4. Bouter H, Schippers EF, Luelmo SA, Versteegh MI, Ros P, Guiot HF, et al. (2002) No effect of preoperative selective gut decontamination on endotoxemia and cytokine activation during cardiopulmonary bypass: a randomized, placebo-controlled study. Crit Care Med 30(1): 38-43
5. Hamilton-Davies C, Barclay GR, Cardigan RA, McDonald SJ, Purdy G, Machin SJ, et al. (1997) Relationship between preoperative endotoxin immune status, gut perfusion, and outcome from cardiac valve replacement surgery. Chest 112(5): 1189-1196
6. Hoffman WD, Danner RL, Quezado ZM, Banks SM, Elin RJ, Hosseini JM, et al. (1996) Role of endotoxemia in cardiovascular dysfunction and lethality: virulent and nonvirulent Escherichia coli challenges in a canine model of septic shock. Infect Immun 64(2): 406-412
7. Holzheimer RG, Molloy RG, Gorlach H, Wilkert S and Hehrlein F. (1994) IL-6 and TNF alpha release in association with neutrophil activation after cardiopulmonary bypass surgery. Infection 22(1): 37-42
8. Kress HG, Scheidewig C, Schmidt H and Silber R (1999) Reduced incidence of postoperative infection after intravenous administration of an immunoglobulin A- and immunoglobulin M-enriched preparation in anergic patients undergoing cardiac surgery. Crit Care Med 27(7): 1281-1287
9. Martinez-Pellus AE, Merino P, Bru M, Canovas J, Seller G, Sapina J, et al. (1997) Endogenous endotoxemia of intestinal origin during cardiopulmonary bypass. Role of type of flow and protective effect of selective digestive decontamination. Intensive Care Med 23(12): 1251-1257
10. Neuhof C, Wendling J, Dapper F, Bauer J, Zickmann B, Jochum M, et al. (2001) Endotoxemia and cytokine generation in cardiac surgery in relation to flow mode and duration of cardiopulmonary bypass. Shock 16(Suppl 1): 39-43
11. Oudemans-van Straaten HM, Jansen PG, Hoek FJ, van Deventer SJ, Sturk A, Stoutenbeek CP, et al. (1996) Intestinal permeability, circulating endotoxin, and postoperative systemic responses in cardiac surgery patients. J Cardiothorac Vasc Anesth 10(2): 187-194
12. Oudemans-van Straaten HM, Jansen PG, Velthuis H, Stoutenbeek CP, Zandstra DF, Deventer SJ, et al. (1996) Endotoxaemia and postoperative hypermetabolism in coronary artery bypass surgery: the role of ketanserin. Br J Anaesth 77(4): 473-479
13. Pilz G, Appel R, Kreuzer E and Werdan K (1997) Comparison of early IgM-enriched immunoglobulin vs polyvalent IgG administration in score-identified postcardiac surgical patients at high risk for sepsis. Chest 111(2): 419-426
14. Reid RR, Prodeus AP, Khan W, Hsu T, Rosen FS, Carroll MC (1997) Endotoxin shock in antibody-deficient mice: unraveling the role of natural antibody and complement in the clearance of lipopolysaccharide. J Immunol. 159(2): 970-975
15. Rothenburger M, Soeparwata R, Deng MC, Schmid C, Berendes E, Tjan TD, et al. (2001) Prediction of clinical outcome after cardiac surgery: the role of cytokines, endotoxin, and anti-endotoxin core antibodies. Shock 16(Suppl 1): 44-50
16. Sablotzki A, Dehne MG, Mann V, Gorlach G, Muhling J, Zickmann B, et al. (1999) Plasma levels of selectins and interleukins in cardiovascular surgery using cardiopulmonary bypass. Thorac Cardiovasc Surg 47(1): 26-31
17. Sablotzki A, Friedrich I, Muhling J, Dehne MG, Spillner J, Silber RE, et al. (2002) The systemic inflammatory response syndrome following cardiac surgery: different expression of proinflammatory cytokines and procalcitonin in patients with and without multiorgan dysfunctions. Perfusion 17(2): 103-109
18. Schedel I, Dreikhausen U, Nentwig B, Hockenschnieder M, Rauthmann D, Balikcioglu S, et al. (1991) Treatment of gram-negative septic shock with an immunoglobulin preparation: a prospective, randomized clinical trial. Crit Care Med 19(9): 1104-1113
19. TIICSG (1992) Prophylactic intravenous administration of standard immune globulin as compared with core-lipopolysaccharide immune globulin in patients at high risk of postsurgical infection. The Intravenous Immunoglobulin Collaborative Study Group. N Engl J Med 327(4): 234-240
20. Trautmann M, Held TK, Susa M, Karajan MA, Wulf A, Cross AS, et al. (1998) Bacterial lipopolysaccharide (LPS)-specific antibodies in commercial human immunoglobulin preparations: superior antibody content of an IgM- enriched product. Clin Exp Immunol 111(1): 81-90
21. Urbaschek B (1985) Quantification of endotoxin and sample-related interferences in human plasma and cerebrospinal fluid by using a kintetic Limulus amoebe lysate microtiter testSeries. In: Leive L(ed) Quantification of endotoxin and sample-related interferences in human plasma and cerebrospinal fluid by using a kintétic Limulus amoebe lysate microtiter test. American Societey for microbiology
22. Urbaschek R, Becker KP (1993) Detection of endotoxin in plasma: specificity and value for development and prognosis of infection. Infusionsther Transfusionsmed 20 Suppl 1: 16-9; discussion 20
23. Warren HS, Novitsky TJ, Ketchum PA, Roslansky PF, Kania S and Siber GR (1985) Neutralization of bacterial lipopolysaccharides by human plasma. J Clin Microbiol 22(4): 590-595
24. Werdan K (1999) Supplemental immune globulins in sepsis. Clin Chem Lab Med 37(3): 341-349
25. Yao YM, Sheng ZY, Tian HM, Yu Y, Wang YP, Yang HM, et al. (1995) The association of circulating endotoxaemia with the development of multiple organ failure in burned patients. Burns 21(4): 255-258

