2).

**IL-6**

Median basal levels of IL-6 did not differ between the groups; 13.5 pg/ml (0-117) and 0 pg/ml (0-64) in the TPEG and open group, respectively. During surgery serum levels of IL-6 gradually rose, peaking after 4 h of reperfusion. This pattern was similar in both groups (Fig. 3), but the response was significantly higher in the conventionally operated group; with median IL-6 levels in serum after 4 h of reperfusion of 249 pg/ml (67-3760) compared to 89 pg/ml (0-443) in the TPEG group.
Fig. 3. Perioperative IL-6 (interleukin-6) response was significantly higher in the open group. Peroperative 1 = before clamping or stent; peroperative 2 = 1 h after placement of stent or clamping; 3 = just prior to distal declamping. Horizontal line is median; 25-75% percentile within boxes; 10-90% percentile within vertical lines. □ TPEG; □ OPEN.

A statistically weak correlation was noted between the perioperative blood loss and IL-6 levels after 4 h of reperfusion (Rho = 0.39; p = 0.021). In the TPEG group a moderate correlation was noted between maximum ischaemic time in the lower extremities and IL-6 levels after 4 h of reperfusion (Rho = 0.41; p = 0.11), whereas in the open group no such correlation was noted (Rho = 0.073; p = 0.8).

From the first postoperative day and onwards, the serum levels of IL-6 were significantly higher in patients who developed major complications (i.e. MODS or bowel gangrene). By day 3, median IL-6 levels in sera from patients with uneventful postoperative periods were close to baseline (27 pg/ml; 0-88). In the complication group, however, the median IL-6 levels postoperative at day 3 were 280 pg/ml (84-18 000), (p < 0.01).

**TNF**

No significant release of TNF into the systemic circulation was noted. No sample contained over 25 pg/ml, which was considered the level of significant release.

**CRP**

The median serum level of C reactive protein (CRP) was <20 mg/l in both groups before and during surgery, but rose the day after surgery to 91 mg/l (76-159) in the TPEG group and 118 mg/l (71-149) in the group with open surgery. During the next 2 days median CRP levels gradually increased in both groups, peaking on the postoperative day 3 at 184 mg/l (91-320) and 128 mg/l (123-240) in the TPEG and conventionally operated groups, respectively (Fig. 4). No significant differences in CRP levels were seen between the groups.

**Temperature**

Postoperative temperature was moderately increased in both groups, without any significant differences between the groups at any measure point. Median peak postoperative temperature in the TPEG was 38.4 °C (37.4-39.6) and in the open group 38.5 °C (37.7-39.6) - a non-significant difference (Fig. 5).  

**Correlations between main variables**

No correlations were found between IL-6 response, CRP response, splanchnic pH or postoperative temperature. For a summary of results see Table 2.
Table 2. Patient material and summary of results as median and range.

<table>
<thead>
<tr>
<th></th>
<th>n Female</th>
<th>Age (years)</th>
<th>Length of operation (min)</th>
<th>Peroperative blood loss (mls)</th>
<th>Leg ischaemia (min)</th>
<th>Peak IL-6 (pg/ml)</th>
<th>Lowest sigmoid colon pH</th>
<th>Lowest gastric pH</th>
<th>Peak postoperative temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPEG</td>
<td>23 1:22</td>
<td>71 (55-84)</td>
<td>220 (120-390)</td>
<td>300 (100-2500)</td>
<td>121 (27-315)</td>
<td>150 (36-18 000)</td>
<td>7.22 (6.96-7.38)</td>
<td>7.32 (7.11-7.43)</td>
<td>38.4 (37.4-39.6)</td>
</tr>
<tr>
<td>Open</td>
<td>14 2:12</td>
<td>71 (59-81)</td>
<td>235 (135-367)</td>
<td>1500 (400-5300)</td>
<td>59 (34-115)</td>
<td>370 (95-3760)</td>
<td>7.10 (6.82-7.38)</td>
<td>7.30 (6.99-7.38)</td>
<td>38.5 (37.7-39.6)</td>
</tr>
<tr>
<td>Statistical significance</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>p&lt;0.001</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>All</td>
<td>37 3:34</td>
<td>71 (55-84)</td>
<td>220 (100-5300)</td>
<td>104 (27-315)</td>
<td>172 (36-18 000)</td>
<td>7.18 (6.82-7.38)</td>
<td>7.30 (6.99-7.43)</td>
<td>38.5 (37.4-39.6)</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

Bowel ischaemia is a well known complication of aortic surgery. In this study it was found that endoluminal grafting for AAA leads to perioperative bowel ischaemia, but to a lesser extent than does open surgery. It was hypothesised that perioperative ischaemia could disrupt the bacterial barrier of the bowel, leading to bacterial translocation and the release of endotoxin, in turn triggering the release of cytokines, such as IL-6 and TNF. These are both pyrogens, and could be possible mediators of the non-infectious postoperative fever following the TPEG procedure. In the present study no significant differences in postoperative temperature were seen between the groups. The median peak postoperative temperature were 38.4 °C and 38.5 °C in the TPEG and conventionally operated groups, respectively.

