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Pre-filling of the extracorporeal circuit with autologous blood is safe, but not effective in optimizing biocompatibility in high-risk patients

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Abstract

Objectives: Haemodilution resulting from crystalloid priming of the cardiopulmonary bypass circuit represents a major risk factor for blood transfusions in high-risk cardiac surgery patients. We designed this study to evaluate the effects of antegrade autologous priming (AAP) on reducing perioperative blood transfusion and markers of the inflammatory response in older patients (>75 years).

Methods: Seventy-two patients undergoing first-time coronary bypass and/or aortic valve replacement were prospectively randomised to a cardiopulmonary bypass (CPB) with or without AAP. AAP was performed by adding the patient's own blood to the prime solution (mean 280ml). Perfusion and anaesthetic techniques were as usual. The haematocrit was maintained at a minimum of 21% during CPB. Patients were well matched for all preoperative variables, including established transfusion risk factors. The primary endpoint was the requirement of red cell transfusion. The surrogate endpoints were renal function, inflammatory response and ischaemic parameters. Blood samples were drawn pre- and intraoperatively and at intervals of 6 hours till POD 6.

Results: Current analysis shows no differences in patients receiving homologous packed red cell transfusions. Also, markers of the inflammatory response (IL6, IL8), renal function (cystatin C, creatinine) and myocardial ischaemia (troponin T, CK-MB) were comparable in both groups ($p>0.05$). Clinical outcomes were similar with respect to pulmonary, renal and hepatic function, length of ICU stay and hospital stay.

Conclusion: These data suggest that antegrade autologous priming is a safe procedure, but an ineffective way for improving biocompatibility and reducing the need for blood transfusion in older patients.

Keywords

antegrade autologous priming; pre-coating; extracorporeal circulation; haemodilution; inflammation; blood loss

Introduction

Haemodilution during extracorporeal circulation is a primary risk factor of blood transfusion requirements in patients undergoing cardiac surgery.[1] Depending on the setup of the cardiopulmonary bypass (CPB), the priming volume can vary between 400 and 2000 ml.[2] This crystalloid volume at the beginning of each perfusion represents the significant part of the total haemodiluting volume in cardiac surgery.[3] In order to reduce this volume, the technique of retrograde autologous priming (RAP) was successfully investigated in several studies.[1,2,4,5] RAP reduces haemodilution during the start-up phase of CPB by prior reduction of the priming volume. This is achieved by retrograde arterial or venous filling of the heart-lung machine (HLM) after cannulation, by a slow exchange of the crystalloid priming solution with the patient's own blood. In order to ensure adequate

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Table 1. Priming volumes of the extracorporeal circulation

Control group	Pre-coat study group
500 ml Poly(O-2-hydroxyethyl) HES 6%	500 ml Poly(O-2-hydroxyethyl) HES 6%
200 ml electrolytic solution	200 ml electrolytic solution
200-400 ml additional crystalloid priming	200-400 ml autologous RBP
250 ml Mannitol $C_6H_8(OH)_6$. 20%	250 ml Mannitol $C_6H_8(OH)_6$ 20%
20 ml Tranexamic acid	20 ml Tranexamic acid
Heparin 10000 I.U.	Heparin 10000 I.U.
1250 ml crystalloid priming solution	≈1000ml crystalloid priming solution
1250 ml total priming	1250 ml total priming

HES: hydroxyethyl starch;

circulation during priming, the application of vasoconstrictive substances or central venous volume loading may be necessary. The technique was first described by Rosengart et al.[6] To provide improved circulatory compliance and safety, the technique was modified for this study and the patient's blood was supplied antegrade to the HLM.[7] This pre-filling of the heart-lung machine with the patient's blood (pre-coating) was intended to improve the biocompatibility of the foreign surfaces. In order to determine possible differences more clearly, a patient selection of older and/or patients with a severely reduced left-ventricular function was undertaken.