Received: October 31, 2002 / Accepted: November 14, 2002

Address for correspondence:
Dr. med. Ivar Friedrich
Department of Cardiothoracic Surgery
Martin-Luther-University Halle-Wittenberg
D-06097 Halle / Saale, Germany
ivar.friedrich@medizin.uni-halle.de

inflammatory cytokines [17]. A possible target for breaking this cycle might be the inactivation of endotoxin in blood.

The design of this study is based on the pathophysiological understanding that removing endotoxin from blood might decrease the inflammatory response and result in improved clinical outcome. Highly efficient endotoxin neutralization by IgM-enriched immunoglobulin has been described by Schedel et al. These authors demonstrated with in vitro studies that IgM-enriched IVIG preparations have a stronger inhibitory effect on TNF-α release from monocytes compared to pure IgG products [18]. Additional protective mechanisms of immunoglobulin treatment as described by Werdan are: toxin inactivation, stimulation of leucocytes and serum bactericidal activity, interference with cytokine effects, modulation of the complement cascade and synergism with acylureidopenicillins [24].

Unexpectedly, endotoxin plasma levels were not reduced by the infusion of IgM-enriched immunoglobulin. On the contrary a slight increase was found in the immunoglobulin treated group at all time points, while levels remained remarkably low in the control group. It has to be mentioned that almost all increased endotoxin levels were still in the range of values found in normal individuals (5.1 ±4.1 pg/ml) [21]. An increase of endotoxin plasma levels during ECC has recently been described [10, 11, 13] and the observed values in group A were lower than published data.. But the reason for the difference between both groups is still unclear. A possible explanation is a cross reaction of the IgM-enriched immunoglobulin preparation or the human albumin (placebo) with the LAL-method. Urbaschek et al. reported that immunoglobulin preparations induced different nonspecific LAL-activation in different lysates [22]. Unfortunately, there are no studies available that address the effect of IgM-enriched immunoglobulin- or human albumin- solutions on the LAL method. The hypothesis of study drugs affecting the analysis is supported by the ENC-measurements. During ECC, ENC was found to be significantly higher after IVIG-infusion than in controls.