Median peak serum levels of IL-6 were more than twice as high in the conventionally operated group, but mean peak postoperative temperature were the same in both groups, and no correlation between serum levels of IL-6 and temperature was noted. Hence IL-6 seemed not to be the cause of postoperative fever.

No blood culture, at any measure point or at shivering, yielded bacterial growth. Unfortunately, for technical reasons, it was not possible to measure endotoxin in the present study, thus leaving the question of endotoxaemia as a cause of the non-infectious postoperative fever still open. However, the absence of both any bacteraemia and any TNF response indicates a non-infectious genesis of the postoperative fever. One possible source is thrombosin, which will be addressed in a separate study.

The induction of TNF response seems to be complex. While Swartbol and co-workers have reported a TNF response in endoluminal but not in open aortic surgery, and suggested this is influenced by graft material, no significant NF response was detected in the present study. The absence of positive TNF analysis was checked by using ELISAs from different manufacturers and by another laboratory verifying the same negative results. Baigre and co-workers did not detect any TNF in portal blood, despite a positive endotoxin test in five out of eight patients operated on for AAA, whereas Cabié and co-workers did. In the present study, the lowest sigmoid colon pH was 7.10 in the open group and 7.22 in the TPEG group, which may not be enough to evoke a TNF or IL-6 response. Studies by Schlichting et al. showed no endotoxin or bacterial translocation in experimental bowel ischaemia in pigs, with pH below of 6.9 and below. Caty et al. has shown that total clamping of the superior mesenteric artery for 60 min was not enough to provoke an endotoxin and cytokine release in rats, whereas clamping for 120 min did, and Froon and co-workers did not detect any TNF in electively operated AAA patients, but it was present in half of the patients undergoing surgery for ruptured AAA. The timing of sampling could also be a possible explanation for the differences in results. In the present series, the first sampling in the reperfusion period was after 4 h, whereas in the Swartbol series the peak level was noted after 60 min reperfusion, and only minor amounts were noted at the other measurepoints.

The ischaemic time in the lower extremities were moderate, but significantly longer in the TPEG group; 121 min vs. 59 min. In the TPEG group a moderate correlation (R=0.41) to IL-6 levels after 4 h of reperfusion was noted, indicating ischaemia reperfusion injury in the lower limbs as being one possible origin for the IL-6 release in TPEG for AAA, whereas in the group of open surgery this was of minor importance. Most likely the IL-6 response in the group of open surgery was evoked by the surgical trauma per se. A correlation between IL-6 levels and the degree of trauma; length of operation; amount of blood loss, has been reported by several groups. In the open group a significantly higher peroperative blood loss was
noted; 3100 ml vs. 350 ml in the TPEG group, with a moderate correlation to IL-6 levels before and after 4 h of reperfusion. The lower postoperative platelet concentrations noted in the open group can possibly be explained by consumption of platelets and more transfusions given in this group, due to the higher blood loss.

Later in the postoperative period IL-6 levels did not correlate to perioperative blood loss or ischaemia but were strongly associated with serious complications. Serum levels of IL-6 on postoperative day 3 and 4 extending 100 pg/ml were in the present series associated with serious complications in 100%, whereas no patient with IL-6 levels <100 pg/ml on postoperative day 4 onwards developed a serious complication.

Impaired bowel perfusion was also associated with bad outcome, shown as a significantly lower sigmoid pH after 4 h of reperfusion in patients who later developed life threatening complications compared to patients without such complications. Thus both serum IL-6 and sigmoidal pH may serve as useful predictors of serious complications in the postoperative period. Probably, this is due to their pathogenic role in remote organ injury. Any risk with high intraoperative IL-6 levels (as in the open group in this study) is not known, however.

IL-6 has been reported to be a trigger of CRP release, but in the present study no correlation (Rho = 0.019) between IL-6 and CRP levels was found. Thus the CRP response seemed to have been triggered by an alternative pathway, independent of IL-6.

**Conclusions**

TPEG procedure for AAA is associated with reduced trauma to the patient with a significantly lower perioperative blood loss and a significantly lower IL-6 response in serum compared to conventional surgery. The less pronounced perioperative bowel ischaemia noted in TPEG patients in this study indicates an advantage of the TPEG technique.

Postoperative temperature did not differ between the groups, and seemed not to be triggered by IL-6, bacteraemia or associated with bowel ischaemia. No correlation was noted between high postoperative fever and a bad outcome.

A persisting decrease in sigmoidal pH in the early postoperative period, or a remaining rise of serum IL-6 levels later in the postoperative period, may serve as valuable predictors of serious complications in the postoperative care of patients treated for AAA, irrespective of which method is used.

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**References**


Responses to AAA Repair


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