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Interleukin-10 Appearance Following Thoraco-abdominal and Abdominal Aortic Aneurysm Repair is Associated with the Duration of Visceral Ischaemia

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Objectives: *to evaluate the plasma IL-10 levels during elective operative repair of thoraco-abdominal and abdominal aortic aneurysm repair. To study whether IL-10 plasma levels are associated with the duration of cross-clamping (ischaemia) and clinical outcome.*
Materials: *fifteen consecutive patients undergoing surgery for TAAA and 10 consecutive patients undergoing surgical repair of AAA were included.*
Methods: *plasma concentrations of IL-10 were measured by ELISA technique. Clinical outcome of the TAAA patients was prospectively analysed.*
Results: *during aortic clamping IL-10 was produced in both populations. The plasma IL-10 peak (934 ± 172 pg/ml) of the TAAA group was seen at 4 h after declamping and remained detectable after 48 h. The plasma IL-10 peak (212 ± 32 pg/ml) of the AAA group was seen 30 min after declamping and fell to undetectable levels by 24 h. These data show that the peak IL-10 plasma levels in TAAA repair are significantly ($p<0.05$) higher compared to the peak IL-10 plasma levels as seen during AAA repair. A positive correlation was seen between cross-clamping and peak plasma IL-10 and organ dysfunction.*
Conclusions: *IL-10 plasma concentrations appear higher, later and are longer detectable in patients undergoing TAAA. Correlations were seen with duration of cross-clamping and MSOD.*

Key Words: IL-10; Visceral ischaemia; Aortic aneurysm.

Introduction

Aneurysmal disease most commonly involves the infrarenal aorta and less frequently the thoracic and/or suprarenal abdominal aorta. While repair of infrarenal abdominal aortic aneurysms (AAA) results in an operative mortality of 2–5%,[1] repair of thoraco-abdominal aortic aneurysms results in significantly higher rates of mortality (5–25%).[2,3] In addition, patients undergoing operative repair of thoraco-abdominal aortic aneurysm experience an increased frequency of pulmonary dysfunction (20–47%), renal dysfunction (20–30%), and spinal cord injury (5–15%).[4–6] These high rates of morbidity and mortality may be related to gastrointestinal ischaemia-reperfusion injury secondary to the suprarenal cross-clamping.[7]

Animal studies have demonstrated that gastrointestinal ischaemia-reperfusion injury provokes the release of pro-inflammatory cytokines, particularly IL-1β and TNFα.[8] Patients undergoing thoraco-abdominal aortic aneurysm repair release IL-1β, TNFα and IL-8 systemically.[9] An array of anti-inflammatory cytokines and cytokine inhibitors regulates the production and function of the pro-inflammatory cytokines. These include IL-1 receptor antagonist (IL-1ra), the shed type I (p55) and type II (p75) TNF receptors, the shed type II IL-1 receptor, IL-4, IL-10, and IL-13. Of particular interest is IL-10, a pleiotropic cytokine that regulates both macrophage and T-cell function. Specifically, IL-10 has been demonstrated to inhibit the production of IL-1α, IL-1β, IL-8, and TNFα by macrophages stimulated with LPS *in vitro*.[10] Exogenous administration of recombinant IL-10 has been demonstrated to protect against lethal endotoxaemia,[11,12] has reduced local and systemic inflammation in an intestinal ischaemia/reperfusion model,[13] and has reduced injury in a hindlimb ischaemia/reperfusion model.[14] Endogenously

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produced IL-10 attenuates the inflammatory response to a mixed flora peritonitis.[15]

The aim of this study was to compare plasma IL-10 levels following abdominal and thoraco-abdominal aortic aneurysm repair and to determine whether this correlates with the ischaemia/reperfusion injury and organ dysfunction.