Methods

This is a block-randomised, prospective, monocentric, non-blinded, two-armed, therapeutic study in patients undergoing cardiac surgery. Data collection and patient recruitment were carried out in 2011 (1/2011-9/2011). The components of extracorporeal circulation were identical in both study arms. A roller pump, HL20 (Maquet, Rastatt, Germany), a membrane oxygenator, Quadrox-i™ (Maquet), a cardiotomy reservoir (Maquet) and a tubing set with an arterial filter, Quart™ (Maquet), were used. Sedation with an anaesthetic gas, Sevorane™ (Abbott, Wiesbaden, Germany), was continued during the perfusion via an anaesthetic gas evaporator (Dräger, Lübeck, Germany). Only the amount of own blood administered in pre-filling (priming) differed, depending on randomisation in the study. (Table1). Intra- and postoperative transfusion and coagulation management were according to the house internal standard algorithm.[8]

Pre-coating procedure

The initial description of the retrograde autologous priming technique by Rosengard et al.[9,10] was modified. After introducing anaesthesia, followed by timely skin incision, a maximum of 400 ml blood was collected from the patient via the central venous line (CVL) with a CPD blood bag (Fresenius Kabi, Bad Homburg, Germany). Stable circulation was to be observed before and during blood collection. Autotransfusion was the only measure permitted to regulate the blood pressure. Blood collection was to be stopped immediately if there was any need to administer additional volume or vasoconstrictors. Ten minutes before commencing with the planned extracorporeal circulation (ECC), the contents of the removed CPD blood bag were added to the heart-lung machine and circulated with the remaining priming volume for approximately 10 minutes in the open system. The extracorporeal circulation (ECC) was controlled with a flow rate between 2.5-3 l/min/m^2 body surface area (BSA). The operation was performed at 32°C at moderate hypothermia. Modified blood cardioplegia was used in all patients. At the end of the ECC, the entire tubing set and the blood remaining in the venous reservoir were collected in a re-transfusion bag. A cell-saver (CATS, Fresenius) was used with blood volumes of more than 600ml. Specific comments in the perfusionist's protocol relate to the cannulisation sites, long perfusion times and a medical history of previous respiratory diseases. If atherosclerotic changes of the ascending aorta or the aortic arch were known about in the patients, the right subclavian artery was preferred as the arterial access.

Inclusion criteria were a patient age of >75 years and/or a reduced left ventricular function of <40%. Furthermore, informed consent and elective, planned surgery using the heart-lung machine were needed. Patients with combined interventions on the aorta and/or carotid arteries and/or multiple valve operations were excluded. Patients were similarly not randomised into the study if the following preoperative exclusion criteria were present: serum creatinine >1.8mg/dl, raised GOT/GPT values double the norm, haemoglobin (Hb) <11mg/dl, myocardial infarction within the last seven days before surgery, and affiliation to the religious community of the Jehovah's Witnesses.

Laboratory tests

Six measurement time points (T1 preoperative, T2-T4 intraoperative, T5-T6 postoperative) were defined. The requirement for blood products was evaluated as the primary endpoint. This includes the number of erythrocyte concentrates, thrombocyte concentrates, fibrinogen, prothrombin concentrates (PPSB) and frozen fresh plasma (FFP) up to time point T6 (discharge). Renal function (creatinine, cystatin C), inflammation (IL6, IL8, TNF-α, C-reactive protein) and ischaemic events (creatine kinase, CK-MB, troponin T) up to time point T6 were determined as secondary endpoints. The central laboratory of the Centre for Internal Medicine and the Study Laboratory of the Clinic for Thorax, Heart and Thoracic

Table 2. Preoperative group distribution with two significant differences (NYHA class and preoperative creatinine value)

	Pre-coat study group	Control group	p-value
Age	74±9ys	75±9ys	Not significant (ns)
Male	78%	77%	ns
NYHA Class≥III	58%	25%	0.005**
Elective surgery	100%	100%	ns
ASA Class>2	44%	31%	ns
LV-function reduced	50%	51%	ns
Diabetes type II	33%	26%	ns
Occlusive arterial disease	8%	9%	ns
Creatinine	1.0±0.3 mg/dl	1.3±0.5 mg/dl	0.03*

NYHA: New York Heart Association; ASA: American Society of Anesthesiologists.

