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Serum concentrations of MCP-1 and RANTES in patients during aortic surgery: the relationship with ischemia-reperfusion

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Summary

Introduction:

Surgical trauma is associated with depression of the immune system, which results in a high complication rate following abdominal aortic aneurysm (AAA) repair. Monocyte chemotactic protein-1 (MCP-1) and regulated-on-activation normal T cell expressed and secreted (RANTES) protein are important mediators of the immune and inflammatory response. The aim of this study was to determine whether there is any relationship between MCP-1 or RANTES and operative injury and ischemia-reperfusion during AAA surgery in human.

Materials and Methods:

Peripheral blood samples were taken from 12 patients before surgery, after anesthesia induction, before unclamping of aorta (PreX_{off}), 90 min after unclamping (90minX_{off}), and at 24 and 48 h after surgery.

Results:

The MCP-1 and RANTES serum concentrations were measured with the ELISA technique. MCP-1 concentration significantly increased after reperfusion (90minX_{off}) in comparison with the PreX_{off} level (p=0.001). Twenty-four hours after AAA repair, MCP-1 significantly decreased 269–225 pg/ml (p=0.005) and reached preoperative value. RANTES level was higher in AAA patients before surgery than in controls (p=0.025) and decreased significantly after ischemia-reperfusion to 13 ng/ml (p<0.001) at 90minX_{off}. We showed increases in RANTES concentration to 26 ng/ml on the 1st and to 31 ng/ml on the 2nd day after surgery (p=0.020, p=0.012, respectively) compared with the 90minX_{off} level.

Conclusions:

Ischemia-reperfusion during AAA repair results in an increase in MCP-1 and decrease in RANTES concentrations in serum. The changes in chemokine concentrations may influence the development of immunosuppression after AAA repair, contributing to the post-operative course.

Key words:

aorta • aneurysm • chemokines • ischemia-reperfusion

Abbreviations:

AAA – abdominal aortic aneurysm, **APACHE** – Acute Physiology and Chronic Health Evaluation, **Induction** – induction of anesthesia, **IL** – interleukin, **MCP-1** – monocyte chemotactic protein-1, **MODs** – Multiple Organ Dysfunction score, **NK** – natural killer, **Preop** – before surgery, **PreX_{off}** – before unclamping of aorta, **90minX_{off}** – 90 min after aortic unclamping, **RANTES** – regulated-on-activation normal T cell expressed and secreted, **SOFA** – Sequential Organ Failure Assessment

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INTRODUCTION

Surgery for abdominal aortic aneurysm (AAA) is associated with a high risk of postoperative complications and mortality, ranging from 4–12% in elective to 33–60% in emergency cases^{10, 13}. Numerous factors such as age, concomitant coronary heart disease, pulmonary or renal insufficiency, blood loss, duration of surgery, and reoperation are known to be responsible for the high mortality rate after AAA repair^{10, 13}. However, the pathophysiologic disturbances that occur during ischemia and reperfusion, starting respectively with aortic cross-clamping and unclamping, are what make the operation different from others, more dangerous and unpredictable in the post-operative course¹⁰. The activation of an inflammatory response and disturbances in immune function have been demonstrated in operative^{21, 29, 31, 36} and non-operative injury^{34, 41}.

Immunological disturbances following surgery are characterized by impaired cell-mediated immunity and the involved lymphocytes, natural killer (NK) cells, granulocytes, and monocytes/macrophages^{4, 5, 16}. Experimental and human studies have shown suppression of T helper (Th)1 and monocyte cytokine synthesis, reduction of antigen presentation capability of monocytes, and depletion of NK cell activity following surgery^{5, 16, 37}. Such disturbances contribute to the development of infectious complications and poor outcome. The mechanisms of this phenomenon, however, are poorly understood. Many factors have to be taken into account, such as neuroendocrine response, anesthesia, operative trauma, blood transfusion, and the great number of mediators: prostaglandin E₂, platelet activating factor, and cytokines^{4, 21, 31}.

There is a group of cytokines that have chemotactic activity and influence the host immune response to surgery. Monocyte chemoattractant protein-1 (MCP-1), also known as CCL2, and regulated-on-activation normal T cell expressed and secreted (RANTES) protein, also known as CCL5, belong to this group of chemoattractant cytokines, called chemokines^{27, 40}. They are small, 6–14 kDa secreted proteins that are characterized by their chemotactic effect on leukocytes. Chemokines are divided into 4 families based on structural and genetic considerations, and MCP-1 and RANTES belong to the CC family^{27, 40}.

