Septic porcine blood does not further activate coagulation during in vitro membrane oxygenation

Christian Bleilevensa,*, Oliver Grottkeb, Sabine Groeninc, Markus Honickela, Rüdger Koppb, Smriti Singhc, Jutta Arensd and Rolf Rossainta

a Department of Anesthesiology, University Hospital RWTH Aachen University, Aachen, Germany
b Department of Intensive Care, University Hospital RWTH Aachen University, Aachen, Germany
c DWI—Leibniz-Institute for Interactive Materials, RWTH Aachen University, Aachen, Germany
d Department of Cardiovascular Engineering, Institute of Applied Medical Engineering, Helmholtz Institute Aachen, RWTH Aachen University, Aachen, Germany

* Corresponding author. Department of Anesthesiology, University Hospital RWTH Aachen, Pauwelsstraße 30, 52074 Aachen, Germany. Tel: +49-241-8037511; fax: +49-241-8082570; e-mail: cbleilevens@ukaachen.de (C. Bleilevens).

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Abstract

OBJECTIVES: For patients with a severe acute respiratory distress syndrome (ARDS), extracorporeal membrane oxygenation (ECMO) represents a life-saving measure. Frequently, patients with severe ARDS also show signs of severe sepsis. As blood contact with the membrane oxygenator surface leads to adverse effects due to insufficient biocompatibility partly caused by activation of platelets, coagulation factors and leucocytes, we hypothesized that these adverse effects would be amplified if septic blood in a preactivated state came into contact with the membrane oxygenator.

METHODS: In a previously established in vitro 12-h ECMO test system (mock loop), we used septic or healthy domestic pig blood to analyse coagulation and inflammatory parameters. Sepsis was induced by a caecal ligation and puncture model in pigs.

RESULTS: At the beginning of the mock loop experiments, the septic blood showed significantly increased thrombin–antithrombin complexes (76.9 vs 27.7 mg/l), D-dimers (1.2 vs 0.3 mg/l) and fibrinogen concentration (1.8 vs 1.5 g/l), as well as elevated extrinsic coagulation activity (shorter EXTEM-CT: 44.2 vs 57 s) and higher lactate (3.4 vs 1.5 mmol/l) and cytokine levels (interleukin-6: 827 vs 31 pg/ml) when compared with the blood from healthy animals. Despite the preactivated status of the septic blood, no further increase of coagulation activity, inflammatory response or increased oxygenator resistance was observed in comparison to the control experiments.

CONCLUSION: Septic porcine blood was not further activated due to the contact with an oxygenator, and no increased clot formation or biocompatibility problems were observed.

Keywords: Sepsis • Extracorporeal membrane oxygenation (ECMO) • In vitro • Biocompatibility • 12 h

INTRODUCTION

Life-threatening oxygenation or decarboxylation disorders due to acute respiratory distress syndrome (ARDS) in neonates, children and adults represent indications for extracorporeal membrane oxygenation (ECMO) [1–4]. In addition to technical complications, such as increasing oxygenator resistance and lowered gas transfer properties triggered by thrombus formation in the membrane, treatment complications arise due to an insufficient biocompatibility of ECMO devices that can result in coagulation disorders. As the most treatment complication during ECMO, uncontrolled bleedings or heparin-induced thrombocytopenia occurs frequently, as a result of indispensable systemic anticoagulation using high doses of heparin to prevent thrombus formation [5].