If these findings were correct, then it would seem unlikely that the plasma endotoxin levels are also elevated. These contradictory findings can only be explained by falsely high endotoxin plasma levels in the IVIG-group or falsely low values in the control group. Although IVIG-therapy did not result in a significant increase in anti-inflammatory and/or decrease in proinflammatory cytokine generation compared to the control group, a significant lower inflammatory response was observed clinically. The incidence of all inflammatory parameters such as fever, tachycardia/hypotension and leukocytosis (leukopenia did not occur in this patient population) were significantly lower after IVIG-infusion than in the control group. These clinical findings strongly support the theory of the endotoxin results being falsified, as corroborated by the ENC-data, and point against truly increased endotoxin levels in the IVIG-group. Sufficient restoration of the endotoxin neutralizing capacity is crucial for a complication-free postoperative course. The loss of endotoxin core antibodies (EndoCab) below a cut off value of 100 MU/ml was correlated with several complications, both cardiac and non cardiac. Interestingly, low EndoCab was not associated with high risk parameters like low cardiac output or higher age, but all patients (specifity 100%) with complications had preoperatively low EndoCab activity [5]. Pilz et al. conducted a prospective study in cardiac surgical patients at risk who had an APACHE II-score of >24 on the first postoperative day [13]. The patients were randomized to receive intravenous IgG or IgM-enriched immunoglobulin solutions. After the infusion, the APACHE II-score values (IgG-group: 6.9; vs. IgM enriched IgG-group: 5.2) fell markedly within four days. In comparison to a previous case-controlled group of a comparable patient population, mortality figures were significantly reduced after immunoglobulin infusion (either IgG alone or IgM-enriched). In contrary to the well known problems of setting the optimal time point for starting treatment in patients suffering from severe sepsis, cardiac surgery patients at risk can be identified early, even preoperatively, before the onset of clinical symptoms. The effectiveness of immunoglobulin therapy relates to the timing of immunoglobulin administration. Promising results may be gained in patients who have not reached the late, anergic phase of sepsis. Further studies in high risk patients may clarify the role of immunoglobulin treatment. Under cost effectiveness perspectives, IVIG-infusions to prevent postoperative infectious complications may only be recommended for selected patients at high risk as has been shown by the clinical study of Kress et al. [8].

Acknowledgment: The authors like to thank Dr. R. Urbaschek and Dr. K.P. Becker, Institute of Microbiology, University Heidelberg-Mannheim, for their continuous advice and critique with regard to endotoxin measurements. We are indebted to Mrs. M. Ulbrich for the statistical analysis of the data.

References

1. Boelke E, Storck M, Buttenschoen K, Berger D, Hannekum A (2000) Endotoxemia and mediator release during cardiac surgery. Angiology 51(9): 743-749
2. Bolke E, Jehle PM, Orth K, Steinbach G, Hannekum A and Storck M (2001) Changes of gut barrier function during anesthesia and cardiac surgery. Angiology 52(7): 477-482
3. Börgermann J, Friedrich I, Flohe S, Spillner J, Majetschak M, Kuss O, et al. (2002) Tumor necrosis factor-alpha production in whole blood after cardiopulmonary bypass: downregulation caused by circulating cytokine- inhibitory activities. J Thorac Cardiovasc Surg 124(3): 608-617

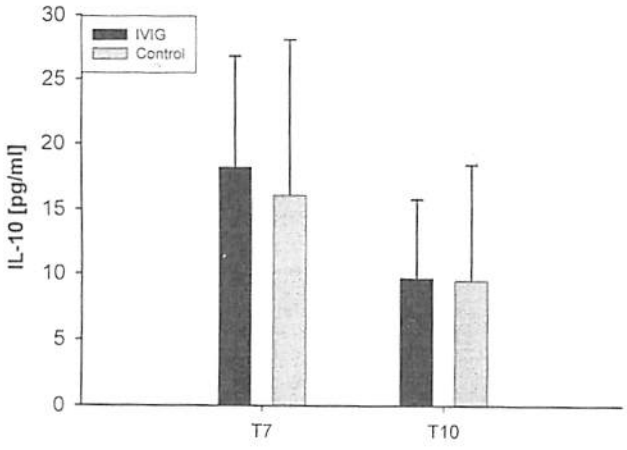

Fig. 5. Postoperative (T7 and T10) interleukin (IL)-10 plasma levels of treatment group A (IVIG) and nontreatment group B (control). Data are presented as mean ± standard deviation.

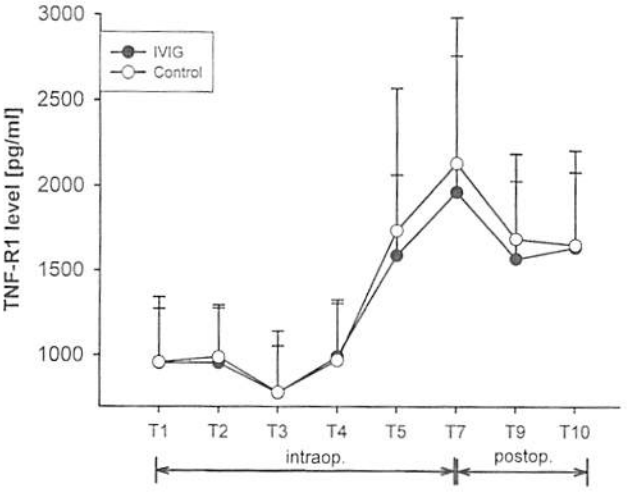

Fig. 6. Intra- and postoperative level of soluble tumor necrosis factor (sTNF) Receptor 1 in plasma of treatment group A (IVIG) and nontreatment group B (control). Data are presented as mean ± standard deviation.