Methods

Fifteen consecutive patients undergoing thoraco-abdominal aortic aneurysm repair and 10 consecutive patients undergoing infrarenal abdominal aortic aneurysm repair were evaluated. Informed consent was obtained from each patient and experimental protocols were approved by the institutional review boards at University Hospital Vrije Universiteit, Amsterdam and The University of Florida College of Medicine. Arterial blood was assayed immediately preoperatively, before the placement of the aortic cross-clamp, immediately after removal of the cross-clamp and at specific time intervals following reperfusion (0, 2, 4, 6, 24 and 48 h). Blood was collected in sterile glass tubes containing EDTA, chilled immediately, then centrifuged at 2000 rpm for 10 min. The plasma portion was then removed, placed into sterile 1.5 ml tubes, and stored at −70 °C until analyses were performed. Plasma concentrations of IL-10 were measured by ELISA using reagents provided by Schering Research Laboratories, Kenilworth, NJ, U.S.A.

The clinical outcome of the patients undergoing thoraco-abdominal aortic aneurysm repair was prospectively analysed. Organ dysfunction was defined as follows: *pulmonary dysfunction* – the requirement of positive-pressure ventilation for >7 days; *renal dysfunction* – an increase in serum creatinine of >2 mg/dl from the preoperative value; *hepatic dysfunction* – an LDH of >500 U/l and an AST >200 U/l; and *haematopoietic dysfunction* – development of a platelet count <50 000/mm^3. Patients with dysfunction of two or more organ systems were considered to have *multi-system organ dysfunction* (MSOD).

Data are expressed as means ± standard error of the mean. Statistical significance was determined by two-way ANOVA, Fisher's exact test, Pearson's correlation, and Student's *t*-test with a *p* value of less than 0.05 (two-tailed) being considered significant.

Results

The patients undergoing both abdominal aortic aneurysm and thoraco-abdominal aortic aneurysm repair produced IL-10 after reperfusion in a monophasic fashion (Fig. 1). Peak levels of IL-10 after thoraco-abdominal aortic aneurysm repair were over four-fold higher than after abdominal aortic aneurysm repair (943 ± 172 pg/ml vs. 212 ± 32 pg/ml, respectively) ($p<0.05$). In the abdominal aortic aneurysm patients, the IL-10 peak occurred 30 min after aortic declamping and fell to undetectable levels by 24 h. In contrast, peak IL-10 concentrations occurred after 4 h of reperfusion in the thoraco-abdominal aortic aneurysm patients and did not decrease to undetectable levels until after 48 h of reperfusion.

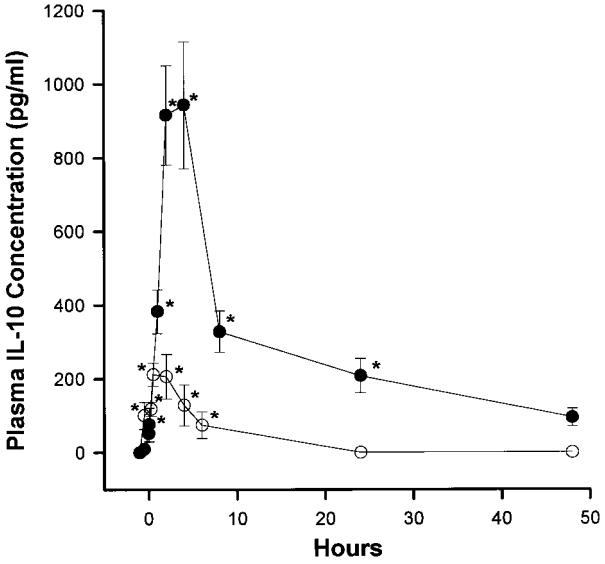

Fig. 1. Mean plasma IL-10 concentrations vs. time for patients undergoing abdominal aortic aneurysm (AAA) repair (○) and thoraco-abdominal aortic aneurysm (TAAA) repair (●). One hour prior to surgery (T = −1), time of clamp on (T = −0.5), clamp off (T = −0.25), time of closure (T = 0) and the postoperative times (T = 2, T = 4, T = 6 and T = 24). In the AAA patients, the IL-10 peak occurred 30 min after aortic declamping and the plasma concentration fell to undetectable levels by 24 h. In the TAAA patients, the IL-10 peak occurred after 4 h of reperfusion and did not decrease to undetectable levels until after 48 h of reperfusion.
* $p<0.05$.