Vascular Surgery at the University Clinic of the Johann Wolfgang Goethe University, Frankfurt am Main have been recognised according to DIN EN ISO 15189; DIN EN ISO 9001:2008 (accredited medical laboratories).

Clinical parameters orientate themselves according to the evaluations of the German Federal Multi-sector Quality Assurance (SQG, Aqua Institute Göttingen, Germany) and were extracted from existing postoperative databases.

Statistics

The block randomisation of n=72 patients resulted in a distribution of 36 patients into each arm of the study. In the pre-coat study group, one patient was not included in the evaluation due to the preoperative administration of an erythrocyte concentrate. In the control group, antegrade autologous priming was performed in one patient. This patient was also not included in the statistical calculations. The calculation of group size is based on the assumption of a difference with regard to the primary endpoint of 20% of the effective size.[11] In a bilateral t-test procedure, a power of 0.8 (1-β error) and an α-error of 0.05 resulted in an overall group size of n=71 (G-power 3.01, Düsseldorf, Germany). Evaluation of the data was performed using SPSS (PASW Statistics 18, SPSS Inc., Chicago, IL, USA). The following statistical procedures: t-test for non-related random samples, Chi^2 test according to Pearson, ANOVA and multiple logistic regression analysis were used for calculating the transfusion requirements. The criterion for rejection of the null hypothesis was $p<0.05$. The median is calculated in addition to the arithmetic mean value and standard deviation.

Conduction of the trial was approved by the Ethics Committee of the Johann Wolfgang Goethe University, Frankfurt am Main, Germany. Patients were informed in writing about the contents of the study and gave their consent to participate with their signature.

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Results

The demographic data, preoperative concomitant diseases and risk scores are summarised in Table 2. There are two significant differences in the group distribution. On the one hand, patients in the pre-coat group are in New York Heart Association (NYHA) Stages III or IV in 58% of cases. As a comparison, only 28% of the patients in the control group are in these two higher NYHA classes. A further difference exists in the preoperative serum creatinine value. The patients in the control group have, on average, a 0.3mg/dl higher initial value compared to the patients in the pre-coat group. There are no significant differences between the remaining preoperative characteristics. The high patient average age of 75±9years is noteworthy. This anomaly is due to the inclusion criteria, as is the high proportion of patients with reduced left ventricular (LV) function.

The items recorded intraoperatively show no differences in the group distribution.

Primary endpoint (requirement for blood products)

No significant differences could be calculated with regard to the requirements for packed red cells (PRC) (Control: 900±780ml / Pre-coat: 730±750ml), platelets (Control: 60±80ml / Pre-coat: 40±80ml), FFP (Control: 150±450 / Pre-coat: 240±630ml) and fibrinogen (Control: 0.7±1.5g / Pre-coat: 1.37±3.2g). The number of re-thoracotomies and postoperative bleeding is also identical in both groups (Table 3). Independent of the study group distribution, 80% of all patients in our institution required blood products during the hospitalisation phase. With regard to the primary endpoint, the pre-coating procedure had no influence on the postoperative requirement for blood products. In a linear regression analysis, the age of the patient, the bypass time and the intra-hospital length of stay were identified as significant risk factors.