tient in group A. 20% of group B patients developed leukocytosis exceeding 15,000/fl, but only 5% of the patients who received IVIG. In summary, 25% of group B patients experienced at least two of the following clinical signs of inflammation: fever, tachycardia/hypotension or leukocytosis, whereas only 5% of patients who had received IVIG were afflicted with these inflammatory symptoms. This observation of reduced clinical inflammatory signs is further supported by a shorter hospitalization period (A: 12.1 ± 3.7 days; 13.5 ± 3.7 days; n.s.).

Discussion

Infections after cardiac surgical procedures can be life threatening and result in significant mortality and morbidity. The increased infection rate is due

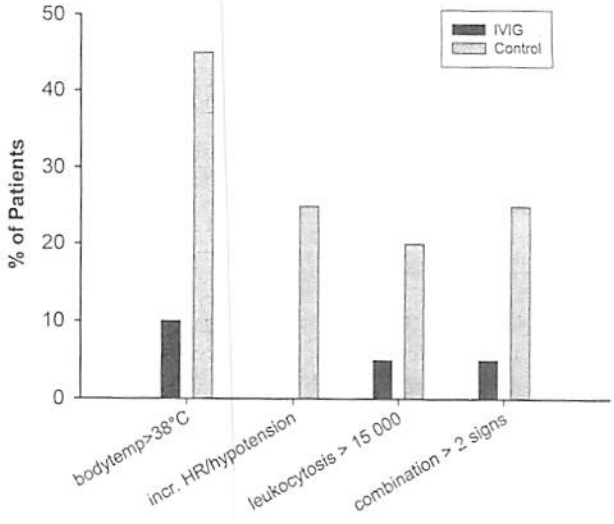

Fig. 7. Clinical signs of inflammation postoperatively.

to several pathophysiological changes, including reduced immunocompetence as a consequence of patients being subjected to extracorporeal circulation (ECC) [3]. The appearance of endotoxin in peripheral blood may have unfavorable consequences [15]. First, increased plasma levels of endotoxin might be an indicator of impaired gut barrier function and increased bacterial translocation [2]. Second, sepsis develops more likely during an immunodeficient state early after surgery with ECC [3]. A previous study by Oudemans-van Straaten et al. revealed a correlation between loss of gut barrier function after cardiac surgery and the increase in endotoxin blood levels [11]. This study supports the hypothesis that excess endotoxin after cardiac surgery originates from the gut. A study by Bouter et al. contradicts the gut hypothesis, because it failed to find improved clinical or biochemical results after selective gut decontamination (SGD) prior to cardiac surgical operations [4]. Especially the amount of endotoxin in blood was not different after SGD than in the placebo group. A study by Martinez-Pellus on the other hand showed protective effects of SGD on clinical outcome and reduced cytokine release [9]. Although the value of gut decontamination in cardiac surgery remains unclear, it is unquestionable that endotoxemia in combination with loss of immunological competence are deleterious. Endotoxin liberation might be a consequence of a sepsis-like reaction of the body to ECC. As a response, whole body inflammation develops. This process is referred to as systemic inflammatory response syndrome (SIRS) [16]. Several indicators are thought to affect endotoxin liberation and cytokine generation: quality of tissue perfusion, duration of ECC, fluid balance and endotoxin core antibody level [1, 10]. In a vicious cycle, endotoxemia leads to further acceleration of the inflammatory response by promoting the liberation of pro-

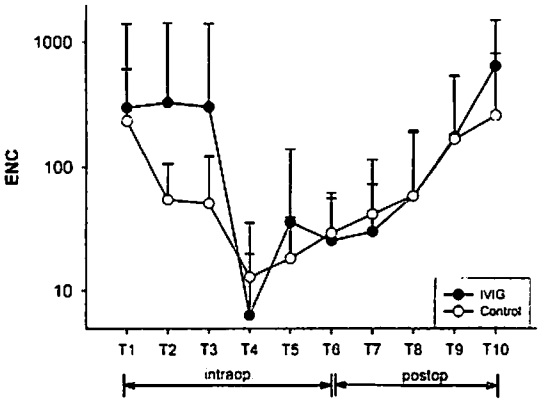

Fig. 2. Intra- and postoperative endotoxin neutralizing capacity in plasma of treatment group A (IVIG) and nontreatment group B (control). Data are presented as mean ± standard deviation.

