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Inflammatory mediators after endovascular aortic aneurysm repair

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ABSTRACT

Objective: To evaluate patterns of inflammatory mediators before and after elective endovascular aortic aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA).

Materials and methods: Inflammatory mediators including soluble urokinase plasminogen activator (suPAR), endothelin (ET)-1, tumour necrosis factor (TNF)-α, interleukin (IL)-6, CD40 ligand (CD40L) and IgM antibodies against phosphorylcholine (IgM anti-PC), were evaluated before and after elective EVAR in 21 patients. Five patients undergoing open AAA repair (OR) were evaluated for comparison.

Results: SuPAR ($p < 0.001$), ET-1 ($p = 0.003$) and IL-6 ($p = 0.02$) increased whereas IgM anti-PC decreased ($p < 0.001$) after EVAR. Both suPAR ($p = 0.04$) and IL-6 ($p = 0.03$) increased in the five patients with unchanged/expanded aneurysm sac after EAR, whereas only suPAR increased ($p = 0.04$) and IL-6 remained unchanged ($p = 0.2$) among the 16 patients with shrinking aneurysm sac. No difference was noted between patients undergoing EVAR and OR regarding levels or changes of studied markers.

Conclusions: These changes in plasma biomarker profile are compatible with on-going inflammatory activation in AAA patients after EVAR. The potential role of IL-6 as a plasma biomarker for treatment failure in surveillance programs after EVAR needs to be further evaluated.

1. Introduction

Abdominal aortic aneurysm (AAA) mainly affects males and is a common and potentially life threatening condition due to the risk for aneurysm rupture [1]. The pathophysiologic mechanisms involved in the development and growth of AAA are multifactorial; previous studies have shown associations with inflammatory activity, changes in coagulation, endothelial dysfunction as well as with the classical risk factors of atherosclerosis [2–5].

Patients with large AAAs can undergo either open (OR) or endovascular (EVAR) aneurysm repair to prevent rupture. The long-term effects of EVAR on systemic inflammatory mediators remain poorly understood. The retention of a biologically active mural thrombus and aneurysm sac following EVAR may be a source of inflammatory mediators, which may influence postoperative protection against aneurysm sac expansion and rupture and overall cardiovascular morbidity [6]. It may also lead to clinical failure, and increase the risk of reintervention [6]. Postoperative levels of inflammatory mediators may also be useful markers of cardiovascular disease activity.

The inflammatory activity in AAA is reflected in increased values of several different inflammatory mediators [2]. One of these is glycosylphosphatidylinositol phospholipase D (GPI-PLD), which is an enzyme that cleaves the GPI anchor of the urokinase plasminogen activator receptor (uPAR), forming a free suPAR. SuPAR is involved in tissue remodelling [7,8] and is a marker of low-grade inflammation associated with risk of developing cardiovascular disease [9]. Endothelin (ET)-1 is a potent vasoconstrictor regulating release of vasoactive substances and stimulating muscle cell mitogenesis [10,11]. It has a putative role in the pathogenesis of atherosclerosis and might also be associated with aneurysm growth [12]. Tumour necrosis factor (TNF)-α [13,14] and interleukin (IL)-6 [15–18] are pro-inflammatory cytokines in the acute phase inflammatory response, and involved in both atherogenesis and AAA development [19]. CD40L is a key mediator in B-cell activation and is also increased in cells involved in the atherosclerotic process [20,21]. IgM anti-PC, on the other hand, are natural antibodies against oxidised low-density lipoprotein (oxLDL), an important mediator in the development of atherosclerosis and atherogenesis [22]. Low levels of IgM anti-PC are associated with an increased risk of atherosclerotic cardiovascular disease [23–25], but the marker has not yet been evaluated in patients with AAA.

The main aims of this study where to evaluate potential relationships between levels of suPAR, ET-1, TNF-α, IL-6, CD40L, IgM anti-PC and aneurysm sac size change after elective EVAR for AAA. A small group of patients undergoing open surgery for AAA was studied for comparison.

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2. Methods

2.1. Patients

We studied AAA patients included in a scientific follow-up program at the Vascular Centre, Malmö University Hospital [26]. Among 57/206 study patients undergoing elective AAA repair between 2003 and 2010, 26 consented to a postoperative follow-up blood sample and were included in the present study in which pre- and postoperative laboratory analyses and repeated computed tomography (CT) scans were evaluated. Among EVAR patients ($n = 21$), 14 underwent standard EVAR and seven underwent fenestrated EVAR (FEVAR). Five patients undergoing open aneurysm repair (OR) were analysed for comparison.

2.2. CT scan

The maximal AAA diameter was defined as the smallest transverse diameter at the widest portion of the aneurysm. A preoperative diameter of >55 mm was defined as "large", 45–55 mm as "medium" and <45 mm as "small". All AAA contained a thrombus at the preoperative CT scan.