The Hb value and the haematocrit did not differ significantly at any of the six blood collection time points. In both groups, however, significant haemodilution

Table 3. Intraoperative comparison of the two study arms

	Pre-coat study group	Control group	p-value
CPB (minute (min))	128±41	111±41	ns
CCT (min)	83±27	69±39	ns
Operation time (min)	262±74	248±62	ns
Grafts (mean)	2.3±0.7	2.2±0.5	ns
A.subclavian cannulation	11%	6%	ns
CABG	66%	85%	p=0.051
Complex procedure	29%	19%	ns

CPB: cardiopulmonary bypass; CCT: cross-clamp time; CABG: coronary artery bypass graft surgery; A. subclavian cannulation

Table 4. Postoperative complication rate without any significant differences between the study arms

	Pre-coat study group	Control group	p-value
Intra-hospital mortality	N=3	N=1	ns
30-day mortality	N=4	N=2	ns
Psycho syndrome	N=2	N=1	ns
Reduced mobilisation	N=3	N=5	ns
Re-thoracotomy	N=1	N=1	ns
Mediastinitis	N=2	N=0	ns
Intra-hospital stay (days)	10.1±12	9.3±6	ns

($p<0.01$) was observed at time point T2, the start of perfusion. The values continued to increase, also due to the administration of erythrocyte concentrates, but did not achieve initial preoperative levels.

Secondary endpoints (renal function, inflammation and myocardial ischaemia)

Four patients (11%) from each of the two comparison groups required kidney dialysis therapy. Serum creatinine, as well as cystatin C, were distinctly elevated compared to the initial preoperative values at T6, the time point of discharge ($p>0.05$). However, no statistically significant difference could be found between the groups in either case of these investigated parameters.

The inflammatory parameters IL6, IL8, TNF-α and the C-reactive protein were identical in the study groups over the period. In both groups, an increase at the end of surgery and a decrease to virtually initial values at time point T6 was observed. The myocardial ischaemic parameters (CK, CK-MB and Troponin T) reached their peaks 24 hours after the end of surgery and decreased again up to the time point of discharge. Also, no influence of the pre-coating procedure could be found in the case of these secondary surrogate endpoints.

Secondary clinical endpoints

Intra-hospital mortality in the pre-coat group, at 8.5%, was clearly higher than in the control group (2.8%). However, a level of significance was not achieved. This fact is also found in the 30-day mortality (n=7 pre-coat / n=3 control). Psychosyndromes were seen in n=2 patients in the pre-coat group and one patient of the control group. A redo thoracotomy due to bleeding complications was necessary in one patient of each group. In two patients in the pre-coat group, a sternum infection occurred during the postoperative period. No infections were observed in the area around the sternum in the control group (Table 4).

Safety

With the anaesthesiological requirement that the amount of blood collected for pre-coating should take place under stable circulatory conditions, the arithmetic mean of 280 ± 40 ml was collected from patients. No vasoactive substances had to be used during the course of the procedure. No transfusion-related incidents were observed. In particular, neither infections nor septic clinical pictures were observed in the pre-coating or the control groups.

Sub-group analyses

In order to analyse any possible differences between the groups, two sub-group analyses for patients older than 75 years and patients with severely reduced LV function were performed. Also, in the sub-groups, no significant differences could be shown with regard to the primary and secondary endpoints.