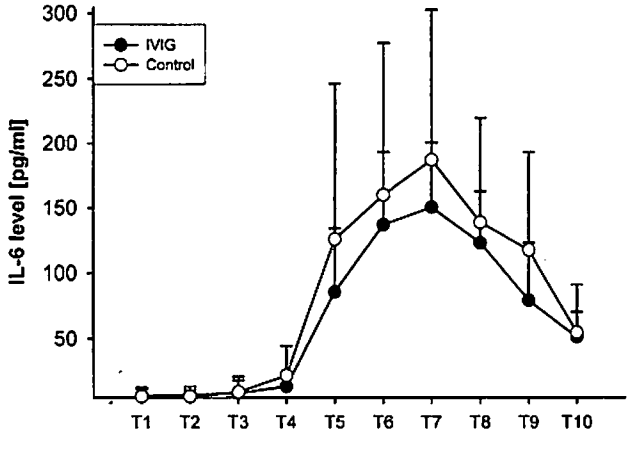

Fig. 3. Intra- and postoperative Interleukin (IL)-6 plasma levels of treatment group A (IVIG) and nontreatment group B (control). Data are presented as mean ± standard deviation.

operative day, the LAL-test still yielded positive results (7.11 ± 6.69 pg/ml). Interestingly, after prophylactic administration of IgM-enriched immunoglobulin (A), the endotoxin plasma levels were generally but not significantly higher than those of the control group (B). The highest endotoxin concentration was found 24 hours after the induction of anesthesia (Fig. 1, Table 2).

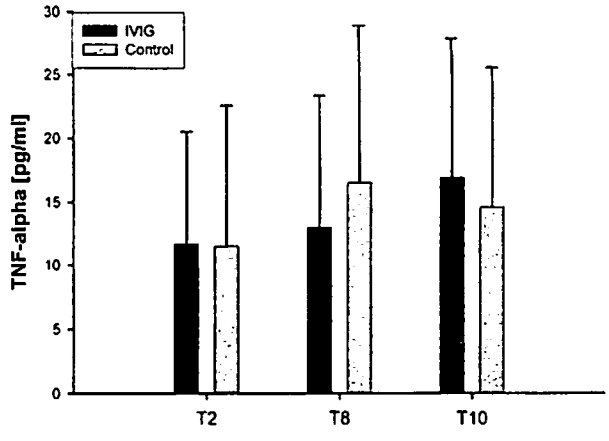

Fig. 4. Intra- (T2) and postoperative (T8 and T10) tumor necrosis factor (TNF)-α plasma levels of treatment group A (IVIG) and nontreatment group B (control). Data are presented as mean ± standard deviation.

A more pronounced decrease of ENC occurred in the control group after commencing surgery (Fig. 2). The ability to inactivate endotoxin was restored during ECC after IVIG infusion, while ENC remained significantly lower in the control group as revealed in the area under curve calculation (A: 785 ± 385,5; B: 227,5 ± 124,6; $p < 0.005$). After ECC, ENC reached a minimum in both groups, and regained preoperative values after 24 h (Table 3).

IL-6 plasma levels peaked 4 h after surgery and declined steadily thereafter. There was no significant difference between group A and group B (Fig. 3). Control group TNF-alpha plasma levels increased slightly after 6h , but this difference was not statistically significant (Fig. 4). Il-10 and sTNF-R1 - two mediators with anti-inflammatory capabilities - increased after cardiac surgical operations, but IVIG infusion did not appear to have any influence on plasma levels. A significant difference between both groups was not detectable (Fig. 5 and 6).

Interestingly, the absence of significant differences in plasma levels of pro- and anti-inflammatory cytokines between IVIG and control group was overshadowed by markedly different clinical parameters in the postoperative course (Fig. 7). In two group A patients, the body temperature rose to above 38 °C during the first 24 to 28 hours; in group B, nine patients developed temperatures above 38 °C. Tachycardia and/or hypotension occurred in 25% of group B patients but in no pa-

Table 3. Endotoxin neutralizing capacity (ENC) calculated as area under the curve for the time intervals T1-T5 (intraoperative) and T6-T10 (postoperative).

	Group-A	Group B	Significance
after Anesthesia	785.7 ± 684.5	227.5 ± 124.6	p = 0.005
after ECC	623.8 ± 422.6	431.8 ± 267.4	p = 0.09

pental and maintained with nitrous oxide/oxygen (50% / 70%), fentanyl, droperidol. The muscle relaxant pancuronium bromide was used. For antibiotic prophylaxis, 1.5 g cefotiam was intravenously administered 60 min prior surgery and then every 8 hours during the two following postoperative days. The entire anesthesiological management followed our standard for cardiac surgical patients. After surgery, all patients were mechanically ventilated upon arrival in the intensive care unit and were weaned from the ventilator within 12 hours.

