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Systemic Inflammatory Response Syndrome in Heart Surgery: New possibilities for treatment through the use of a cytokine adsorber during ECC?

ABSTRACT

The ECC is still the key technology in the performance of cardiac surgery. Currently used conventional extracorporeal circulation (CECC) systems need to be further optimized [14]. At LMU Munich positive experiences with minimized perfusion were consistently implemented. Minimized/optimized perfusion can reduce the inflammation by advanced perfusion technology [15, 16, 17, 18], but in complex interventions such as re-operations, hypothermic arrest or multiple interventions you reach the limits. Despite the use of modern perfusion technology, it is possible that a post-perfusion syndrome (PPS) can develop during long operations leading to SIRES in 2-10% of all cases. The newly introduced CytoSorb technology is a promising treatment option in patients with SIRS due to cardiopulmonary bypass surgery and increased cytokine values. Procedures involving the aortic arch, selective antegrade cerebral perfusion and hypothermic arrest require extra-long perfusion and ischemic time. It is postulated that the preventative use of a cytokine adsorber during open heart surgery with heart-lung machine has a positive impact on significant clinical and inflammatory parameters. In a retrospective study two patient groups (n=20) were evaluated. The aim of this retrospective observational study is thus to analyze the effect of CytoSorb on the inflammatory response evolving. The IL-6 differs significantly in control and investigatory group during the postoperative course; fibrinogen reacts with significantly lower activation. The leucocyte shows a positive trend in the CytoSorb group. The CRP in the CS group showed a lower rise and a faster normalization. The procalcitonin increased with high significance in the control group.

KEY WORDS

Inflammation, CECC, MAPS, Cytokines

INTRODUCTION

Cardiac surgical interventions are associated with post-OP SIRS

The occurrence of the systemic inflammatory response syndrome (SIRS) is one of the most significant complications after operations in which the heart-lung machine (HLM) is employed. Clinically, the spectrum ranges from short-term limitations of organ function to multiple organ failure and death.

Triggers and mechanisms

The triggers for this complex syndrome are multifactorial (Fig. 1). In addition to the surgical and anesthesiological operative trauma, per se, it is primarily the pathophysiological conditions of extracorporeal circulation (ECC), such as hemodilution, mechanical damage to cellular blood components, and contact of the blood with air and with artificial surfaces, that leads to the activation of the non-specific immune response and associated systemic inflammatory cascade.

Ischemia reperfusion injury and the ischemia-related release of endotoxin from the intestinal tract also represent potential triggers [1]. The systemic activation of the complement system and the formation of complement factors C3a, C5a and C5b-C9 can similarly occur within minutes [2]. C5a brings about cellular reactions in mastocytes, granulocytes and monocytes, and ultimately leads to the systemic activation of the endothelium. The activation of neutrophil granulocytes triggers the release of lytic enzymes (e.g. elastase) and oxygen radicals, thus leading to endothelial lesions, as well as to organ damage [3].

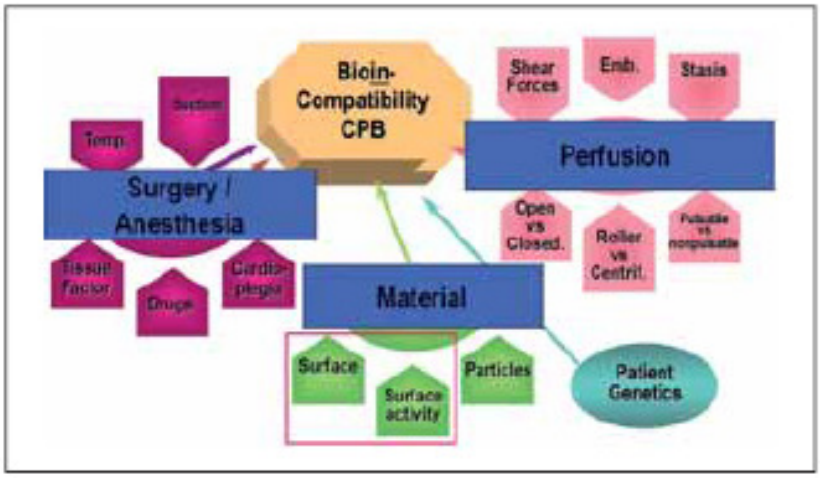
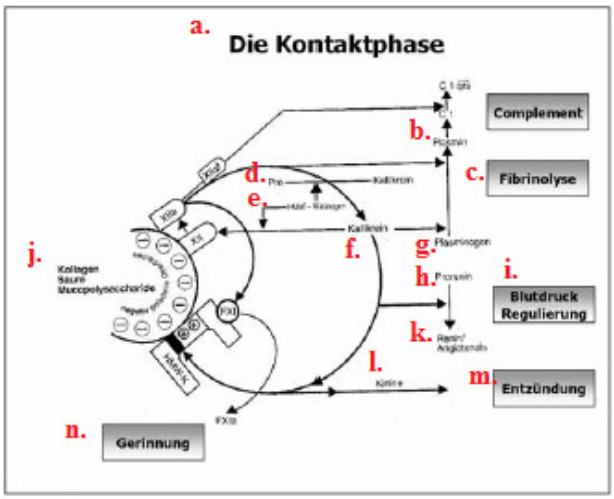


