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MIF and markers of the inflammatory response following cardiac surgery under extracorporeal circulation*

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Abstract

Background: Cardiac surgery under extracorporeal circulation (ECC) is associated with a complex physiological response that is clinically manifested as a systemic inflammatory response syndrome. Perioperative levels of human intercellular adhesion molecule 1 (sICAM-1), macrophage migration inhibitory factor (MIF), and other cytokines (IL-6, IL-8) could potentially predict postoperative outcome.
Methods: In this prospective study, serum levels of sICAM-1, IL-6, IL-8, and MIF from patients undergoing cardiac surgery under ECC were analyzed at eight time points in the perioperative setting using enzyme-linked immunosorbent assays. The results were compared with patient characteristics, past medical history, present surgical intervention, postoperative complications, and length of stay in the ICU (ICU-LOS).
Results: Serum levels of sICAM-1, IL-6, IL-8, and MIF from 73 patients were investigated. IL-6, IL-8, and MIF had a peak upon admission to the ICU or 6 h after ECC ($p<0.05$) and decreased in the following 7 days after cardiac surgery. sICAM-1 initially showed a significant decrease from the pre-op level to the time point directly before start of the ECC and admission to the ICU. Thereafter, sICAM-1 levels increased significantly up to the seventh day after cardiac surgery ($p<0.05$). No correlation was found between the levels of sICAM-1, IL-6, and IL-8 with the parameters duration of ventilation, ICU-LOS, or duration of ECC. However, the peak level of MIF in the perioperative course correlates with ICU-LOS ($r=0.35$, $p<0.01$). The higher the maximum level of MIF, the longer the stay in the ICU was.
Conclusions: sICAM-1, IL-6, IL-8, and MIF are influenced by ECC. No correlation was found between level of sICAM-1, IL-6, or IL-8 with duration of ventilation, ICU-LOS or duration of ECC.

Key words: macrophage migration inhibitor factor, sICAM, cardiac surgery, systemic inflammatory response

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Introduction

Cardiac surgery using extracorporeal circulation (ECC) is associated with a complex physiological response that is clinically manifested as a systemic inflammatory response syndrome (SIRS) [23, 31, 32]. This phenomenon of inflammatory reaction to ECC is similar to sepsis but lacks a microbiological correlate; however, it might influence postoperative morbidity and mortality [8]. Ultimately, SIRS could lead to (multiple) organ dysfunction and failure [4, 24].

It is well known that cytokine synthesis increases during ECC in the intra- and postoperative setting [12, 14, 15, 22, 26, 29]. However, the currently available data cannot determine whether a given level of cytokines corresponds to postoperative outcome [25]. ICAM-1 is a human intercellular adhesion molecule that belongs to the immunoglobulin superfamily: it mediates the contact between leukocytes and endothelial cells and seems to be an indicator for endothelial cell damage, whereas sICAM-1 is a marker of cellular activity [3, 32, 33]. Here, ECC is commonly associated with an increased level of sICAM-1 [1, 29].

IL-6 is a cytokine produced by monocytes, macrophages, and endothelial cells in response to different stimuli, and ECC also increases IL-6 levels [16]. Likewise, tissue damage and infections are associated with increased levels of IL-6, too. Therefore, IL-6 levels are measured frequently in intensive care patients and after cardiac surgery [27, 30]. Similarly to IL-6, trauma and hypoxia increase the levels of IL-8, another cytokine [28].

Macrophage migration inhibitory factor (MIF) is a cytokine and a central mediator of the innate immune response [6, 13]. Experimental studies have suggested that MIF is produced in sepsis and that cytokine production and mortality can be reduced by inibiting MIF [6, 13].

The aim of the present study was to find predictors of postoperative outcome after cardiac surgery under ECC. Therefore, we investigated the association between the levels of sICAM-1, IL-6, IL-8, and MIF at eight different time points and with respect to clinically important outcome parameters.

Patients and Methods

This prospective study was approved by the local ethics committee. After obtaining informed consent, patients who underwent cardiac surgery under ECC were enrolled consecutively. Patient characteristics and demographic data, past medical history, present surgical intervention, and subsequent ICU stay were recorded.

Postoperative problems were evaluated up to the seventh day after surgery. Infection included pneumonia, pleuritis, mediastinitis, superficial wound infection, urinary tract infection, catheter infection, and fever of unknown cause. Pulmonary edema, pleural effusion, pneumothorax, and adult respiratory distress syndrome (ARDS) were considered pulmonary complications. Acute renal failure and renal insufficiency were defined as renal complications (according to the estimation of the treating physician), and stroke, stupor, coma, encephalopathy, transient ischemic attack (TIA), and seizure as postoperative neurological complications.