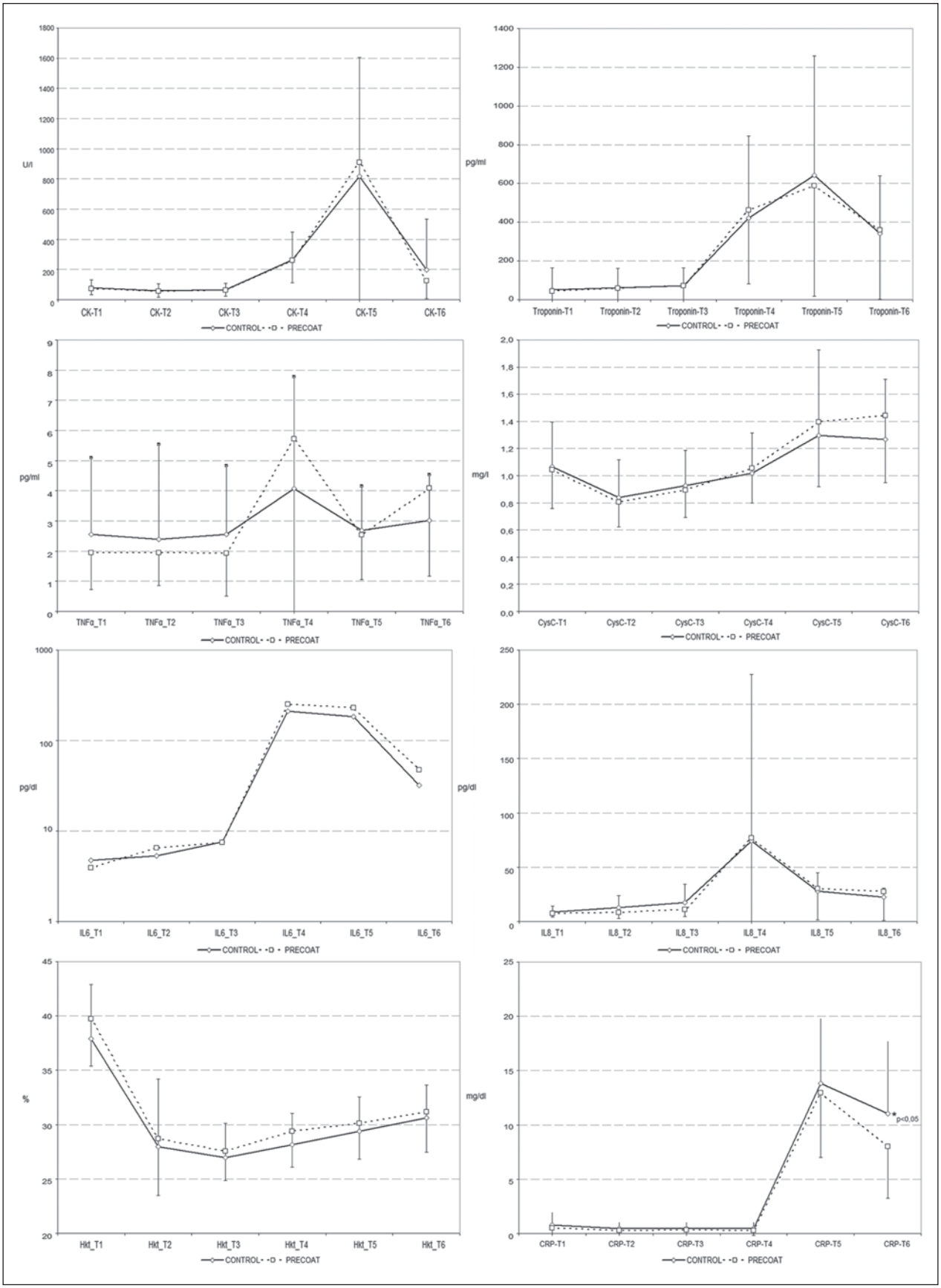

Figure 1. Kinetics of haematocrit (Hct), creatinine kinase (CK), troponin T (TropT), TNF-α, interleukin 6/8 (IL6, IL8), cystatin C (CysC) and C-reactive protein (CRP). Significant differences at any blood sample time points were only found in CRP on T6.