Fig. 1: Influencing factors for the emergence of SIRS after interventions using the heart-lung machine

Systemic inflammation due to the contact phase of coagulation

The foreign surface of the extracorporeal system, temporary ischemia, and subsequent organ reperfusion, as well as surgical trauma, cause an activation of the cascade systems (Fig. 2):

- Kallikrein-kinin system
- Complement system
- Coagulation and fibrinolysis system
- Blood pressure system



Legend:

a. The contact phase
b. Plasmin
c. Fibrinolysis
d. Pre-Kallikrein to Kallikrein
e. High Molecular Weight Kininogen
f. Kallikrein
g. Plasminogen
h. Prorenin
i. Blood pressure regulation
j. Collagen / Acid / Mucopolysaccharides
k. Renin / angiotensin
l. Kinins
m. Inflammation
n. Coagulation

Fig. 2: Contact phase of plasmatic coagulation and interactions between inflammation and hemostasis

With the initial skin incision, thromboplastic material is released, which in turn leads to an activation of the coagulation system. The initial trigger is tissue factor, which converts Factor VII (proconvertin) into Factor VIIa. This results in the tenase complex, which mediates plasmatic coagulation. In the contact system, bradykinin is formed via Factor VIIa/f from high molecular weight kininogen. Bradykinin, in turn, brings about the intensification of the inflammatory reaction, whereas kallikrein and C1 result in a systemic drop in blood pressure, increased capillary membrane permeability, and increased edema.

Role of cytokines

The inflammatory process in the body can be triggered not only by pathogens, but also by toxins, trauma, immune factors and ischemia [5]. In principle, the inflammatory process serves to deactivate and remove the inciting cause, with the goal of initiating the reparative healing process. While the contribution of operative trauma to the inflammatory response can be estimated in the context of isolated coronary artery surgery, a substantial increase in inflammatory parameters is observed in more complex interventions (e.g., multiple

surgical interventions, aortic dissection).

Accordingly, the release of various pro- and anti-inflammatory cytokines (TNF-α, IL-1β, IL-8) represents a common final stage of the activation cascades described above [6, 7, 8, 9]. These intercellular messengers are produced by various cells in response to different stimuli (e.g., IL-1β, TNF-α, endotoxin, free oxygen radicals), with the production and release being mediated by the intracellular transcription factor NF-kB [10].

After initiation of cardiopulmonary bypass, plasma cytokine concentrations rise very quickly. The extent of cytokine production and release was found to correlate with HLM time and aortic clamping time [11]. Cremer et al. showed that high plasma cytokine concentrations, especially of IL-6, are associated with a more significant progression of the inflammatory response and more pronounced post-operative complications [12]. Interleukin-6 therefore serves as a marker for this inflammatory reaction.

Clinical impact

Clinically, the inflammatory response manifests itself in various post-operative complications. They range from myocardial dysfunction, arrhythmia, stroke, acute lung failure, and neurocognitive dysfunction, to disorders of coagulation and kidney and liver dysfunction. Depending on the progression, multiple organ failure or death may occur. The degree of severity of the SIRS response, as well as the extent of organ dysfunction or failure, varies greatly from patient to patient and depends on a multitude of factors (e.g. type of intervention, machine time, HLM used, comorbidities, genetic predisposition). For this reason, it is extremely important to precisely characterize the severity of the inflammatory reaction and the degree of organ dysfunction.