Anesthesia was performed in accordance with the institutional standard. After oral premedication with 10-20 mg dicaliumclorazepate overnight, the patients received 1-2 mg flunitrazepam directly before being transfered to the operating room. The patients were continuously monitored by ECG, pulsoximetry, and invasive blood pressure measurement. After preoxygenation, anesthesia was induced with 1-3 mg midazolam, 0.5-1 µg/kg sufentanil, 0.15-0.3 mg/kg etomidate, and 0.1 mg/kg pancuronium. After intubating the trachea, the patients were ventilated with air/oxygen. Thereafter, anesthesia was maintained using sufentanil, midazolam, and sevoflurane. Cardiac surgery was performed under ECC using a continuous-flow membrane oxygenator (Stoeckert S3, Stoeckert Instumente GmbH, Munich, Germany).

Central venous blood samples were drawn at eight defined time points: directly before induction of anesthesia (pre-op), directly before starting the ECC (start ECC), directly after admission to the ICU (ICU-admisson), 6 h after the end of ECC (6h post ECC), and at the first (POD1), second (POD2), third (POD3), and seventh (POD7) day postoperatively. Serum was obtained by centrifugation at 1000 g for 10 min and kept frozen at −80°C until assayed. Serum levels were assayed by enzyme-linked immuno sorbent assays to determine levels of IL-6 (DY 406, R&D Systems Inc., Minneapolis, USA), IL-8 (DY 208, R&D Systems Inc., Minneapolis, USA), MIF (DY 289, R&D Systems Inc., Minneapolis, USA), and sICAM-1 (BBE 1B, R&D Systems Inc., Minneapolis, USA) in accordance with the manufacturer´s recommendations.

Statistical analysis

All data were entered into a database (Excel, Version 2002, Microsoft Inc.) and analyzed (SPSS, Version 11.5.1, SPSS Inc., Chicago, USA). The results were expressed as means ± SEM when distribution was normal; they were expressed as median and range (minmal and maximum value) when distribution was not normal. The normal distribution was verified using the Kolmogorov-Smirnov test. To assess sequential variations in cytokines and sICAM-1 at the different time points, we used an analysis of variance for repeated measures (ANOVA) with the Bonferroni test.

Results

Patient demographic data and perioperative characteristics

A total of 73 patients were investigated in this study. Patient characteristics are shown in Table 1. As summarized in Table 2, 10 (13.7%) of the patients had a history of smoking before cardiac surgery. A history of diabetes, myocardial infarction, arrhythmia, stent implantation, pulmonary disease, renal disease, or hepatic disease was present in 16 (21.9%), 8 (11.0%), 14 (19.2%), 17 (23.3%), 26 (35.6%), 22 (30.1%), and 27 (37.0%) of the investigated patients, respectively. The most common problems in this study population after cardiac surgery were pulmonary complications (n=56; 73.7%), followed by infections (n=33; 45.2%), neurological complications (n=17; 23.3%), and renal complications (n=12; 16.4%) (Table 2).

Table 1: Patient demographic data and perioperative characteristics

Number of patients, n	73
Male sex, n (%)	51 (70.0%)
Age, years	63.8 ± 1.1 (range: 38-78)
Weight, kg	80.0 ± 1.5 (range: 52-110)
Height, cm	170.3 ± 1.0 (range: 152-187)
Duration of ECC, min	104.2 ± 3.5 (range: 36-182)
Duration of ventilation, min	1,151.4 ± 676.8 (range: 440-4,979)
Length of stay in ICU, min	2,972.2 ± 410.9 (range: 435-17,301)
CABS, n (%)	68 (93.1%)
Valve replacement/repair, n (%)	1 (1.4%)
Combined CABS and Valve replacement/repair, n (%)	4 (4.5%)

ECC = extracorporeal circulation, ICU = intensive care unit, CABS = coronary artery bypass surgery
Mean Value ± SEM

Table 2: Subgroups of patients and postoperative outcome

Medical history	
History of pulmonary disease before cardiac surgery, n (%)	26 (35.6)
History of hepatic disease before cardiac surgery, n (%)	27 (37.0)
History of renal disease before cardiac surgery, n (%)	22 (30.1)
History of diabetes before cardiac surgery, n (%)	16 (21.9)
History of stent implantation before cardiac surgery, n (%)	17 (23.3)
History of arrhythmia before cardiac surgery, n (%)	14 (19.2)
Smoker, n (%)	10 (13.7)
History of myocardial infarction before cardiac surgery, n (%)	8 (11.0)
Postoperative Outcome	
Pulmonary complications after cardiac surgery, n (%)	56 (73.7)
Infection after cardiac surgery, n (%)	33 (45.2)
Neurological complications after cardiac surgery, n (%)	17 (23.3)
Renal complications after cardiac surgery, n (%)	12 (16.4)