These ECMO-specific biocompatibility complications may be reinforced by pathophysiological situations as present in septic patients for instance. Recently, a retrospective single-centre study in the USA focusing the epidemiology of ARDS in patients with severe sepsis reported that the incidence for ARDS was 6–7% in all septic patients [6]. Nearly all patients suffering from ARDS are septic. Furthermore, 20–40% of all septic patients are closely associated with disseminated intravascular coagulation (DIC), which is triggered by occluded capillaries as well as fibrin accumulation in small blood vessels. Subsequent activation of coagulation occurs due to impaired functionality of anticoagulant components, such as antithrombin, the tissue factor (TF) inhibitor system via protein-C or fibrinolysis [7]. Therefore, the observed clinical complications of ECMO may occur not only because of ECMO but also because...
of a combination of sepsis and the ECMO system. Thus, when testing elements of an extracorporeal lung assist device in a mock loop system, it is important to differentiate between effects in the blood of healthy individuals and in the blood of septic individuals. We hypothesized that ECMO-specific coagulation activation, thrombus formation and inflammation would be amplified if septic blood in a preactivated state came into contact with the membrane oxygenator. To the best of our knowledge, no study has yet been conducted to monitor the biocompatibility of membrane oxygenators coming into contact with the blood of healthy or septic animals. Therefore, we chose an in vitro model, to enable the investigation of the proinflammatory and procoagulant effect of septic blood, isolated from the complex mechanisms in a complete septic organism, compared with blood withdrawn from healthy animals. We used a previously established in vitro 12-h test setting for membrane oxygenators (mock loop) [8] and assessed the platelet (PLT) and coagulation cascade activation at different time points of the mock loop experiments.

MATERIALS AND METHODS

Extracorporeal circuit (mock loop)

The mock loop was assembled as previously described [8]. Twelve paediatric membrane oxygenators (MEDOS® HILITE® 800 LT, MEDOS® AG Stolberg, Germany) were used for the experiments, consisting of a Rheoparin®-coated microporous polymethylpentene hollow-fibre membrane. We chose the smallest version of the oxygenator type, which is commercially available, in order to minimize the foreign surface within the circuit. Additionally, as described previously, heparin-like coatings per se increase biocompatibility of oxygenators [9-11]. The initial blood flow rate was set at 0.4 l/min. The oxygenator resistance was calculated according to the method described by Lafayette et al. [12]

\[
\text{pressure pump inlet (pi) – pressure pump outlet (po) (mmHg),} \\
\text{blood – flow in L/min(Q)}
\]

We applied 1 l/min of CO₂-enhanced gas (5% CO₂/21% O₂/74% N₂) to the circuit. Fluid loss caused by evaporation was countered via continuous infusion of 4 ml/h nutrient solution (PAGGSM: disodium hydrogen phosphate=16 mM/mansodium phosphate=8 mM/adenine=1.4 mM/guanosine=1.4 mM/glucose=0.85 mM/sodium chloride=72 mM/mannitol=55 mM). To keep the pH stable, 0.2-0.4 ml of sodium bicarbonate solution (NABI) was continuously administered.

Blood donation from healthy pigs

After ethical approval [Landesamt für Natur, Umwelt und Verbraucherschutz NRW (LANUV) No. 84-02.04.2014A141] was obtained, 150 ml of whole blood from six healthy male domestic pigs was withdrawn and collected in blood bags containing 5.66 mg/ml of citrate sodium hydrogen phosphate (final concentration in the bag). The blood was then equilibrated on a shaker for 15 min before the mock loop was loaded with a total volume of 120 ± 2 ml, and no priming was necessary to fill the small circuit properly, without bubbles or no flow areas. No dilution effects were observed, as the haematocrit (HCT) did not decrease. The fluid loss via evaporation effects was covered by continuous administration of nutrient solution. Each blood sample taken from the circuit during the experiments was replaced by the same amount of whole blood from the original blood bag.

Blood donation from septic pigs

To obtain septic blood for the mock loop, a porcine caecal ligation and puncture (CLP) model was performed as described by Ackermann et al. [13] in six animals. During sepsis, all vital parameters of the pigs were monitored continuously (HR: heart rate; BT: tail pulse oximetry and body temperature; MAP: mean arterial pressure; CO: cardiac output) on a standard anaesthesia monitor (AS/3; Datex, Ohmeda, Helsinki, Finland). When the diagnostic criteria for sepsis from previously established CLP models and sepsis as defined by the European-American Consensus Conference were obtained [13-19] (Table 1), 150 ml of septic blood was withdrawn via the arterial line for the mock loop experiments, before animals were sacrificed by a fentanyl, propofol and potassium chloride injection. Figure 1 illustrates the protocol for the two experimental groups (healthy = CON, septic = SEP).