Strategies and approaches

In recent years, many attempts have been made to confront SIRS in relation to cardiac surgical interventions using a HLM by means of pharmacological and technical strategies. Paparella et al. provides a very good overview of these approaches [10]. On the technical side, the following three strategies have been pursued:

- Prevention or reduction of the inflammatory response by creating the best possible physiologic conditions and biocompatibility. Here, the optimization of existing perfusion methods, surface coatings, fill volumes, flow rates, and pump-types, play an essential role.
- Conservative intra-operative treatment of blood (aspirator/vent blood separation) in order to limit the activation of the inflammatory cascades and to prevent post-operative SIRS to the greatest extent possible The use of ultrafiltration in the ECC with the purpose of reducing inflammatory mediators and the use of techniques for depleting leukocytes are also possible.
- Post-operative treatment for controlling SIRS by reducing the plasma levels of inflammatory mediators during the postoperative period.

All of the above mentioned approaches have resulted in only moderate success in the past. For instance, no clinical advantage of any kind for the patient have been observed as a result of the reduction of cytokines and other inflammatory mediators with the aid of ultrafiltration [13].

CytoSorb as a new therapeutic option?

One promising therapeutic option is the newly introduced CytoSorb technology for use as adjunctive therapy in patients with SIRS as a result of cardiopulmonary bypass, cardiac surgery, and elevated cytokine levels. CytoSorb is based on highly biocompatible, porous polymer spheres that are able to remove a broad spectrum of inflammatory mediators such as cytokines, chemokines, as well as various proteins and metabolites such as free hemoglobin or myoglobin with molecular sizes up to 55 kDa from the circulation. The auto-regulatory characteristics of the polymer help to ensure that excessive levels of these mediators in plasma are reduced to manageable levels where the body can regain control of the previously out-of-control immune response. CytoSorb has been tested as a hemoperfusion device in combination with continuous renal replacement therapy (CRRT), in a bypass circuit during cardiopulmonary bypass (CPB) on the HLM, as well as alone.

Current state of knowledge on perfusion methods: MECC and MAPS systems

ECC continues to be the primary technology in the performance of heart operations. In the past, perfusion systems and perfusion strategies have been repeatedly modified and adapted to the respective technical capabilities of the time. Conventional Extracorporeal Circulation

Systems (CECC) used today, still require further optimization [14]. Due to positive experiences with minimized perfusion technologies (MECC), the Modified Adult Perfusion System (MAPS) is used at LMU München.

The MAPS system (Fig. 3) differs fundamentally from the CECC systems. It has a minimized foreign surface, reduced tubing with a smaller diameter (venous 3/8"), a smaller fill volume, and is completely covered.

It is understandable that, as a result, there is a decreased negative impact on cellular blood activation [15, 16]. This may result in a lower incidence of organ dysfunction. In one study, Teoh et al. were able to provide evidence for the influence of mediators (e.g. IL-6) on the cardiac index and peripheral vascular resistance [17]. An increasing number of authors are showing that the use of completely covered systems with reduced fill volumes and minimized blood-air contact have a favorable influence on patients' clinical results, such as reduced administration of noradrenaline and reduced need for blood products [18]. Despite the use of the latest perfusion technologies, more complicated operations (e.g. re-interventions, hypothermic cardiovascular arrest, and multiple interventions with long perfusion times) can result in the development of a so-called Post-Perfusion Syndrome (PPS), which can result in full-blown SIRS in 2-10% of cases. In interventions that involve the aortic arch, in selective cranial perfusion (Fig. 4), and in hypothermic cardiovascular arrest, the perfusion and ischemia times are especially long.

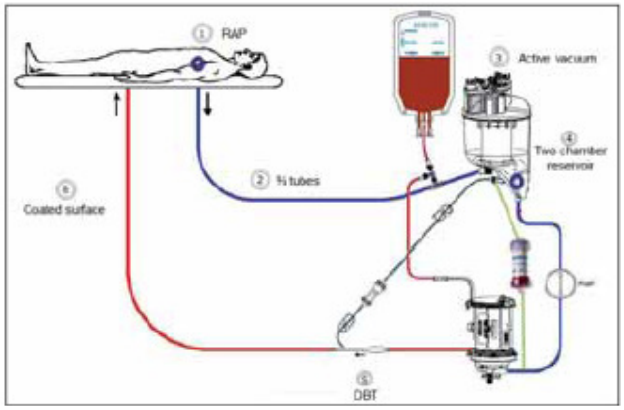


Fig. 3: Modified Adult Perfusion System (MAPS)