Kinetics of inflammatory markers

sICAM-1

As demonstrated in Figure 1, sICAM-1 dropped significantly from the preoperative level of 251.6 ± 10.6 ng/ml to 136.5 ± 7.1 ng/ml directly before starting the ECC ($p < 0.01$). Thereafter, the levels of sICAM-1 increased significantly and remained elevated up to POD2 at 346.7 ± 17.8 ng/ml, and plateaued up to POD7 at 346.0 ± 14.0 ng/ml.

IL-6

As shown in Figure 1, IL-6 was significantly increased in all patients from the preoperative level of 13.4 ± 7.4 pg/ml and the level directly before starting the ECC of 14.0 ± 3.6 pg/ml to a level of 269.9 ± 60.8 pg/ml after admission to the ICU ($p < 0.01$; post-op vs. pre-op/start ECC). The peak levels of IL-6 at 279.4 ± 44.1 pg/ml were observed 6 h after decannulation ($p < 0.01$; 6h post ECC vs. pre-op/start ECC). Thereafter, IL-6 levels dropped significantly each subsequent day after surgery and nearly approached the pre-op levels.

IL-8

As demonstrated in Figure 1, IL-8 increased from pre-op and start ECC levels of 5.9 ± 3.7 and 4.9 ± 3.2 pg/ml, respectively, to significantly higher post-op levels of 29.9 ± 7.7 pg/ml ($p < 0.01$; post-op vs. pre-op/start ECC) and to significantly higher levels at 6h post ECC of 25.7 ± 9.3 pg/ml ($p < 0.01$; 6h post ECC vs. pre-op/start ECC). Thereafter, IL-8 levels decreased progressively to the lowest level at the POD3 of 2.4 ± 1.2 pg/ml.

MIF

As demonstrated in Figure 1, MIF significantly increased in all patients from the pre-op level of 1.2 ± 0.5 pg/ml to a start ECC level of 2.5 ± 0.4 pg/ml ($p < 0.01$; pre-op vs. start ECC), and also increased significantly to a peak postop level of 3.3 ± 0.5 pg/ml ($p < 0.01$; pre-op vs. post-op). At the time point 6 h post ECC the level of MIF dropped to 2.0 ± 0.4 pg/ml ($p < 0.01$; post-op vs. 6 h post ECC) and then increased again significantly at POD7 to 2.1 ± 0.4 pg/ml ($p < 0.01$; POD7 vs. pre-op).