All operations were performed through a median sternotomy under moderate hypothermia with an esophageal temperature of 28 °C and a rectal temperature of 32 °C. All patients received cold blood cardioplegic-solution. The priming solution for the extra corporeal circulation consisted of 2300 ml of lactated Ringer's solution supplemented with 5000 IU of heparin and 500 ml of a 5% plasma protein solution containing > 90% human albumin (Hormon Chemie, Munich, Germany) or 1 unit of blood depending on the preoperative hemoglobin concentration. During ECC, flow rates of 2.4 l/m² body surface area were maintained.

Human IgM-enriched Immunoglobulin (IVIG) Preparation

Pentaglobin® (Biotest Pharma GmbH, Dreieich, Germany) is a commercially available intravenous human immunoglobulin preparation. Pentaglobin® contains high concentrations of IgA and IgM. The polyclonal human IVIG preparation is active against a variety of gram-negative and gram-positive bacterial pathogens and toxins, including Streptococcus pyogenes, S. faecalis, group B streptococci, Staphylococcus aureus, S. epidermidis, toxic shock syndrome toxin, Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Legionella species, Yersinia pseudotuberculosis, Proteus vulgaris and Serratia marcescens. Pentaglobin® contains 50 mg/ml human plasma proteins, > 95% of which are immunoglobulins: 76 % IgG, 12% IgM and 12% IgA. Additional components are glucose (27.5 mg), sodium chloride (75 µmol) and distilled water. The Pentaglobin® preparation is proven to be endotoxin-free according to pyrogen testing in rabbits.

Endotoxin Assay

To measure endotoxin and endotoxin neutralizing capacity (ENC), we used the turbidimetric, kinetic LAL test with internal standardization, as described by Urbaschek and Becker [22]. Endotoxin standard (NP-3 (KSE), Salmonella abortus equi 100 ng/ml) and lysate (Limulus amebocyte lysate (LAL), Cape Cod, USA) were provided by Pyroquant Diagnostik (Walldorf, Germany). Each sample was spiked with a known concentration of endotoxin. The kinetic reaction was read continuously in an ELISA plate reader (Molecular Devices, MWG Biotech, Ebersberg, Germany). The sensitivity of the endotoxin test was 0.5 pg/ml. ENC is an index describing the activity of human plasma to neutralize endotoxin added to the plasma in known quantities [23]; it is influenced by plasma proteins and other factors known to neutralize endotoxin.

Cytokines and sTNF-RI

To measure the cytokines IL-6, IL-8, IL-10, TNF-α and sTNF-α-RI, commercially available ELISA kits were used (Quantikine, R&D Systems Inc., Minneapolis, MN). The detection limits were 7 pg/ml for IL-6, 1 pg/ml for IL-10, 4.4 pg/ml for TNF-α, and 1.5 pg/ml for sTNF-R1.

Statistical Analysis

All data are presented with means and standard deviation. A t-test was performed for all independent variables and ANOVA testing when required. The cut-off for statistical significance was 0.05. All statistical analyses were performed by an independent statistics institute (IFNS, Cologne, Germany)

Results

Endotoxin and Endotoxin Neutralizing Capacity (ENC)

In the untreated group (B), plasma endotoxin (Fig. 1) was first detected at the beginning of extracorporeal circulation (0.8 ± 1.2 pg/ml). A peak level was reached 4 hrs after ECC (2.2 ± 3.5 pg/ml). Plasma endotoxin levels continued to be elevated until the second postoperative day (0.65 ± 0.52 pg/ml). In the IVIG group (A), the LAL-tests (6.47 ± 13.84 pg/ml) were already positive at the induction of anesthesia. On the second post-

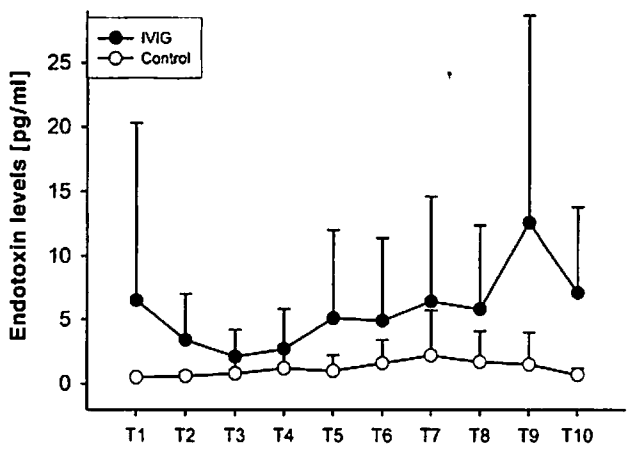

Fig. 1. Intra- and postoperative endotoxin plasma levels of treatment group A (IVIG) and nontreatment group B (control) . Data are presented as mean ± standard deviation.