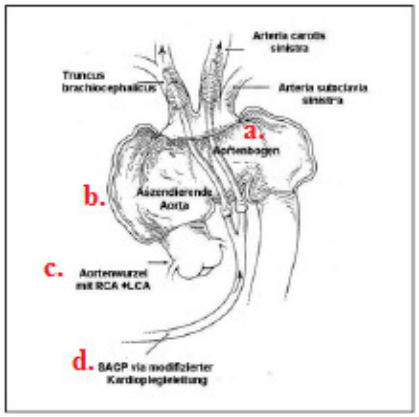


Fig. 4: Intervention involving the aortic arch

Legend:
a. Aortic arch
b. Ascending aorta
c. Aortic root with RCA + LCA
d. SACP (selective antegrade cerebral perfusion) via modified cardioplegia line

Objective and statistical evaluation

It is postulated that the prophylactic use of CytoSorb during cardiac surgery procedures using cardiopulmonary bypass will have a positive influence on essential clinical and inflammatory parameters.

The objective of the retrospective observational study presented here is to analyze the effect of CytoSorb on the developing inflammatory immune response. The statistical evaluation was performed using the program WinSTAT for Microsoft®. The collected data were entered into Microsoft® Excel, and all diagrams and calculations were prepared using WinSTAT. In order to test the differences between the groups, the t-test was performed. The statistical significance value was regarded as $p \leq 0.05$.

MATERIALS AND METHODS

The protocol for hypothermic arrest (HA) is standardized at LMU. The core body temperature is reduced to 25° C. Antegrade cranial perfusion is performed with flow rates of up to 800 mL/min at 18° C with an average pressure of about 60-75 mmHg. Near-Infrared Spectroscopic Monitoring (NIRS) is applied during these interventions in order to monitor a target oxygen saturation of about 60-80% per cranial hemisphere. Since February 2013, the cytokine adsorber CytoSorb® (CytoSorbents Corporation, New Jersey, USA) has also been integrated into the perfusion system for these operations (Fig. 5).

Technical data	
Max. blood flow:	400 mL/min
Max. pressure:	500 mmHg
Surface area:	40,000 m^2
Priming volume:	275 mL
Duration of application:	up to 24 h

Fig. 5: Cytokine adsorber CytoSorb

In the retrospective investigation, two groups (n = 20) were analyzed. 20 patients (01/2012 through 12/2012) undergoing hypothermic cardiovascular arrest and antegrade cranial perfusion were included in the control group (A). Likewise, 20 patients treated from 02/2013 through 11/2013) with hypothermic cardiovascular arrest and antegrade cranial perfusion, but with an additional CytoSorb cytokine adsorber, were included in the test group (CS). In both groups, the HS protocol was used. Blood samples were drawn from the patients immediately after the operation and 1-3 days post-operatively and analyzed in the laboratory.

The following laboratory parameters were investigated:

- C-reactive protein (CRP; MW: 23 kDa): CRP is an acute-phase protein. Besides its importance as a diagnostic marker of tissue trauma, it has an important significance as a protein in relation to the inflammatory response. Changes in the CRP concentration can be detected in the blood after a delay of about 18 hours.
- Procalcitonin (PCT; MW: 17 kDa): PCT is the best diagnostic marker for bacterial infection and is standard in many hospitals. PCT is used to manage antimicrobial chemotherapy. Caveat: False positive results may occur after heart surgery and after cytokine storm [19].
- Leukocytes (Leu): White blood cells phagocytize pathogens, tumor cells and toxins. An elevated leukocyte count reflects activation of inflammation.
- Fibrinogen (Fib; MW: 340 kDa): Fibrinogen is released in relation to the acute-phase reaction from endogenous stores. This occurs in the context of tissue damage (trauma, infection) or as part of a non-specific immune reaction within 6-48 hours.
- Interleukin-6 (IL-6; MW: 25 kDa): IL-6 belongs to the group of pro-inflammatory cytokines. It is activated via IL-1β. Interleukin-6 is an important mediator between the non-specific and specific immune response with respect to inflammatory processes.

RESULTS

There were no significant differences between the two groups with respect to machine times, ischemia and reperfusion times, and the duration of cardiac arrest and of cranial perfusion (Table 1). Thus, the two groups were comparable and statistically evaluable.