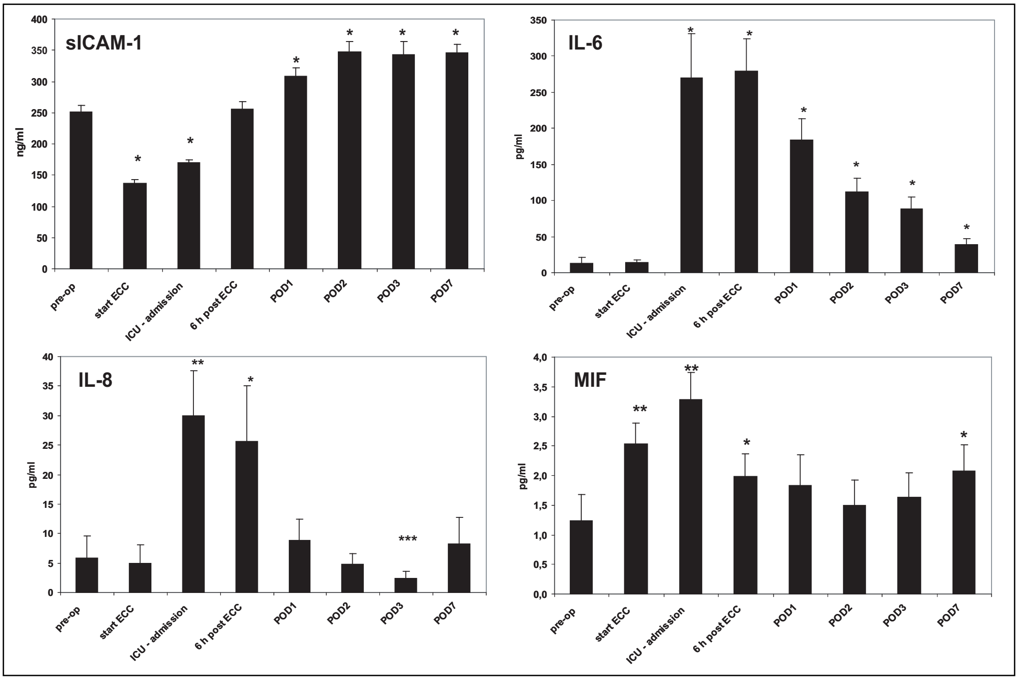

Figure 1: Kinetics of sICAM-1, IL-6, IL-8, and MIF at the eight investigated time points in the course of cardiac surgery and extracorporeal circulation: directly before induction of anesthesia (pre-op), directly before starting the extracorporeal circulation (start ECC), directly after admission to the ICU (ICU-admisson), 6 h after ECC (6h post ECC), and at the first (POD1), second (POD2), third (POD3), and seventh (POD7) day postoperatively.

No correlation of sICAM-1, IL-6, and IL-8 with clinical parameters

We found no correlation between the levels (mean value, maximum value, and quantitative increase) of sICAM-1, IL-6, and IL-8 with the duration of ventilation, ICU-LOS, or the duration of ECC.

Maximal levels of MIF are correlated with length of stay at ICU

As shown in Figure 2, the peak level of MIF in the perioperative course correlates with length of stay at ICU (ICU-LOS) ($r=0.35$, $p<0.01$). The higher the maximum of the level of MIF, the longer the stay in the ICU was. The other values of MIF (mean value and quantitative increase) did not show any significant correlation with the clinical parmeters (duration of ventilation, duration of ECC, or ICU-LOS).

Discussion

The present study shows that sICAM-1 and the cytokines IL-6, IL-8, and MIF are influenced by ECC. We found no correlation between levels of sICAM-1, IL-6, and IL-8 with the duration of ventilation, ICU-LOS, or the duration of ECC. However, we did find a correlation between the peak level of MIF in the perioperative course and ICU-LOS.

The course of sICAM-1 levels, which initially decreased at the start of ECC, is in line with the results of others studies [32]. The reasons for this are probably related to the effects of hemodilution at the beginning of anesthesia. The increased level of sICAM-1 after ECC has also been shown by other au-

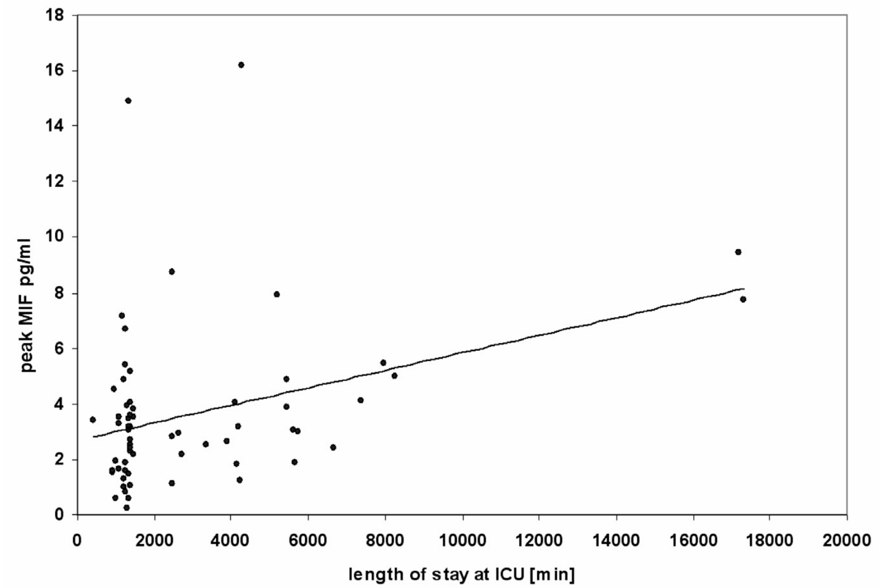

Figure 2: Correlation of peak level of macrophage migration inhibitory factor (MIF) with the length of stay in the ICU (r=0.35; p<0.01).

thors [32]. Activated endothelial cells could produce sICAM-1 by means of IL-1β, TNF-α, and lipopolysaccharide. Furthermore, proteolytic division of cell formations causes cell damage and leukocytes might migrate to the area of infection [17, 18]. Therefore, in the past, the increase in ICAM-1 after surgery was thought to be a marker for multiple organ dysfunctions [32]. This hypothesis could not be confirmed by the present study. sICAM-1 probably reflects cellular ICAM-1 and seems to be a proinflammatory marker in the perioperative course of cardiac surgery under ECC, but we found no correlation between sICAM-1 levels and clincal outcome. Therefore, sICAM-1 does not seem to be a predictor for clinical outcome in patients in whom cardiac surgery was performed under ECC, in contrast to sICAM-1 as a marker of liver failure and mortality in septic shock [33].