mune system activation including stimulation of leukocytes and serum bactericidal activity, interference with cytokine effects and modulation of the complement cascade. Endotoxin clearance is dependent on adequate IgM-plasma levels. Experimental studies in an endotoxin shock model in mice showed that the endotoxin clearance in IgM-deficient animals was dramatically reduced and could be restored by infusing purified IgM [14]. Several trials have been carried out to determine the prophylactic efficacy of intravenous immunoglobulins in surgical patients. A mortality reduction could not be observed in most previous studies but the outcome did improve in subgroups of immunological impaired patients [19]. The objective of this randomized controlled study is to evaluate the effect of prophylactically administered Pentaglobin® on toxin neutralization, production of pro- and anti-inflammatory cytokines, and clinical signs of inflammation in cardiac surgical patients.

METHODS

STUDY DESIGN

Prospective, double-blind, randomized study in cardiac surgery patients. Treatment with is compared to treatment without intravenous immunoglobulin infusion. Each group comprises 20 patients.

PATIENTS

41 patients, admitted for elective coronary surgery were included in the study. One patient showed minor signs of allergy (skin rash, dizziness) during the infusion of Pentaglobin®. The infusion was stopped and the patient was eliminated from the study. Follow-up was uneventful. The patient population consisted of 31 men and 9 women with a mean age of 61.2 years with a range from 42.0 to 70.9 years. The average weight was 73.6 kg (Table 2). Nine of 40 patients had co-morbidities (kidney agenesia, abdominal aortic aneurysm, diabetic retinopathy, nephrolithiasis, goiter, fatty liver, status post partial nephrectomy, hemicolectomy). None of the patients characteristics were statistically different between both groups (data not shown).

The APACHE II score ranged from 5 to 12 (men 4-8, women 5-12; mean 7.0). In 27 patients, the ejection fraction (EF) was above 0.55 and in 13 patients below 0.55. In three patients, one coronary artery bypass was constructed, in 5 patients two bypasses, , in 22 patients three, and in 10 patients four bypasses. Total operating time, ECC time, , ischemic time, and reperfusion are given in Table 1.

21 patients were randomized into group A (one drop out) and received the IgM enriched immunoglobulin preparation (Pentaglobin®), 20 patients into group B who were to receive placebo before induction of anesthesia. Both groups were homogenous with regard to gender, age, severity of coronary artery disease and comorbidity. The study was approved by the local ethics committee and each patient was included after an informed consent had been obtained. The study followed the guidelines for clinical studies defined in the Helsinki declaration of the World Medical Association 1964 (most recently updated in 2002).

Table 1. Pre-, intra- and postoperative patient parameters. Data are presented as mean ± standard deviation.

	Group A	Group B
Apache II Score	4.4 ± 2.3	5.2 ± 3.0
Duration of surgery (min)	204 ± 58	230 ± 80
ECC-time (min)	107.4 ± 25.3	113.9 ± 42.6
Crossclamp (min)	55.5 ± 13.3	61.3 ± 22.6
Days in the ICU	3.5 ± 1.2	4 ± 1.9
Days in hospital	12.1 ± 3.7	13.45 ± 3.7

BLOOD SAMPLING

Clinical and laboratory tests were performed prior to treatment, intra- and postoperatively, daily until the seventh postoperative day, and finally on the day of discharge (Table 2). On the day of surgery, blood samples were drawn at different time points. In detail, endotoxin, endotoxin neutralizing capacity (ENC), TNF-α, IL-6, sTNF-α Receptor I (sTNF-α RI), IL-8, IL-10 were measured after thoracotomy, when commencing extracorporeal circulation, after removal of the aortic clamp, and 1h, 2h, 4h, and/or 6h after terminating extracorporeal circulation.

Table 2. Blood sampling schedule.