Groups	HLM time	Cross clamp	Reperfusion	Arrest	Cranial perfusion
A (n=20)	224,45	144,30	68,75	50,30	47,95
CS (n=20)	213,05	138,55	59,20	40,80	43,45
	n.s. p= 0,463	n.s. p= 0,618	n.s. p=0,223	n.s. p=0,169	n.s. p=0,568

Table 1: Characterization of the patient averages with respect to machine times, ischemia and reperfusion times, time of cardiac arrest and cranial perfusion (times in minutes)

CS group vs. A group	post-OP (1)	1st day (2)	2nd day (3)	3rd day (4)
IL-6	s. p = 0,033	s. p = 0,031	h.s. p = 0,004	h.s. p = 0,005
Fib	n.s. p = 0,657	n.s. p = 0,550	n.s. p = 0,151	s. p = 0,019
Leu	n.s. p = 0,788	n.s. p = 0,652	n.s. p = 0,536	n.s. p = 0,234
CRP	s. p = 0,028	n.s. p = 0,079	n.s. p = 0,747	n.s. p = 0,516
PCT	h.s. p = 0,008	h.s. p < 0,002	h.s. p < 0,001	h.s. p < 0,001

Table 2: Statistical evaluation of the post-operative profile of the inflammation parameters in both groups (s. = significant; n.s. = not significant; h.s. = highly significant)

There were significant differences in the inflammation parameters between the two groups immediately following surgery (Table 2). Thus, the treatment with CytoSorb had a direct effect on the scope of SIRS. As an acute-phase protein, fibrinogen shows a trend toward attenuating this reaction. The individual laboratory values are presented below.