MCP-1 is produced by a variety of cell types, including lymphocytes, mononuclear phagocytes, and vascular endothelial cells, in response to interferon γ , interleukin (IL)-1 β , tumor necrosis factor α , ischemia, and Gram-negative and Gram-positive bac-

terial products^{20, 27, 39, 42}. MCP-1 serves as a chemotactic and stimulating factor for monocytes, memory T lymphocytes, basophils, NK cells, and dendritic cells, and can induce the expression of integrins required for chemotaxis and monocyte production of IL-1 and IL-6^{27, 28, 40}. The function of MCP-1 is mediated through the CCR2 and CCR4 receptors that are mainly expressed on monocytes and lymphocytes, inducing their chemotaxis and accumulation in inflamed tissue²⁷.

The other member of the CC chemokine family that mediates immune response is RANTES. Fibroblasts, epithelial cells, endothelial cells, and monocytes/macrophages have been shown to express RANTES within hours after stimulation³³, but T lymphocytes about 3–5 days later²⁵. Transcription factors, IL-1, and a diminished intracellular glutathione level are able to enhance the expression of RANTES in the course of inflammation^{15, 25, 33}. Since the chemokine receptors CCR1, CCR3, or CCR5 are located on T lymphocytes, NK cells, monocytes and eosinophils, RANTES is able to attract these cells to inflammatory sites⁴⁰. RANTES activates T lymphocytes, NK cells, and antigen-presenting cells, mediates cytokine release, chemotaxis, and proliferation of these cells^{6, 27, 40}, augments the expression of adhesion molecules needed for chemotaxis, and induces transendothelial migration of memory T lymphocytes after endothelial activation^{2, 27}. Recent studies have shown that RANTES and MCP-1 play important roles in regulating T cell differentiation²².

Therefore these two chemokines modulate the host immune response by indirect effects on antigen-presenting cells and direct effects on differentiating T cells. They are both active factors that play a regulatory function in host response to infection⁴⁰ and may influence the development of immunosuppression and complications after surgery. Although the immunomodulatory functions of MCP-1 and RANTES are well documented, their relation to ischemia-reperfusion in a clinical setting has not been elucidated.

The aim of the present study was to determine whether there is any relationship between serum MCP-1 or RANTES concentrations and operative injury and ischemia-reperfusion during abdominal aortic surgery.

MATERIALS AND METHODS

The ethics committee controlling research on humans and animals of the Medical University of Białystok granted approval to perform this study. All

patients signed an agreement for participation in the study.

Twelve consecutive male patients with confirmed infrarenal AAA and with negative histories of neoplastic, rheumatological, and immunological diseases were included in the study. They underwent elective abdominal aortic aneurysm repair with bifurcated graft placement at the Medical University Hospital in Białystok. Identical stents, Uni-Graft KD.V. supplied by B/Braun (Easculap AG & CO KG, Germany), were used.

All patients were qualified by an anesthesiologist the day before surgery and perioperative risk was estimated according to the American Society of Anesthesiologist score²⁴ and Goldmann Cardiac Risk Index¹². The characteristics of the patients are shown in Table 1. The operations were performed under general anesthesia with ethomidate and cis-atracurium for induction and were maintained with sevoflurane, oxygen/air mixture, and opioids. Epidural catheter was used where possible. Antibiotic prophylaxis consisted of 1.0 g of cefazolinum on induction followed by two further postoperative doses.

Table 1. Clinical characteristics of patients with abdominal aortic aneurysm (AAA) and the control group

	AAA patients	Control group
Number of patients	12	8
Age (years)	70 (48–77)	51 (36–61)
ASA score	3 (2–4)	
Goldmann score	11 (3–29)	
Duration of surgery (min)	248 (185–305)	
Duration of clamping (min)	76 (53–88)	
Duration of hospital stay (days)	14 (9–29)	
Blood transfusion (ml)	800 (0–1600)	

Values are showed as medians and ranges.

ASA score – American Society of Anesthesiologist score.

Peripheral venous blood samples were taken before surgery (Preop), after induction of anesthesia (Induction), just before aortic unclamping (PreX_{off}), 90 min after unclamping (90minX_{off}), and 24 and 48 h after surgery. Each time, 3 ml of the blood were taken for serum and centrifuged for 10 min at 3000 rpm. The serum was transferred to 2-ml microtubes and stored at a temperature of –70°C until measurement. The cytokines MCP-1 and RANTES were measured by enzyme-linked immunosorbent assay (R&D Systems, Abingdon, UK) according to the manufacturer's instructions. The manufacturer claims a sensitivity less than 5 pg/ml and an intra-assay variability of 4.7% at a MCP-1 concentration of

364 pg/ml, and less than 8 pg/ml sensitivity and an intra-assay variability of 2.9% at a RANTES concentration of 1120 pg/ml.