The desired effect of EVAR is postoperative aneurysm shrinkage, and EVAR patients were evaluated in this respect with a postoperative CT scan after a median follow up of 53 (44–77) months. Expansion or shrinkage after EVAR was defined as a maximal AAA diameter change of $\geqslant 5$ mm, respectively, compared to preoperative CT images [27]. EVAR patients with postoperative AAA shrinkage at CT scan ($n = 16$) where defined as group 1, and patients with unchanged ($n = 3$) or increased ($n = 2$) postoperative AAA diameter ($n = 5$) as group 2.

2.3. Laboratory markers

Samples were stored at −80 °C and analysed together. Laboratory markers where analysed both pre- and postoperatively. Median time to postoperative sampling was 63 (IQR 37–82) months and mean time was 62 (SD ± 27) months. The suPARnostic® ELISA kit (Virogates, Denmark) with a detection limit of 0.1 ng/ml, and intra- and inter-assay coefficients of variability (CVs) of 2.9% and 2.8% was used for quantitative determination of suPAR in human EDTA-plasma. IgM anti-PC was analysed using the CVDefine® immunoassay (Athera Biotechnologies AB, Sweden), with detection limit of 0.5 U/ml and intra- and inter-assay CVs of 5.2% and 1.0%. Levels of IL-6, CD40L and ET-1 in EDTA-plasma were analysed with Quantikine®ELISA kits (R&D Systems Europe Ltd., United Kingdom). Detection limits of IL-6 and CD40L were <0.7 pg/ml and 4.2 pg/ml, and intra- and inter-assay CVs were 4.2% and 3.3% and 5.1% and 6.4%, respectively. ET-1 detection limit was 0.09 pg/ml, and intra- and inter-assay CVs were 4.0% and 7.6%. Levels of TNF-α were analysed with Quantikine® high sensitivity ELISA kit (R&D Systems Europe Ltd., United Kingdom), with a detection limit of 0.11 pg/ml, and intra- and inter-assay CVs of 8.5% and 7.3%. CVs given are data from the manufacturer.

2.4. Other definitions

Diabetes mellitus was defined as ongoing anti-diabetic treatment (diet, oral hypoglycaemic agents, or insulin) or fasting blood glucose level $\geqslant 7.0$ mmol/l. Anaemia was defined as haemoglobin <134 g/L in men, and <117 g/L in women. Hypertension was defined as ongoing antihypertensive medication, and uncontrolled hypertension as systolic blood pressure (BP) > 140 mmHg or diastolic BP > 90 mmHg (systolic BP > 130 mmHg or diastolic BP > 80 mmHg in patients with diabetes mellitus). Peripheral vascular disease was defined as intermittent claudication, critical ischemia or previous revascularization. Cardiovascular disease was defined as ischemic heart disease or congestive heart failure. Both current and former smokers were classified as smokers.

2.5. Statistical methods

SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for data managing and statistical analysis.

Results are expressed as median and inter-quartile range (IQR), mean and standard deviation (SD) or number (%). Differences between the two groups were tested by the Mann–Whitney U test. Analyses within groups were carried out using Wilcoxon signed-rank test. Correlation between variables was evaluated by Pearson's Correlation analysis. $P < 0.05$ was considered as significant.

2.6. Ethical approval

The Ethical Committee of Lund University approved the study and all patients accepting gave written consent to participate in the study.

3. Results

3.1. Patient characteristics

Twenty-six patients (23 [89%] men) with a median age of 74 (IQR 69–78) years were included in this study. Twenty-three (88%) were smokers and 20 (77%) suffered from hypertension. At a preoperative CT scan, 12 (46%) patients had medium sized AAA, whereas nine patients had large aneurysms. Five patients had small AAAs and were operated because of either rapid growth or symptomatic AAA (Table 1).

3.2. Preoperative correlations between laboratory markers and AAA diameter

A significant inverse correlation ($r = -0.41$, $p = 0.04$) was found between preoperative level of suPAR and AAA diameter, whereas no significant correlations were found between AAA diameter and preoperative levels of IgM anti-PC, CD40L, IL-6, ET-1 or TNF-α (Table 2).

3.3. Pre- and postoperative levels of laboratory markers

Among EVAR patients, levels of suPAR increased significantly after EVAR (from 5.4 [4.3–6.5] ng/ml to 7.3 [5.8–8.0] ng/ml; $p < 0.001$). Likewise ET-1 ($p = 0.003$), and IL-6 ($p = 0.02$) also increased significantly after EVAR, whereas IgM anti-PC decreased

Table 1
Characteristics of 26 patients undergoing elective AAA repair.

Variable	*N* (%)
EVAR/OR	21 (81)/5 (19)
Male gender	23 (89)
Smokers	23 (88)
Arterial hypertension	20 (77)
Cardiovascular disease	8 (31)
Previous ischemic stroke	3 (12)
Peripheral arterial disease	5 (19)
Diabetes mellitus	3 (12)
Anaemia	10 (39)
Aneurysm maximal diameter (mm)	
Large (>55)	9 (35)
Medium (45–55)	12 (46)
Small (<45)	5 (19)