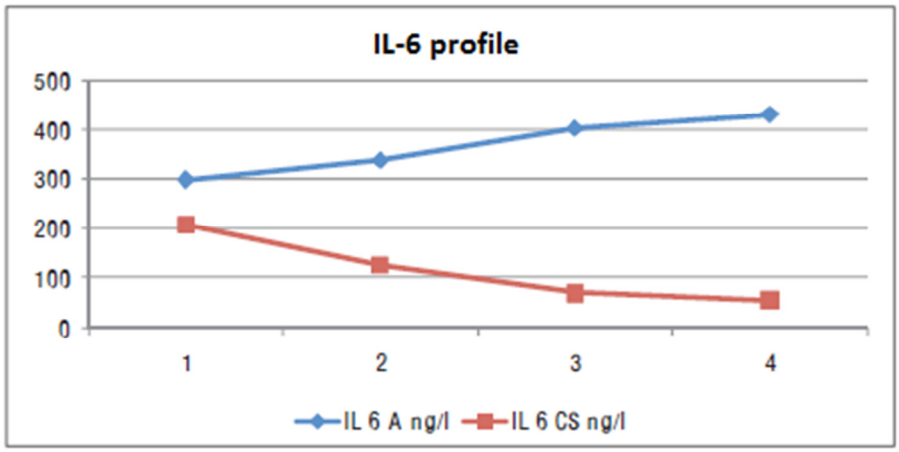


Fig. 6: Post-operative progression of IL-6 in the two comparative groups

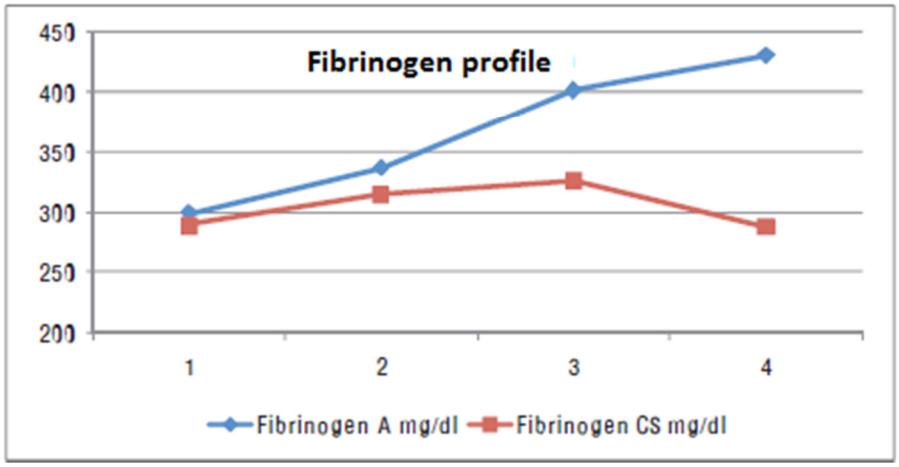


Fig. 7: Post-operative profile of fibrinogen in the two comparative groups

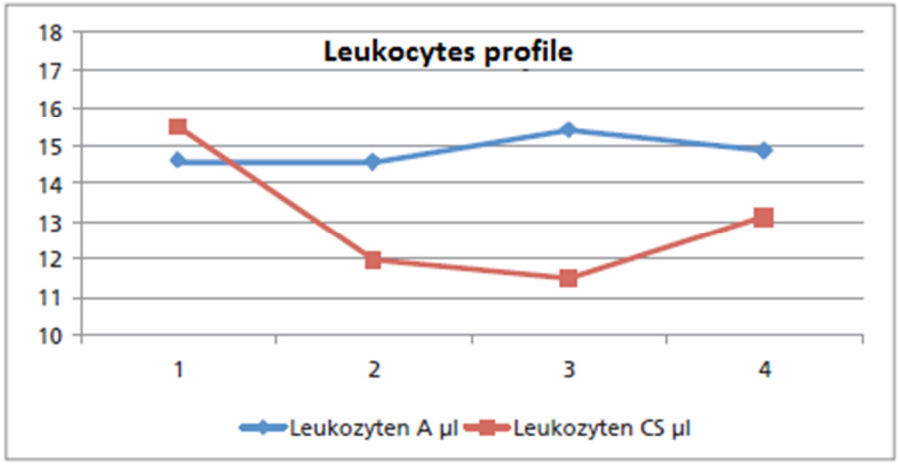


Fig. 8: Post-operative leukocyte count profile in the two comparative groups

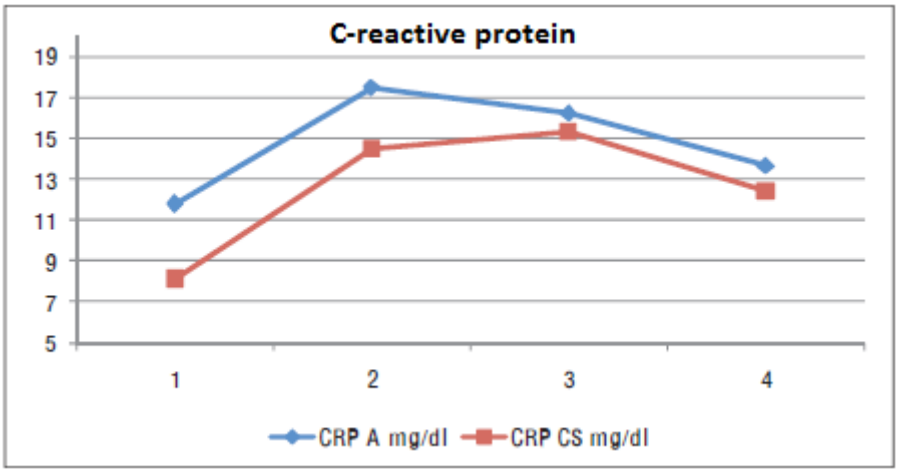


Fig. 9: Post-operative profile of CRP in the two comparative groups

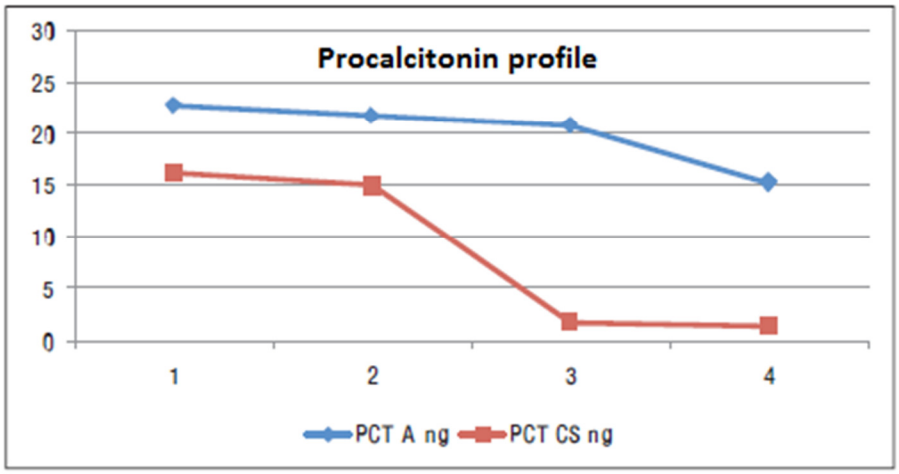


Fig. 10: Post-operative profile of CRP in the two comparative groups

Interleukin-6
During the post-operative period, IL-6 differs significantly between the control and test groups (Figure 6). IL-6 is moderately elevated in the CytoSorb group post-operatively and approaches the normal level again over the course of the following 3 days. The control group IL-6 values, which are already elevated post-operatively, show a trend that continues to increase over the same period.

Fibrinogen
In the CytoSorb group, there is a reduced post-operative increase in fibrinogen than in the control group (Fig. 7). Values of up to 400 mg/dL are within the normal range [20]. The values for fibrinogen consistently remain within the normal range in the CytoSorb treatment group during the post-operative period and begin to drop after the third day post-operatively. In contrast, the values rise significantly above the upper threshold value of the normal laboratory range in the control group.

Leukocytes
Immediately after conclusion of the operation, leukocytosis occurs in both groups (Fig. 8). The number of activated leukocytes drops visibly faster with CytoSorb and remains below the leukocyte count of the control group for the entire observation period.

C-reactive protein
Over the following 3 days, the CRP value returned to a nearly physiologically normal level (Fig. 9). Here, too, the increase is less pronounced on CytoSorb, and normalization occurs more rapidly.

Procalcitonin
The increase in procalcitonin is significantly less pronounced using CytoSorb therapy than in the control group and the difference is highly significant at all measurement time points (Fig. 10). In addition, the PCT drops more quickly in the CytoSorb group throughout the post-operative period.

DISCUSSION
The reduction of post-operative SIRS following interventions where the HLM is used is a major objective in cardiac surgery. It leads to a reduction in operation-related complications and reduces the mortality of those interventions. Excessive inflammation and acute-phase reactions play an essential role in SIRS [2]. This manifests itself through elevated cytokine and fibrinogen levels in the blood [11, 12]. Through the use of a cytokine adsorber, clinicians now have an available option to reduce this excessive reaction. If the adsorber is used during cardiopulmonary bypass, there is a significant reduction in cytokines, such as IL-6, for example. CytoSorb can therefore significantly attenuate an excessive inflammatory reaction.