On the 1st and 2nd days after surgery, clinical assessment of the patients was performed according to the Acute Physiology and Chronic Health Evaluation II and III scores (APACHE II and APACHE III)^{18, 19}, Sequential Organ Failure Assessment (SOFA)³⁸, and Multiple Organ Dysfunction score (MODs)²³. The control group comprised 8 healthy volunteers: hospital personnel, all men, without medical histories of any inflammatory disease.

Data were collected and transferred to Microsoft® Excel 97. Statistical analyses were performed using Statistica for Windows version 5. Since our data on the measured chemokines were not normally distributed, the results were reported as the median value, 25th and 75th quartiles, and range. The non-parametric Wilcoxon and Mann–Whitney U tests were used for comparison within and between the groups, respectively. In all calculations, $p < 0.05$ was regarded as statistically significant. For correlation studies, the Spearman rank correlation coefficient was used.

RESULTS

Twelve consecutive patients undergoing AAA repair were included in the study. They were all men, with a median age of 70 (range 48–77) years. Nine patients made an uncomplicated recovery. One patient developed minor wound infection and in another an acute ischemic heart attack was observed. There was one death from acute heart failure and multiple organ dysfunction syndrome on day 9 after operation. The control group comprised 8 healthy men with a median age of 51 (range 36–61) years.

Concentration of MCP-1 in serum

Median serum MCP-1 concentration was higher in the control group than in the AAA patients before operation (313 pg/ml vs. 224 pg/ml, $p=0.208$; Fig. 1). During the course of the operation, MCP-1 level showed a slight elevation after induction (241 pg/ml vs. 224 pg/ml, $p=0.427$), followed by non-significant depletion to 217 pg/ml at PreX_{off} ($p=0.865$ vs. Induction). Ninety minutes after cross-clamp release, MCP-1 level increased significantly compared with the PreX_{off} level (269 pg/ml vs. 217 pg/ml). During the postoperative time, MCP-1 concentration fell from 269 pg/ml at 90 min after clamp release to 225 pg/ml and 203 pg/ml 24 and 48 h after surgery, respectively. We found a lack of statistically significant differences between MCP-1 serum concentra-

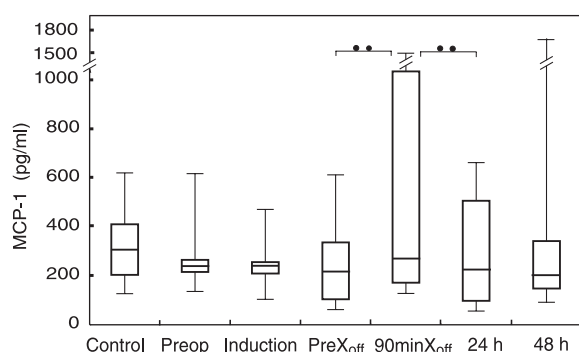


Figure 1. Serum concentration of MCP-1 (pg/ml) in patients with AAA before operation (Preop), after anesthesia induction (Induction), before unclamping of aorta (PreX_{off}), 90 min after unclamping (90minX_{off}), 24 and 48 h after surgery and in control group. Values are presented as median (line), 25th and 75th percentile (box) and range. ** $p < 0.01$ in comparison with other points of measurement (Wilcoxon test).

tion in AAA patients and the control group before, during, and after surgery.

Concentration of RANTES in serum

The highest serum RANTES concentration of 61 ng/ml was observed in patients with AAA repair before surgery (Fig. 2). It was significantly elevated in comparison with the control group (26 ng/ml) and with other times of measurement: at Induction (41 ng/ml), PreX_{off} (27 ng/ml), 90minX_{off} (13 ng/ml), and 24 h (26 ng/ml) and 48 h after surgery (31 ng/ml). After induction we observed a slow decrease in serum RANTES level, with the lowest value of 13 ng/ml 90 min after unclamping the aorta. This was significantly lower than the RANTES level after induction, before clamp release, at 24 and at 48 h after surgery. On the 1st and 2nd postoperative days the concentration of RANTES was higher by 100 and 138%, respectively, than the 90minX_{off} value and reached the level of the control group.