Blood sampling and analysis

The proinflammatory status of the CLP-animals and a persisting mock loop proinflammatory state were analysed using ELISA Kits for tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (P6000B, PTA00; R&D Systems, Wiesbaden, Germany). For all parameters, the data from septic animal blood samples at 6 h serve as the baseline (BL) data for the corresponding mock loop experiment. Thromboelastometry was performed on a ROTEM analyser (TEM International, München, Germany) according to the previously established protocol for porcine blood [8]. Using appropriate reagents (EXTEM, INTEM, HEPTEM) thromboelastometry enables the detection of extrinsic or intrinsic coagulation activation, as well as the detection of heparin within blood samples, by measuring the clotting time (CT) in seconds. Prolonged CT indicates weaker, and shorter CT indicates stronger coagulation activation. Flow cytometry was used to detect cell surface expression of P-selectin (CD62P) as an activation marker on porcine CD61 positive PLTs, as described previously [8, 20]. Higher levels of CD62P PLTs indicate enhanced coagulation activity. PLT-poor plasma samples were screened for thrombin-antithrombin complex (TAT) by ELISA (#OWMG Enzygnost; Dade Behring, Marburg, Germany). TAT complexes are the result of thrombin-triggered cleavage of its inhibitor antithrombin, and formation of an enzyme intermediate. Elevated TAT levels indicate enhanced coagulation activity. A steel ball coagulometer (MC4plus; Merlin Medical, Lemogo, Germany) was used to measure fibrinogen concentration which indicates coagulation activation, if the concentration is decreased whereas the D-dimer concentration (cleavage product of fibrinogen) is increased. D-dimers were determined on a BCS XP autoanalyser (Innovance D-dimer®; Siemens, Marburg, Germany).

Statistical analysis

Data are presented as the mean ± standard error of the mean. Parameters were tested for significant differences between the
groups at distinct time points by two-way analysis of variance with Holm–Sidak correction for multiple comparisons with a confidence interval of 95%. The effects of time, or time and group, were calculated by multivariate analysis for repeated measurements (IBM SPSS statistics, version 20). The results were regarded as significantly different if the calculated $P$-value was <0.05.

**RESULTS**

**Porcine caecal ligation and puncture model**

HR (Fig. 2A), MAP (Fig. 2B), CO (Fig. 2C) and BT (Fig. 2D) met previously described specific criteria for porcine sepsis (Table 1) after 6 h. The lactate concentration (Fig. 2E) and urine production (ml/kg/h, Fig. 2F) met the criteria for porcine sepsis 1 h after sepsis induction. TNF-$\alpha$ and IL-6 levels were significantly increased 6 h after sepsis induction when compared with BL (Fig. 2G).

**Mock loop operating conditions**

The initial blood flow was adjusted to 0.41/min (Fig. 3B) at a pump speed of 1550 ± 87 UPM (Fig. 3A) for the six experiments in the CON group and 1617 ± 65 for the six experiments in the SEP group and remained stable in both groups. The calculated resistance of the oxygenator slightly increased in both groups from BL [CON: 30 ± 10; SEP: 49 ± 24 mmHg/(l/min)] until the end of the experiments [CON: 59 ± 7; SEP: 80 ± 20 mmHg/(l/min)] without becoming significant (Fig. 3C). The temperature was constant over time in both experimental groups (data not shown).

**Blood gas analysis**

The pH-value changes over time, but was kept within a physiological range (pH 7.4–7.5) by continuous administration of CO$_2$-enhanced gas (1 l/min) and NABI (0.2–0.4 ml/h) (Fig. 4A). Haemolysis increased significantly over time with no difference between the groups (Fig. 4B). The lactate concentration was significantly increased at the beginning of the experiments in the SEP group (3.6 mmol/l) in comparison to the CON group (1.5 mmol/l) and remained elevated during the whole experiment (Fig. 4C). White blood cell and PLTs counts remained stable over time, showing no difference between groups. Compared with the CON group, the red blood cell (RBC) counts and the HCT were significantly increased in the SEP group (Table 2).