This fact has a positive impact on the other systems that are linked to each other via the contact phase [10]. These components also show a clearly reduced level of activation. One marker that reflects the extent of the acute-phase reaction and inflammation is the release of fibrinogen from endogenous stores. As a large molecule, it can influence the rheology of the blood at pathophysiological concentrations of >400 mg/dL.

One important criterion for SIRS is the occurrence of leukopenia or leukocytosis. Both reflect increased inflammation. Here as well, one observes a positive trend

in the CytoSorb group. Due to its slow progression, the increase in CRP value (activation via IL-6) can only be detected after 24 hours. This is also the reason why CRP has lost its importance as a marker for inflammation. In the future, CRP may provide valuable information on the extent of a patient's tissue injury.

The normal level of procalcitonin is 0.5 µg/mL. In bacterial infections, PCT is a reliable diagnostic marker. In cardiac surgery interventions, false positive values can occur as a result of the cytokine storm or translocation of bacteria and/or their components from the intestinal lumen. For the cardiac surgeon, this results in the dubious need for antibiotics that may not be necessary. The less pronounced rise and the quick physiological normalization using CytoSorb may prevent this, and may also lead to a reduction in the development of SIRS.

At the same time, in patients who develop severe SIRS, a barrier disorder with capillary leakage can occur [8]. Preventing this from occurring is essential for the clinician. In this case, the attenuation of immune hyper-reactivity using CytoSorb can be the key to prevent complications in these patients that are associated with SIRS.

The data presented here demonstrate the reliability of the new CytoSorb therapy in the area of cardiac surgery. Nevertheless, the collected data need to be validated in a controlled clinical study. If the results are also confirmed in such a study, CytoSorb could establish itself as a routine measure in cardiac surgery.

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CONFLICT OF INTEREST

The authors have no financial interests or relationships that might lead to conflicts of interest.

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