Correlation calculations

We analyzed the relationship between the serum levels of the studied chemokines and patient demographic and intraoperative data known to influence morbidity and mortality. We found that serum MCP-1 level correlates with the time of aortic cross-clamping, the duration of surgery, and the number of days the patient needed to stay in the hospital after surgery (Table 2). We also assessed the relationship between the levels of measured mediators and APACHE II, APACHE III, SOFA and MOD scores calculated on the 1st and 2nd days after AAA repair. Positive correlations between MCP-1 concentration

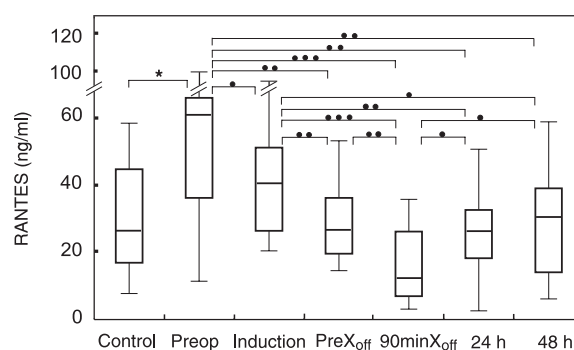


Figure 2. Serum concentration of RANTES (ng/ml) in patients with AAA before operation (Preop), after anesthesia induction (Induction), before unclamping of aorta (PreX_{off}), 90 min after unclamping (90minX_{off}), 24 and 48 h after surgery and in control group. Values are presented as median (line), 25th and 75th percentile (box) and range. * $p < 0.05$ in comparison with control group (Mann-Whitney U test); • $p < 0.05$, •• $p < 0.001$, ••• $p < 0.001$ in comparison with other points of measurement (Wilcoxon test).

Table 2. Correlation between patient data and MCP-1 or RANTES concentration in serum of patients undergoing abdominal aortic aneurysm surgery

	MCP-1	RANTES
Duration of clamping	$R = 0.517, p < 0.001$	$R = 0.146, p = 0.219$
Duration of surgery	$R = 0.444, p < 0.001$	$R = 0.179, p = 0.133$
Duration of hospitalization	$R = 0.233, p = 0.049$	$R = -0.114, p = 0.340$

Spearman rank correlation coefficients (R) and p-values are presented.

and APACHE III score ($R = 0.263, p < 0.05$) as well as RANTES concentration and both SOFA and MOD scores ($R = 0.271, p < 0.05$ and $R = 0.313, p < 0.01$, respectively) on the 1st day after AAA repair were found (data not shown).

DISCUSSION

MCP-1 is a strong chemotactic factor for monocytes/macrophages and subpopulations of T cells during inflammation and injury. The expression of this chemokine is induced by infectious and noninfectious factors^{39, 42}. Some evidence suggests that MCP-1 modulates the differentiation of monocytes to dendritic cells, which display a reduced production of IL-12, suggesting the inhibition of Th1 cell development²⁵.

The serum profiles of the chemokines MCP-1 and RANTES during ischemia and reperfusion and their roles in the development of complications following surgery in humans have not been yet evaluated. In our study, baseline MCP-1 serum concentration was lower in patients with AAA than in controls, the difference, however, was not statistically significant. It is

likely that dysregulation of monocyte function occurred in response to a chronic inflammatory state, concomitant aneurysmal formation and degeneration. The recruitment of monocytes into the aortic wall was previously observed during AAA development, and elastine degradation peptides were shown to be responsible for the presence of MCP-1 molecules in human AAAs¹⁴. We found a lack of significant differences in MCP-1 level between the control group and AAA patients at any time-point of measurement. A decreased capacity of monocytes to lipopolysaccharide-induced IL-1 and IL-8 synthesis was shown by Faist et al.⁵ in 17 patients undergoing elective surgery within 24 h after operation. The authors suggest that the emergency recruitment and functional immaturity of the monocytes and the presence of many circulating mediators account for the dysregulation of monocytes during surgery. In an experimental study, Yamaguchi et al.⁴² found an enhancement of MCP-1 macrophage production by human neutrophil elastase or oxygen radicals following ischemia-reperfusion in rat liver. Indeed, in our study a significant increase in MCP-1 concentration was found 90min- X_{off} . During the next 24 h the chemokine level fell significantly, nearing the pre-operative value. An increased concentration of MCP-1 in serum was observed by Fujiwara et al.⁷ in 20 subjects during coronary artery bypass graft surgery. The level of MCP-1 was higher and persisted longer in complicated patients than in those without complications. Similarly, Economou et al.³ showed a significantly higher serum MCP-1 level in patients undergoing percutaneous transluminal coronary angioplasty or coronary angiography in the course of coronary artery disease in comparison with a control group. An increased concentration of MCP-1 was also found in the course of acute myocardial infarction in serum²⁶ and in the bronchoalveolar lavage fluid of patients with chronic obstructive pulmonary disease¹⁷. In contrast, a low cerebrospinal fluid level of MCP-1 was observed in patients with multiple sclerosis and correlated negatively with mediators of inflammation³⁵.

