Original Research

Systemic Inflammatory Response Syndrome After Extracorporeal Circulation: A Predictive Algorithm for the Patient at Risk

Jens Litmathe[1], Udo Boeken[1], Gabriele Bohlen[1], Dilek Gursoy[1], Christoph Sucker[2], Peter Feindt[1]

[1]Department of Thoracic and Cardiovascular Surgery, [2]Department of Hemostaseology and Transfusion Medicine, Heinrich Heine University Hospital Düsseldorf, Germany

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Address:
Jens Litmathe

Dept. of Thoracic and Cardiovascular Surgery Heinrich Heine University Hospital Moorenstrasse 5 D-40225 Düsseldorf, Germany
e-mail: jens-litmathe@t-online.de

Introduction: Perioperative systemic inflammatory response syndrome (SIRS) remains a catastrophe in cardiac surgery and adequate patient screening is still lacking. We present a prospective trial starting with preoperative data collection. For the first time, the postoperative outcomes of patients after open-heart surgery are evaluated to predict a hazard-constellation for the patient at risk of developing SIRS.

Methods: Of 2315 patients undergoing cardiac surgery over a 2-year period, 107 were considered likely to develop perioperative SIRS based on a high-risk stratification; 12 of them actually developed SIRS and were recruited for this study. Another 20 uneventful consecutive patients served as controls. Blood samples were collected from before the induction of anaesthesia until the morning of the second postoperative day and were analysed for complement, cytokines, adhesion-molecules, endothelin-1 (ET-1), plasminogen-activator-inhibitor (PAI), the coagulation and fibrinolysis cascade and routine laboratory analysis.

Results: Significant preoperative differences were observed in leukocytes, lymphocytes, alkaline phosphatase, ICAM-3 and VCAM-1 ($p<0.05$). Significant positive correlations were found for ET-1 and lactate in the SIRS group. The increase in these parameters was correlated with a prolonged duration of extracorporeal circulation. The best predictive combination for SIRS consisted of alkaline phosphatase, ET-1, ICAM-1, -2, -3, VCAM-1 and ELAM-1.

Conclusions: The results suggest a new theory regarding the development of perioperative SIRS. It is not the extracorporeal circulation itself that represents the main trigger, but rather an *a priori* activation of the endothelial cells, lymphocytes and leukocytes. This activation impairs the microcirculation and finally leads to multi-organ failure. The current data allow the identification of the patient at risk and can thus influence the individual operative schedule.

Systemic inflammatory response syndrome (SIRS) is a whole-body inflammation that still remains a major clinical problem, despite improved diagnostics and therapy. Depending on the underlying subpopulation, the mortality may be as much as 90%.[1] The non-infectious reasons include acute pancreatitis, polytrauma or severe burns. In the frame of a common end result, which is independent from the trigger, an uncontrollable activation of different humoral and cellular mediator pathways occurs. The clinical symptoms are known to be peripheral vasodilatation, loss of volume due to capillary leakage, myocardial dysfunction and finally multi-organ failure (MOF), summarised as SIRS.[2-4] Thus SIRS represents a special, non-bacterial phenomenon of sepsis.

In open heart surgery the contact of blood with the artificial surface of the car-

diopulmonary bypass (CPB) device leads to an activation of mediator systems and consequently to the perioperative development of SIRS, as well as to ischaemia and reperfusion of the organs, the formation of heparin-protamine complexes, changes in blood temperature, and subsequently to translocation of endotoxins from the bowel.[5-7] The main underlying molecular mechanisms of such inflammation are activation of the complement system, increasing production of cytokines, oxygen radicals, release of endothelin (ET) and the expression of adhesion molecules on leukocytes and the endothelium.

Under normal conditions these processes help remove noxious substances from the organism. However, if the abovementioned mediator systems are activated without control and proportion this mechanism leads to an imbalance between the endogenously released inflammation cascade and the physiological inhibitor potential.[8,9] A general capillary leakage results, caused by changes of the vessel permeability, with the clinical consequences of deterioration of the microcirculation, impairment of organ perfusion with oedema, and finally MOF occurs.