1	Induction of Anesthesia	0 h
2	Thoracotomy	0.75 h
3	Beginning of ECC, X-Clamp	1.5 h
4	end of ECC, X-clamp off	3.5 h
5	1 h after ECC	5 h
6	2h after ECC	6 h
7	4h after ECC	8 h
8	6h after ECC	10 h
9	1 st postop day	24 h
10	2nd postop day	48 h
11	3rd postop day	72 h
12	4th postop day	96 h
13	5th postop day	120 h
14	6th postop day	144 h
15	7th postop day	168 h
16	Hospital discharge	280 h

ANESTHESIOLOGICAL AND SURGICAL MANAGEMENT

Anesthesia was induced with fentanyl and flunitrazepam, occasionally supplemented with thio-

Eur J Med Res (2002) 7: 544-550

IgM-enriched Immunoglobulin Preparation for Immunoprophylaxis in Cardiac Surgery

I. Friedrich[1], R. E. Silber[1], B. Baumann[2], C. Fischer[2], R. G. Holzheimer[3]

[1]Department of Cardiothoracic Surgery, Martin-Luther-University Halle-Wittenberg,
[2]Department of Cardiothoracic Surgery, University Würzburg,
[3]Praxis-Klinik, Sauerlach, Germany

Abstract

Objective: Evaluating the effects of prophylactic administration of IgM-enriched immunoglobulins (IVIG) on immunological- and clinical parameters in cardiac surgical patients.

Patients and Methods: 41 patients were randomized to receive either an IgM-enriched immunoglobulin (Pentaglobin®) preparation (1300 ml immunoglobulin, equivalent to 65 g protein) combined with routine antibiotic prophylaxis (Group A; n = 20, 1 drop-out), or routine antibiotic prophylaxis plus placebo (Group B; n = 20). Patients were comparable with respect to their APACHE II score, comorbidity, coronary risk, operating time, clamp, and ischemic time. Endotoxin and endotoxin neutralizing capacity (ENC) were determined by a kinetic turbidimetric Limulus amebocyte lysate (LAL) assay with internal standardization. Serum levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF)-α, soluble TNF-Receptor I (sTNF-R1), and interleukin-10 (IL-10) were determined by ELISA. Data analysis was performed by area under the curve (AUC) calculation and ANOVA for endotoxin neutralizing capacity and by ANOVA for all other cases.

Results: All patients survived. Endotoxin plasma levels were generally but not significantly higher in group A than in controls, while the difference in endotoxin neutralizing capacity (ENC) reached significance. IL-6, TNF-α, IL-10 and TNF-R1 were not different between both groups, however. There were significantly less patients with signs of inflammation (fever, leukocytosis, hypotension) in group A (group A n = 2; group B n = 9; $p < 0.05$). This was paralleled by a slightly reduced hospitalization period in group A patients compared to group B patients (A:12.05 ± 3.66 vs. B:13.45 ± 3.72 days; n.s.). All data are given as mean ± standard deviation (SD).

Conclusion: The results of this study support that IgM-enriched IVIG preparation are effective when used prophylactically in patients undergoing procedures with cardiopulmonary bypass. The mechanisms of endotoxin neutralization and the effect of the host immune status on the efficacy of IVIG treatment remain to be elucidated.

Key words: Cardio-pulmonary bypass; IgM-enriched immunoglobulin; prophylaxis; endotoxin - cytokines; endotoxin neutralizing capacity; fever - complications

Introduction

Despite recent substantial improvements in intensive care, infectious complications continue to be a serious problem in surgical patients and represent a major determinant of postoperative outcome. The amount of endotoxin (LPS) originating from disintegrated cell walls of gram-negative pathogens is a good indicator for the severity and prognosis of the septic process [6, 25]. As a result of using ECC, immune-competence is profoundly reduced in patients undergoing open heart surgery [3]. Further promoters for infectious complications after cardiac-surgery with ECC are hypoperfusion, hypothermia and hemodilution. Increased plasma endotoxin concentrations after cardiopulmonary bypass may be caused by poor tissue perfusion and ischemic damage to the bowel. This ischemic injury is thought to result in translocation of endotoxins and enteric bacteria from the gut [10]. Circulating endotoxin is a strong trigger for the liberation of proinflammatory cytokines. A corresponding increase in cytokine concentrations has been observed during and after cardiopulmonary bypass surgery. Patients undergoing cardiac surgery with ECC are prone to develop systemic inflammatory response syndrome (SIRS) [7]. Excessive cytokine production can lead to organ dysfunction, organ failure, and death [1].

The rationale for prophylaxis and treatment with IgM-enriched immunoglobulins is based on the finding that antigen-antibody complexes are much stronger activators of phagocytosis than antigen alone [20]. Immunoglobulins bound to antigen structures like endotoxin enhance im-

*The study was supported by a grant from Biotest Pharma, Dreieich, Germany and NATO Collaborative Research Grant No. 910960