**Platelet activation and coagulation analysis**

The septic mock loops started with similar amounts of CD62-P positive PLTs compared with the CON group (SEP: 41.6 ± 2.7% vs CON: 39.3 ± 2.8%), which increased over time without significant differences after 12 h between the groups (SEP: 71.1 ± 4.7% vs CON: 61 ± 5.7%) (Fig. 5A). Prothrombin time did not change during the experiments, whereas the activated partial thromboplatin time (aPTT) increased and exceeded the measurement range after 6 h. Thus, between the first and the 12th hours of the mock loop experiments, the measurement values were pit of range. At 1 and 12 h, not for all the samples aPTT values were measurable (Fig. 5B and C). The TAT levels (SEP: 76.9 ± 7 mg/l vs CON: 27.7 ± 13.1 µg/l, Fig. 5E), fibrinogen (SEP: 1.8 ± 0.1 g/l vs CON: 1.5 ± 0.1 g/l, Fig. 5D) and D-dimer concentration (SEP: 1.2 ± 0.4 mg/l vs CON: 0.3 ± 0.05 mg/l, Fig. 5F) were significantly higher at the beginning of the septic mock loops compared with the CON group. TAT levels remained on a significantly higher

| Table 1: Diagnostic criteria for sepsis according to previously established porcine caecal ligation and puncture models |
| Parameter | Value |
| Mean arterial pressure | 40% drop from baseline |
| Body temperature (°C) | >40 |
| Heart frequency (BPM) | >140 |
| Cardiac output | 50% drop from baseline |
| Lactate (mmol/l) | >1.5 |
| White blood cells (WBC/10$^3$/µl) | >20 000/<9000 |
| Urine production (ml/kg/h) | <0.5 |

![CLP model](image_url)  
**Figure 1:** Protocol and experimental groups. CLP: caecal ligation and puncture.
level during the first 1 h, whereas the D-dimer concentration remained increased after 12 h. The EXTEM-CT was significantly shorter in the SEP group (SEP: 44.2 ± 2.1 s vs CON: 57 ± 3.3 s) and dropped to even lower levels within the first hour of extracorporeal circulation (SEP: 27.7 ± 2.3 s vs CON: 38.2 ± 1.3 s). However, the drop did not continue after 6 h, and comparable CON group values were observed after 12 h (Fig. 5G). The INTEM-CT was prolonged immediately after starting the experiments and remained high in both groups (Fig. 5H). This effect was related to unfractionated heparin released from the membrane, as indicated by the HEPTEM-CT value, which represents the intrinsic coagulation system activity after heparinase administration. The increasing CT-value over time indicates decreasing activity, without differences between the experimental groups (Fig. 5I).

**Inflammatory response**

At the beginning of the septic mock loops, a significantly higher level of IL-6 and a slightly elevated TNF-α concentration were detected in comparison to the CON group. For 7 h, the elevated IL-6 concentration in the SEP group remained stable, whereas the TNF-α concentration increased. After 12 h, the IL-6 concentration showed no significant difference between the groups, but TNF-α levels were significantly higher in the SEP group (Fig. 6A and B).

**DISCUSSION**

It is well known that the coagulation system, PLTs and the inflammatory system are activated due to blood cell contact with membrane oxygenator surfaces. We hypothesized that the degree of activation may be intensified if preactivated septic blood comes into contact with the oxygenator. However, neither elevation of coagulation markers in septic blood or increasing oxygenator resistance was measured during in vitro ECMO.

Septic blood for the mock loop experiments was withdrawn from pigs after inducing sepsis in a CLP model. Sepsis was indicated by both clinical and laboratory parameters. According to the International Society on Thrombosis and Haemostasis score, a total score of 2 was obtained [21]. Consequently, we defined our septic blood for the mock loop experiments as preactivated blood in a procoagulant and proinflammatory state, as evidenced by increased TAT and D-dimer concentration as well as lower EXTEM-CT values, and increased concentrations of proinflammatory cytokines in comparison to blood from healthy animals.