So far, the development of perioperative SIRS in open heart surgery was thought to be associated with the use of the extracorporeal circulation (ECC); however, this hypothesis lacks any evidence-based data foundation. After the initial influence of the humoral mediator systems, the role of the endothelium seems to be most crucial. Many authors consider the release of different mediators during ECC to be equivalent to the development of manifest perioperative SIRS.[10,11] However, we have insufficient knowledge concerning the temporal and causal correlations between the preoperative status and the clinical symptoms.

Thus, the aim of the current study was to perform for the first time a prospective trial in order to investigate the development of perioperative SIRS in patients undergoing open heart surgery. We focused on pathophysiological changes in the SIRS-related systems and tried to find a temporal and causal relationship. The data were compared with those from age- and sex-matched patients who had an uneventful perioperative course, in order to derive specific observations concerning the role of the ECC with respect to the development of perioperative SIRS and to predict the patient at risk.

Methods

The current study represents a prospective evaluation and was performed according to the Declaration of Helsinki. It was approved by the local ethics committee after a full review and all patients gave their informed consent prior to the investigation. We included 32 patients (8 female, 24 male) aged between 50 and 83 years (median: 68 years). The patients were divided into 2 groups:

- Control group: 20 consecutive patients with an indication for CPB operation but without exclusion criteria (ejection fraction <35%, emergent operation, no coagulopathy, no disturbance in any of the cascade systems).
- SIRS group: Out of 2315 patients we recruited a high-risk group of 107 patients with a critical cardiac status, multiple comorbidities, and those who were undergoing simultaneous procedures (e.g. valve replacement and revascularisation) with an estimated long-duration CPB. In this group manifest SIRS was diagnosed perioperatively in 12 patients, including at least 3 of the SIRS criteria according to the guidelines of the consensus conference of the American College of Chest Physicians,[12] with an additional need for catecholamine therapy. Only those 12 patients were enrolled in the SIRS group of the present study.

Operative details

All operations were performed following a standardised scheme. Premedication was started using 1 mg lorazepam in the evening prior to the operation and was maintained with midazolam immediately before the induction began. Main anaesthesia was then started with the application of thiopental (1-3 mg/kg b.w.) and fentanyl (3-5 mg/kg b.w.) followed by neuromuscular blockade using pancuronium bromide (0.1-0.15 mg/kg b.w.). Anaesthesia was maintained using Ethrane as inhalation gas or as injection during CPB. A Swan-Ganz catheter was employed in all patients.

All patients undergoing revascularisation received venous (*V. saphena magna*) as well as arterial (*A. thoracica interna*) grafts. Before establishing CPB, 300 IU/kg b.w. heparin was given. During CPB the coagulatory status was checked every 15 min with a targeted anticoagulation time of more than 500 s. CPB was performed using two venous cannulas from the right atrium and the arterial line into the ascending aorta. A left ventricular drainage ("vent") via the right upper lung vein was inserted in all patients. After appli-

cation of cold Bretschneider's cardioplegia, the anastomoses were performed under moderate hypothermia (32°C). The central anastomoses were also performed under partial clamping of the ascending aorta and with the heart beating. Valve replacement was carried out using crystalloid cardioplegia, that was infused either via the ascending aorta or in the case of aortic regurgitation via the coronary ostia. In no case was a protease inhibitor, such as aprotinin, employed.

Blood samples

All samples were taken at different time points in both groups:

1. before the induction of anaesthesia;
2. 30 min after starting the ECC;
3. 30 min after finishing the ECC;
4. after arrival in the intensive care unit (ICU);
5. the morning of the first postoperative day;
6. the morning of the second postoperative day.

The following measures were determined: blood count, routine coagulation status, GOT, GPT, γGT, LDH, alkaline phosphatase, CK-MB, creatinine, urea, bilirubin, C-reactive protein, lactate, sodium, potassium, blood gas analysis, endothelin 1 (ET-1), complement, cytokines, interleukins and adhesion molecules (ICAM-1, -2, -3, VCAM-1, ELAM-1). The determination of the adhesion molecules was performed using an ELISA assay (Diaclone© company, Besançon, FR).