In the present study, we found a significant increase in the levels of IL-6 after beginning the ECC and postoperatively, as other studies have also reported [9, 14, 15, 21]. Previous studies demonstrated that levels of IL-6 are correlated with a future cardiac disease [22] and that levels of IL-6 are increased preoperatively in patients suffering from cardiac disease [12]. Indeed, those proinflammatory properties of IL-6 are well known [14, 15, 21]. In one study the maximum level of IL-6 was correlated with SIRS [15]. Another study showed that proinflammatory cytokines such as TNF-α and IL-1β can damage cardiac function, and cytokines are associated with negative outcome in patients undergoing cardiac surgery [5]. Here, however, IL-6 does not seem to affect clinical outcome. Our data did not demonstrate a correlation between the levels of IL-6 with the duration of ventilation, ICU-LOS, or the duration of ECC. The course of IL-8 levels in the present investigation are comparable to findings from other studies [14, 15, 22, 29]. Cytokine levels are higher in patients suffering from cardiac disease than in patients without cardiac disease [22]. These findings support the hypothesis that the proinflammatory properties of IL-8 increase with respect to a postoperative increase in IL-8 levels. However, this increase is not correlated with clinical outcome. By comparison, a study in children with congenital cardiac defects in whom cardiac surgery was performed unter ECC demonstrated a correlation between duration of ECC and levels of IL-8 [11]. However, the results may be limited by the relatively small number of 18 children who were investigated.

MIF is released in patients with sepsis, in particular, and has a critical role in the outcome [1, 6, 9]. A recently published study showed that levels of MIF were increased under ECC; however, in this study no correlation with postoperative organ failure was observed [13]. In our investigation the mean level of MIF had increased already by the second time point, although ECC had not started. This may be because the operation had started and surgical stress activated the hypophyseal-hypothalamic axis. The levels of CTRH and ACTH correlated with the severity of surgical trauma [1]. In spite of the increased levels of monocytes, macrophages, and T-lymphocytes, MIF is secreted by the adenohypophysis and this may explain the increased levels of MIF before ECC has started. Studies have shown that MIF had hormone-like properties and is secreted after stress [7, 10]. Interestingly, mean concentrations of MIF were not increased in patients suffering from multiple trauma without any signs of systemic inflammatory processes [2].

In the present study postoperatively elevated levels of IL-6, IL-8, sICAM-1, and MIF confirm laboratory findings of SIRS. This is in line with the association between SIRS and ECC reported in various studies [3, 19, 20, 31]. The postoperatively increased levels of proinflammatory cytokines reported in the present investigation support this. With respect to these findings, the duration of ECC had no effect on the postinflammatory parameters. Our results support those of a previous study by Prondzinsky et al., who showed that for cardiac surgery both surgical trauma and cardiopulmonary bypass had an effect on inflammation, but surgical trauma is the most important one [21].

The postoperative ventilation of patients undergoing cardiac surgery is mainly influenced by perioperative complications. Therefore, parameters that correlated to predict this association are of high interest. Unfortunately, we were not able to find any correlation between the postoperative duration of ventilation and the levels of sICAM1, IL-6, IL-8, and MIF.

Cardiac surgery and ECC induce a systemic inflammatory response; unfortunately, however, the levels of inflammation markers did not predict outcome. Additionally, ICU-LOS is very interesting from an economic point of view. In order to find a predictor of ICU-LOS in patients undergoing cardiac surgery under ECC, the levels of sICAM1, IL-6, IL-8, and MIF were correlated with ICU-LOS. The course of sICAM1, IL-6, and IL-8 levels did not show any correlation with ICU-LOS. In contrast to our findings, DeMendonca-Filho et al. found a correlation between the preoperative levels of MIF and the use of a high dose of vasopressors in patients with cardiovascular impairment and also to lower values of the ratio of partial arterial oxygen tension to fraction of inspired oxygen registered in the first 24 hours after ECC [9].

In the present investigation we found a correlation between the peak level of MIF in the perioperative course and ICU-LOS.

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