RANTES, similarly to MCP-1, plays an important role in chronic and acute inflammation¹. Lymphocytes, NK cells, dendritic cells, eosinophils, and monocytes constitute the main cells influenced by RANTES^{6, 25}. This chemokine regulates the response of leukocytes in allergic inflammation, leukocyte infiltration, bronchial hyperresponsiveness, and the pathogenesis of asthma and inflammatory nervous system diseases¹. In our study, a significantly increased RANTES level was observed in patients with AAA only before operation in comparison with the control group. It is likely that a high concentration of this chemokine results from chronic inflam-

mation coexisting with enhanced activity of cathepsins, collagenases, elastases, and exoglycosidases in aneurysmal arterial walls^{8, 9}. However, it can also be associated with the advanced age of patients with AAA¹¹. Schönbeck et al.³² found that AAAs predominantly express Th2-associated cytokines, such as IL-4, IL-5 and IL-10, and lack Th1 mediators. The shift in the balance of the Th1- and Th2-mediated immune responses in the vessel wall suggests the role of Th2 cells in the pathogenesis of AAA, but may also influence the immune response to surgery, including post-operative course. Interestingly, decreased type 1 cytokine production and a shift to type 2 response together with higher serum levels of MCP-1 and RANTES were observed in healthy elderly subjects¹¹. Since Saito et al.³⁰ found that coexistence of IL-4 and RANTES enhances IL-4 production, associated with Th2 response, it is possible that a high serum level of RANTES mediates the shift of T cells to type 2 response in patients with AAA. IL-4 modulates the transition of B cells to memory phenotype, preventing the chemotactic response of B cells and inhibiting the expression of L-selectin, thereby influencing the immune response to injury and infection.

We have shown that a median of 76 min of ischemia results in a significant depletion of RANTES concentration in serum. Interestingly, after 90 min of reperfusion, the RANTES level decreased even more, i.e. by 79% in comparison with the baseline value, which was the lowest concentration of this chemokine observed. However, as the RANTES concentration was 100% higher than the minimum value on the 1st and 138% higher on the 2nd day after surgery, reaching the concentration observed in the control group, it is likely that the depletion of this chemokine level following ischemia-reperfusion may contribute to the immune response during AAA repair. It is still not clear if the observed changes in chemokine levels are the consequence of ischemia-reperfusion or if they result from the operative injury. Continuation of the study in patients undergoing other surgical procedures will allow us to evaluate this problem. We are also not able to eliminate the possibility of an effect of blood transfusion on chemokine levels. It should be stressed that among the 12 patients in our study, 5 had blood transfusion during surgery and this procedure was started about 30 min after declamping of the aorta.

Despite the small number of patients undergoing surgery, we tried to assess the relationship between chemokine concentrations and the course of surgery or clinical course after operation. Significant correlations were found between serum MCP-1 level and the duration of aortic cross-clamping and the duration of

surgery. Although in our study MCP-1 concentration correlated positively with the duration of hospitalization and APACHE III score on the 1st day after surgery, and RANTES correlated with SOFA and MOD scores on the 1st day after surgery, the correlation coefficients were relatively weak. A larger population study would be required to estimate this relationship precisely.

The immunomodulatory functions of MCP-1 and RANTES with the observed changes in their serum concentrations suggest a possible role of these chemokines in the development of immunosuppression and complications following AAA repair.

In conclusion, AAA is associated with elevated RANTES serum concentration. The induction of anesthesia generated a slight increase in MCP-1 and a decrease in RANTES serum level. Ischemia-reperfusion results in a significant elevation of MCP-1 and depletion of RANTES concentration in serum during AAA repair. We suppose that changes in the MCP-1 and RANTES levels may influence the clinical course after AAA repair through the immunomodulatory roles of these chemokines. Further studies are needed to elucidate the relationship between chemokines, immunological disturbances in the course of ischemia and reperfusion, and the development of complications after AAA surgery.

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