Statistical analysis

In a first step, two-factorial analyses of variance (with group and time factor) together with t-tests were performed to identify the variables that differed significantly between the two groups. A p-value <0.05 was considered to be statistically significant. For those "significant" variables, stepwise discriminant analyses were performed to isolate the minimal set of predictive factors. For this set the rate of correct prediction was calculated. Discriminant analysis is a multivariate method that allows the classification of individuals into one of different known groups according to the values of our clinical measures. All statistics were computed using SAS software version 8 (Microsoft© corporation, USA).

Results

All important pre- and intraoperative data are summarised in Tables 1-3.

Preoperative data

The demographic data of the patients in the control and the SIRS groups were comparable. There were no significant differences in age, sex, or incidence of cardiovascular risk constellation. Only the incidence of diabetes mellitus was higher in the SIRS group compared with the control group (50% vs. 20%). Heart failure according to the New York Heart Association classification was 3.3 ± 0.7 in the SIRS group and 2.7 ± 0.5 in the control group. The ejection fraction was 55.3 ± 7.6% in the SIRS group and 58.3 ± 7.4% in the control group. Allergic predisposition was higher in the SIRS group (33% vs. 10%, p<0.05).

Intraoperative data

The incidence of concomitant procedures was significantly higher in the SIRS group (58% vs. 0%, p<0.05). The ECC time (133 ± 32 min vs. 115 ± 27 min) and the reperfusion period (64 ± 39 vs. 57 ± 35

Table 1. Demographic data and preoperative variables in both groups.

Parameter	Control group	SIRS group	p
Age (years)	66.1 ± 7.3	72.9 ± 8.5	0.0337*
Sex (f/m)	5/15	3/9	1.0000
NYHA class (I/II/III/IV)	1/5/10/2	0/0/9/3	0.1766
Active smoker	10 (50%)	7 (58%)	0.7257
Diabetes mellitus	4 (20%)	6 (50%)	0.1190
Allergic predisposition	3 (15%)	4 (33%)	0.0184*
Hypercholesterinaemia	16 (80%)	7 (58%)	0.2400
Previous anterior wall infarction	2 (10%)	1 (10%)	1.0000
Previous posterior wall infarction	14 (70%)	5 (45%)	0.1502
Ejection fraction (%)	58.3 ± 7.6	55.3 ± 7.4	0.7092

SIRS – systemic inflammatory response syndrome; NYHA – New York Heart Association. *statistically significant.

Table 2. Main intraoperative data in both groups.

Parameter	Control group	SIRS group	p
Combined surgery (coronary/valve)	0	7 (58%)	
Operation time (min)	237.45 ± 30.653	252.08 ± 43.831	0.323
ECC time (min)	114.45 ± 26.512	132.73 ± 31.963	0.124
Cross-clamp time (min)	51.4 ± 11.241	78.83 ± 29.44	0.009*
Reperfusion time (min)	56.5 ± 34.976	64.2 ± 38.447	0.601
Lowest Hb (mg/dl)	8.13 ± 1.286	8.35 ± 0.794	0.553
Lowest Hct (%)	24.87 ± 5.026	25.9 ± 2.381	0.462
Red cell concentrates (ml)	283 ± 413.828	890.9 ± 1368.543	0.178
Auto-transfusion (ml)	1304.95 ± 414.025	1450 ± 180.278	0.187

SIRS – systemic inflammatory response syndrome; ECC – extracorporeal circulation; Hb – haemoglobin; Hct - haematocrit *statistically significant.

Table 3. Intraoperative complications in both groups.

Parameter	Control group	SIRS group	p
Major complications	1 (5%)	10 (83.3%)	0.00001*
Need for catecholamines	5 (25%)	11 (91.6%)	0.00031*
Reperfusion support	0	2 (16.7%)	0.1331
Intra-aortic balloon pump	0	3 (25.0%)	0.0444*

SIRS – systemic inflammatory response syndrome. *statistically significant.

min) were longer in the SIRS group, as was the ischaemia in the SIRS group (79 ± 29 vs. 51 ± 11 min, $p<0.05$). Intraoperative complications, such as a need for catecholamines (92 vs. 25%, $p<0.05$) or intra-aortic counterpulsation (25% vs. 0%, $p<0.05$) occurred more frequently in the SIRS group.