Discussion

The pre-filling of the heart-lung machine with the patient's own blood is a method which was developed in 1960 in order to reduce the extent of haemodilution during extracorporeal circulation.[12] The original technique was essentially modified by Rosengart in the 1990s.[6] Over the course of history, the technique, as well as the primary question, was modified in a series of studies. However, all the studies have autologous filling via the arterial or venous cannulisation line in common.[1,2,13-15] Filling of the heart-lung machine by a CPD bag has not been published to date. We describe this procedure as antegrade autologous priming or pre-coating. The extent to which this procedure affects the national transfusion laws will not be discussed in depth. However, there is an important difference in filling volumes. In the retrograde procedure described by Rosengart et al.,[6] distinctly larger volumes of patient blood are filled into the heart-lung machine compared to our study. In order to avoid negatively influencing the circulatory situation of the patient, we dispensed with administering vasoconstrictors. As a consequence, 280 ± 40 ml could be obtained by using this procedure. These are distinctly lower volumes than those described in the working group of Lange and coworkers in 2004.[5,16,17] By administering noradrenaline, up to 1200 ml of the priming volume of the heart-lung machine could be replaced by autologous patient blood. These different volumes could also be seen as a reason why there are no uniform results for transfusion reduction. In a review by Saczwoski,[11] publications from 1966-2007 were included in a Forrest analysis. Six prospective, randomised studies[1,2,4,5,13,14] were evaluated, with the result that the number of transfused patients with a retrograde autologous procedure is lower, but that the total number of transfused blood products is not dependent upon the selected procedure. The basic issue is due to the study design. Only a few studies on the priming procedure of the heart-lung machine are designed prospectively and randomised. A multi-centre study has not been published previously. Adherence to the transfusion algorithm in the study protocol is also a critical point. It is difficult to ensure that all treating physicians are informed in detail about the study and consistently adhere to the protocol requirements over 24 hours. Thus, the haemoglobin or haematocrit limit for the transfusions cannot always be strictly adhered to. Empirical or individual arguments are often decisive here and these do not always conform to the protocol. Our study design has no defined limitations with regard to the operating surgeon, although the surgeon certainly has an influence on the transfusion volume. The performed logistic regression analysis, however, showed no indication of a significantly increased transfusion risk due to the operating surgeon. The duration of the operation and the total period of hospitalisation, as well as the age of the patient, were the only independent risk factors for the administration of blood products. The surgical, anaesthesiological and perfusion procedures were unchanged during data collection. The large volumes of transfused blood products in comparison to other studies[6] cannot, at first sight, be explained by the protocols and transfusion guidelines. One attempt at an explanation may certainly be the patient selection, as patients with a higher age as well as patients with a distinctly reduced LV function received more generous transfusions than younger patients and those with greater myocardial vitality. These arguments must also be included in the explanation of comparably higher mortality.[18] The random sample for the study includes high-risk patients who do not have a high risk from transfusions, but rather an increased mortality risk. In order to randomise patients with a higher transfusion risk, one would have had to define the inclusion criteria for patients with a low body mass index (BMI), low initial Hb value, and/or complex surgery.

As with the primary endpoint, no significant differences could be found with the surrogate parameters. By pre-coating with autologous patient blood, the foreign surface of the tubing systems and the oxygenator were to be wetted in a biocompatible manner. The systemic inflammatory reaction syndrome (SIRS) was to be influenced positively due to a lower haemodiluton. However, no differences could be demonstrated on the basis of the parameters IL6, IL8, and TNF-α. The fact that the three selected parameters are sensitive to detecting a SIRS reaction can be demonstrated by the distinct increase of the values at the end of surgery. In this case too, the low volume of transfused own blood or too low a number of patients may also serve as a possible explanation.

Less pronounced haemodilution during the extracorporeal circulation may have acted favourably on the incidence of renal complications according to Cormack.[4] In the present study, no advantage could be demonstrated for patients with regard to renal function. This also applies to the new prognostic parameter cystatin C, which remained unaffected by the distribution in the study groups. In the four patients requiring kidney dialysis therapy postoperatively, the value was not superior to the creatinine value time-wise.

Jansen et al.[3] were able to demonstrate a relationship between the decrease in the crystalloid priming and the hospitalisation period after bypass operations. Similarly, secondary clinical endpoints remained outside the significance level in this study.

The reasons for the negative outcome of the study are probably explained by the low amount of priming volume. One must, however, consider that drug counteraction with vasoactive substances (e.g. noradrenaline) is required with larger volumes. This was not necessary in our study design. A second explanation possibly is that the number of cases was too low. The transfusion

difference of 20% on which the protocol calculation was based could not be reproduced. In order to establish the effectiveness and the benefit of the pre-coating procedure, a multi-centre, randomised study with a large number of cases needs to be initiated.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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