During the first hour of extracorporeal circulation, the TF-dependent extrinsic pathway was activated in both experimental groups, as indicated by the HEPTEMS-CT value, which represents the intrinsic coagulation system activity after heparinase administration. The increasing CT-value over time indicates decreasing activity, without differences between the experimental groups (Fig. 5I).
coagulation activation might be the limited half-life of the involved coagulation factor VIIa (fVIIa) which is essential for the final clot formation after TF stimulation. fVIIa is stable for \(\frac{24}{2.5}\) h in blood plasma [23]. Independent from the experimental group, this in vitro model lacks the liver as the native source for coagulation factors, negating the effects of a stronger coagulation activation triggered by higher amounts of TF at the beginning of the septic experiments.

Comparably, TAT, fibrinogen and D-dimer concentrations were elevated in the preactivated septic blood during the first six hours of extracorporeal circulation compared with the control group. After 12 h of extracorporeal circulation, the D-dimer concentration was the only marker still significantly elevated in the septic group. All other markers decreased to comparable levels as in the control group. No visual thrombus formation or critical changes in oxygenator resistance could be observed. Decreasing fibrinogen concentration in both experimental groups could be explained by fibrinogen binding to the oxygenator surface. Subsequent attachment of PLT to the fibrin network might further explain the reduced PLT count after 12 h in both groups. Although both parameters are indicators for enhanced coagulation activity and clot formation on the membrane, this was not affirmed by increasing oxygenator resistance or any visible thrombus on the membrane.

Due to the limited half-life of coagulation factors and in combination with the Rheoparin® release from the MEDOS® oxygenator membrane, which generated a heparinized flow path of \(\frac{17}{1.4}\) IU of heparin within the device [24], both excessive coagulation activation and in vitro thrombus formation on the membrane were prevented. Heparin release was monitored by a prolongation of INTEM-CT values immediately after the beginning of the experiments, which was further validated by HEPTEM measurements and prolonged aPTT values. These results support our previous findings and provided proof of the heparin release from coated oxygenator membranes [8]. For 12 h of in vitro extracorporeal circulation, these effects prevented a further activation of the extrinsic or intrinsic coagulation pathway and therefore impacted thrombus formation. This effect was independent of the experimental group and functioned independently of the preactivated status of the septic blood.

Further improvements could be made to the previously established mock loop system [8]. The fluid loss caused by evaporation via the membrane was addressed by continuous infusion of PAGGSM solution rather than repetitive applications after blood sampling. Furthermore, we supplied the system with a NABI infusion in addition to the application of CO₂-enhanced room air. Thus, we achieved a stable pH at a constant flow and pump speed. The moderate haemolysis and comparable resistance to previously described mock circulation loops [12] ensured the suitability of the system. However, we observed an elevated RBC count, accompanied increased HCT values in the septic group.

**Table 2:** Red blood cell, white blood cell, platelet counts, haemoglobin concentration and haematocrit value over time