Postoperative data

The stay in the ICU was significantly longer in the SIRS group (8.33 ± 2.11 vs. 2.97 ± 0.89 days, $p<0.05$). The incidence of the following complications was higher in the SIRS group: fever, i.e. body temperature >38°C (91.7 vs. 0%, $p<0.05$); cardiac complications, such as rhythm disturbances (83.3 vs. 30%, $p<0.05$); haemodynamic imbalance with need of catecholamine therapy (100% vs. 45%, $p<0.05$); and renal failure with need of dialysis (50% vs. 0%, $p<0.05$). Eight of the 12 patients in the SIRS group died, whereas all the patients in the control group survived.

In order to construct a predictive index for perioperative SIRS, a combination of parameters with the highest possible sensitivity and specificity with the minimal number of measures needed to be determined. Therefore, t-tests were first performed for each parameter, in order to detect the best ones for the discriminant analysis. At the same time, it was determined which parameters could discriminate between the SIRS and control groups at different time points.

Perioperative courses of different routine laboratory parameters

Leukocytes, lymphocytes, alkaline phosphatase, urea and creatinine in the two groups were significantly different ($p<0.05$) before the induction of anaesthesia. The mean values and the standard deviation of leukocytes and alkaline phosphatase are shown in Table 4.

Perioperative courses of different special laboratory parameters

ICAM-3 differed significantly before anaesthesia and on the first postoperative day. Similarly, VCAM-1 was different 30 min after the onset of ECC and also on the first postoperative day. The ET-1 concentration was significantly higher in the SIRS group before the induction of anaesthesia and on the first postoperative day (Table 4).

ET-1 and lactate were correlated significantly in the SIRS group but not in the control group after arrival in the ICU. An increase in these parameters was also correlated with a longer ECC duration (Figure 1).

Table 4. Routine and special laboratory measures in the SIRS- and the control group that were significantly different ($p<0.05$; mean ± SD).

Parameter	Blood sampling	SIRS group	Control group
Leukocytes (/µl)	Before anaesthesia	7.6 ± 2.2	6.55 ± 1.75
Alkaline phosphatase (U/l)	Before anaesthesia	110.19 ± 21.71	48.67 ± 48.45
ICAM-3 (ng/ml)	Before anaesthesia	269.9 ± 86.69	202.28 ± 63.75
VCAM-1 (ng/ml)	30 min after onset of ECC	512.1 ± 248.14	740.45 ± 276.88
ICAM-3 (ng/ml)	Morning of the first postop. day	222.04 ± 41.15	159.64 ± 65.96
VCAM-1 (ng/ml)	Morning of the first postop. day	786.38 ± 292.39	957.4 ± 340.92
ET-1 (pg/ml)	Before anaesthesia	2.51 ± 0.72	1.26 ± 0.60
ET-1 (pg/ml)	Morning of the first postop. day	3.21 ± 1.53	2.22 ± 1.41

SIRS – systemic inflammatory response syndrome; ECC – extracorporeal circulation; ICAM – intracellular adhesion molecule; VCAM – vascular adhesion molecule; ET – endothelin.

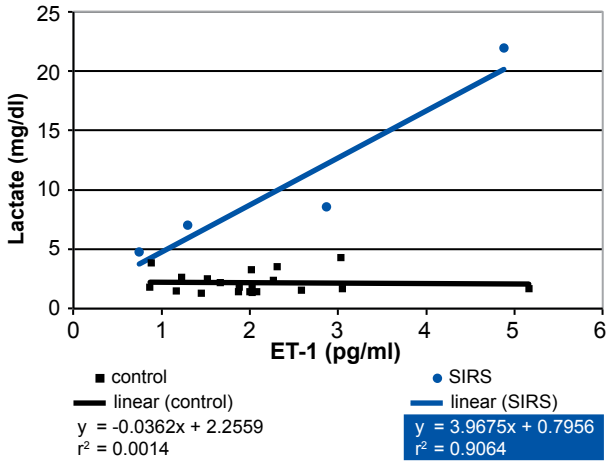

Figure 1. Correlation between lactate and endothelin-1 (ET-1) after arrival in the intensive care unit. r^2 – coefficient of determination. SIRS – systemic inflammatory response syndrome.