In the patients undergoing thoraco-abdominal aortic aneurysm repair, IL-10 levels directly correlated with organ dysfunction and longer aortic cross-clamp times ($p<0.05$) (Table 1). Patients with IL-10 concentrations >950 pg/ml after 4 h of reperfusion were more likely to experience hepatic, haemopoietic and multi-system organ dysfunction. There were also higher rates of pulmonary and renal dysfunction in these patients, although these were not statistically significant. Patients with IL-10 concentrations >950 pg/ml at 4 h also had significantly longer gastrointestinal ischaemic times as determined by supracoeliac aortic cross-clamp times (60 min vs. 36 min, $p<0.05$).

Table 1. Organ dysfunction and aortic cross-clamp time vs. IL-10 concentrations measured at 4 h after cross-clamp removal in patients undergoing thoraco-abdominal aortic aneurysm repair (MSOD = multi-system organ dysfunction).

	IL-10 <950 pg/ml ($n=8$)	IL-10 >950 pg/ml ($n=7$)
MSOD	13%	86%*
Pulmonary dysfunction	25%	71%
Renal dysfunction	25%	57%
Hepatic dysfunction	0%	86%
Haematopoietic dysfunction	13%	71%
Supracoeliac cross-clamp time	36 min	60 min**

* $p<0.05$ vs. Fisher's exact test.
** $p<0.05$ by t-test.

Discussion

The present study demonstrates that IL-10 is produced after ischaemia-reperfusion injury secondary to elective abdominal aortic and thoraco-abdominal aortic aneurysm repair. In a recent study a similar IL-10 pattern was reported in patients undergoing abdominal aneurysm repair compared to controls.[16] IL-10 levels have also been reported by others to be elevated in patients with sepsis.[15,17–19]

The elevation in plasma IL-10 levels seen after gastrointestinal ischaemia-reperfusion injury and operative trauma secondary to thoraco-abdominal aortic aneurysm repair is greater and of longer duration than that observed after infrarenal abdominal aortic aneurysm repair. The infrarenal abdominal aortic aneurysm repair has less gastrointestinal ischaemia and could be seen as primarily a model of operative trauma and skeletal-muscle ischaemia-reperfusion injury. The differential response as seen between the two types of repairs may be related to the large macrophage and lymphocyte populations in both the gut and the liver which are made ischaemic by the supracoeliac aortic cross-clamping.

Although the number of patients undergoing thoraco-abdominal aortic aneurysm repair was limited, correlations were seen among IL-10 concentrations, incidence of postoperative organ dysfunction and the duration of cross-clamping.

Another study showed the correlation of IL-10 and aortic clamping time in AAA repair.[16]

Patients with IL-10 concentrations at 4 h >950 pg/ml had more postoperative organ dysfunction and longer gastrointestinal ischaemia.

These associative relationships are not meant to suggest that a systemic IL-10 response is contributory to the organ injury that develops, although that explanation cannot be ruled out. Elevated IL-10 concentrations may partially contribute to the immunosuppressive response that occurs several days after major operative trauma.[20] Conversely, the increased endogenous IL-10 response could (indirectly) reflect an exaggerated pro-inflammatory cytokine response, *in toto*, since we have previously reported that patients undergoing thoraco-abdominal aneurysm repair also have elevated plasma levels of TNFα and IL-1β.[9] The systemic IL-10 response to ischaemia-reperfusion injury could be a counter-regulatory mechanism intended to attenuate the subsequent production of systemic pro-inflammatory cytokines, such as TNFα and IL-1.[21] A similar response occurs in septic mice as blocking the endogenous IL-10 response under these conditions exacerbates the tissue injury.[15,22] It may well be that augmentation of the IL-10 response in patients undergoing thoraco-abdominal aortic aneurysm repair by administering recombinant protein perioperatively may result in organ protection and a decreased rate of organ dysfunction in the postoperative period.[23,24]

The present study confirms IL-10 production following the two types of aneurysm repair and supports the concept that there is an association between the extent of operative injury including visceral ischaemia/reperfusion and IL-10 plasma concentrations. Within its limitations we consider the correlation of IL-10 plasma levels and multi-system organ dysfunction as very interesting for future investigation.

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