Discriminant analysis

The results showed good prediction with many parameter combinations (error quota less than 20%). From these we made a selection according to the criteria of lowest possible number of parameters and best possible predictive ability, especially for true positive SIRS prediction. For each parameter, data concerning the proportions of true positives and negatives, and false positives and negatives were tabulated. The entire error proportion was calculated according to the formula: E = (1-sensitivity)/2 + (1-specifity)/2. The data from 3 of the patients who developed SIRS could not be used for the discriminant analysis since at least one of the values that should be included were missing.

All endothelium-associated parameters showed excellent predictive ability for perioperative SIRS. The prediction could be further improved by inclusion of single routine parameters. The best combination of routine and special laboratory parameters with the prediction rates are summarized in Tables 5 and 6.

Discussion

The literature includes many references to whole-body inflammation and SIRS in open heart surgery.[13-15] Based upon the traditional hypothesis that the extracorporeal circulation (ECC) is the main trigger of perioperative SIRS, it is possible to conceive of prospective studies in which at least a temporal relationship of ECC and SIRS should be definable. Such studies are in contrast to investigations of SIRS of other genesis, e.g. polytrauma; however, an evidence-based data foundation is still lacking. This might be due to the problematic appearance of the typical SIRS symptoms, which occur at times ranging from immediately after the start of the ECC until the first hours in the ICU. Additionally, the incidence of SIRS in a specialised cardiac surgical unit is relatively rare. Thus, the ECC *per se* seems not to represent the main trigger for perioperative SIRS. From our results, we focused on the role of leukocytes, endothelial cells, adhesion molecules and ET-1. Additionally, these parameters seem to be extremely important with regard to the microcirculation that may be affected by the ECC.[16-18]

Both the ECC and the activation of the complement cascade are able to activate neutrophils (PMN) as well as endothelial cells. The phenomenon of rolling and sticking of the PMN on the vessel wall and

Table 5. Combination of routine and special laboratory measures for the prediction of perioperative systemic inflammatory response syndrome (SIRS) before the induction of anaesthesia (time point 1). The individual values of a patient's alkaline phosphatase (AP), endothelin-1, etc., are entered into both formulas and the sums are calculated for both groups. The patient is predicted to belong to the control group if the sum for this group is higher than that for the SIRS group and vice versa. The rules were derived from all 20 controls and 9 of 12 SIRS patients.

Formula for SIRS group (SIRS expected)			Formula for control group (no SIRS expected)		
- 16.53188			- 11.24681		
+ 0.03297	·	AP in U/l	+ 0.01936	·	AP in U/l
+ 0.92756	·	ET-1 in pg/ml	+ 0.68954	·	ET-1 in pg/ml
+ 0.02437	·	ICAM-1 in ng/ml	+ 0.01359	·	ICAM-1 in ng/ml
+ 0.02724	·	ICAM-2 in ng/ml	+ 0.02567	·	ICAM-2 in ng/ml
+ 0.03491	·	ICAM-3 in ng/ml	+ 0.01298	·	ICAM-3 in ng/ml
- 0.0009156	·	VCAM-1 in ng/ml	+ 0.00553	·	VCAM-1 in ng/ml
+ 0.0003882	·	ELAM-1 in ng/ml	+ 0.00744	·	ELAM-1 in ng/ml
resulting value = y_{SIRS}			= $y_{no\ SIRS}$		

ELAM – endothelial leukocyte adhesion molecule. Other abbreviations as in Table 4.

Table 6. Best predictive combination of routine and special laboratory investigations at time point 1 (before induction of anaesthesia) for the prognosis of perioperative systemic inflammatory response syndrome (SIRS), based on the patients of Table 1. All 9 patients with SIRS and complete data were predicted correctly (3 other patients were excluded from the analysis because of missing values). Only 1 patient without SIRS was predicted incorrectly to develop SIRS; the other 19 controls were predicted correctly.

		Prognosis		
		No SIRS	SIRS	Total
Patient developed	No SIRS	19 (95%)	1 (5%)	20 (100%)
	SIRS	0 (0%)	9 (100%)	9 (100%)
Row percent	All	19 (65.52%)	10 (34.48%)	29 (100%)
	Error quota	0 %	5 %	2.5%

diapedesis is mediated by surface molecules of the PMN and endothelial cells, i.e. by the adhesion molecules.[19,20] These molecules are divided into the integrin receptors of the leukocytes, which interact with the surface of the endothelial cells, the selectin receptors, which are expressed on both leukocytes and endothelial cells, and the immunoglobulin super-family, which are only expressed on endothelial cells. An increased expression of adhesion molecules and the consequent activation of PMN represent one of the crucial factors of perioperative capillary leakage syndrome and myocardial reperfusion injury.[21,22] Previous studies have already shown that a blockade of adhesion molecules before reperfusion significantly reduces myocardial failure.[23] In our study, we found significantly higher preoperative levels of ICAM-3 in the SIRS group. Other studies have reported increased concentrations of ICAM-1 and VCAM-1 in patients with myocardial failure, which correlate with the extent of pulmonary arterial hypertension and impaired left ventricular function.[24,25]

All the consequences of the increased adhesion molecule expression can be summarised as progressive tissue damage with impairment on the basis of microcirculation and a release of tissue-toxic substances. This tissue deterioration takes place in different organs, individually corresponding with the typical expression of the adhesion molecules in the particular organ.

ET-1 represents one of the most powerful vasoconstrictors that play a crucial part in the regulation of the blood pressure.[26] It is mainly released from the endothelium of the pulmonary vessels, and former studies have shown that its concentration correlates with the duration of the ECC.[27] In the present study, ET-1 concentrations before anaesthesia in the SIRS group were twofold higher than in the control group. Because the groups did not differ significantly in terms of their demographic data and the incidence of concomitant diseases, it can be postulated that such different preoperative values might be caused by a different impact of endothelium activation or even damage. Reasons for this can be seen in chronic hypertension, nicotine abuse, diabetes mellitus, or hy-

percholesterolaemia, with their special risk for atherosclerosis.[28] The positive correlation between ET-1 and lactate with regard to a longer ECC-duration reflects the already intraoperatively impaired organ perfusion owing to pre-existing endothelial activation.

In summary, the present study compared prospectively for the first time patients with or without SIRS following open heart surgery. We found significant differences between both groups even preoperatively, which suggests a new theory concerning the development of perioperative SIRS: it is not the ECC itself that represents the main trigger, but rather a pre-existing activation of the endothelium, leukocytes and lymphocytes. After the beginning of the ECC this activation leads to impaired perfusion at the microcirculatory level, and finally causes a multi-organ dysfunction syndrome. This end result is similar to the SIRS courses of other genesis, such as those of bacterial genesis, that are unrelated to artificial surfaces. Because of the complex underlying processes of SIRS in cardiovascular surgery, a causal therapy is still lacking. Thus, the prevention and the recognition of the patient at risk come to the fore. With the results of the current study this objective can now be achieved. A combination of routine and special laboratory measures – i.e. alkaline phosphatase, ET-1, ICAM-1, -2, -3, VCAM-1, ELAM-1 – proved to have the best predictive power. Thus, at least in the frame of elective procedures, SIRS can be avoided by postponing the operation. Although perioperative SIRS occurs in only 2% of all ECC procedures, the mortality is high and comparable to that of severe sepsis.[29] In addition, it is precisely this patient group that, because of its high perioperative morbidity, is mostly responsible for increased costs in terms of intensive therapy. Because of the rising number of older and critical ill patients in cardiac surgery, the perioperative management of SIRS needs more attention in the future.

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