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter</th>
<th>BL</th>
<th>1 h</th>
<th>6 h</th>
<th>7 h</th>
<th>12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (CON)</td>
<td>RBC ((\times 10^6/\mu l))</td>
<td>4.8 ± 0.2*</td>
<td>4.6 ± 0.3*</td>
<td>4.7 ± 0.2*</td>
<td>4.7 ± 0.2*</td>
<td>4.7 ± 0.3*</td>
</tr>
<tr>
<td></td>
<td>WBC ((\times 10^3/\mu l))</td>
<td>13.9 ± 1.7</td>
<td>12.2 ± 1.1</td>
<td>12.2 ± 1.5</td>
<td>12.0 ± 1.2</td>
<td>9.7 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>PLT ((\times 10^5/\mu l))</td>
<td>249.7 ± 25.3</td>
<td>211 ± 21.5</td>
<td>242.2 ± 19</td>
<td>231 ± 14.9</td>
<td>228.2 ± 24.6</td>
</tr>
<tr>
<td></td>
<td>Hgb (g/dl)</td>
<td>8.5 ± 0.8</td>
<td>7.7 ± 0.4</td>
<td>8.2 ± 0.5</td>
<td>8.2 ± 0.4</td>
<td>8.4 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>Hct (%)</td>
<td>26.3 ± 1.5*</td>
<td>24.6 ± 1.3*</td>
<td>25.6 ± 1.5**</td>
<td>26.2 ± 1.2**</td>
<td>26.8 ± 2.6***</td>
</tr>
<tr>
<td>Septic (SEP)</td>
<td>RBC ((\times 10^6/\mu l))</td>
<td>6.0 ± 0.3</td>
<td>5.9 ± 0.3</td>
<td>6.0 ± 0.3</td>
<td>5.8 ± 0.3</td>
<td>5.8 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>WBC ((\times 10^3/\mu l))</td>
<td>15.7 ± 1.8</td>
<td>15.2 ± 2.2</td>
<td>14.0 ± 1.8</td>
<td>13.6 ± 2.1</td>
<td>12.8 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>PLT ((\times 10^5/\mu l))</td>
<td>275 ± 5.5</td>
<td>212.4 ± 12.7</td>
<td>215.8 ± 9.3</td>
<td>217.7 ± 14.3</td>
<td>211 ± 22.5</td>
</tr>
<tr>
<td></td>
<td>Hgb (g/dl)</td>
<td>10.9 ± 0.5</td>
<td>9.9 ± 0.5</td>
<td>9.9 ± 0.5</td>
<td>9.7 ± 0.5</td>
<td>10 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Hct (%)</td>
<td>31.6 ± 1.3</td>
<td>30.1 ± 1.7</td>
<td>31.9 ± 2.1</td>
<td>32.1 ± 2</td>
<td>34.1 ± 3.2</td>
</tr>
</tbody>
</table>

BL: baseline; RBC: red blood cell; WBC: white blood cell; PLT: platelet; Hgb: haemoglobin; Hct: haematocrit.
* P < 0.05 vs septic, ** P < 0.01 vs septic, *** P < 0.001 vs septic.
which remained on significantly higher levels during the mock loop experiments. A possible explanation and proof of persisting septic conditions in the mock loop system might be the reduction of rouleaux aggregate formation by RBCs as a reaction to the contact with bacteria or lipopolysaccharides in septic blood. This mechanism facilitates the passage of constricted blood vessels during sepsis for single RBCs in comparison to rouleaux aggregates, and consequently more single cells could be detected [25, 26]. In addition to the preactivated coagulation status in the septic blood, we observed significantly increased TNF-α and IL-6 concentrations at the end of the CLP model. Both cytokines are known to be elevated in the serum of septic patients, but IL-6 in markedly higher concentrations compared with TNF-α because it is additionally released by endothelial cells, as a further source besides leucocytes in vivo [27]. This additional release is triggered by nuclear factor kappaB signalling, as described after TNF-α or
endotoxin stimulation [28]. Thus, the septic mock loop experiments started with significantly higher IL-6 concentrations compared with the control group, but no further increase was observed during the extracorporeal circulation. In contrast, the IL-6 concentration in the control group started at lower levels and increased until there was no significant difference to the septic group any more. Two possible explanations could be discussed. Endothelial cells are missing in both the mock loop groups as additional source for IL-6, whereas the cytokine is further released by circulating leukocytes. Thus, a kind of threshold seems to be reflected by the stagnation in IL-6 concentration for the limited cell population in this in vitro circuit. Furthermore, heparin seems to deploy its anti-inflammatory properties binding capacity of cytokines, at least for the IL-6 concentration [29]. It remains questionable, as the TNF-α concentration would have shown further increase beyond 12 h of extracorporeal circulation. Thus, the elevated TNF-α levels in both groups, the elevated IL-6 amount in the control group and the persisting IL-6 amount in the sepsis group may reflect the cytokine release via activated immune cells during extracorporeal circulation without additional sources for cytokine release in combination with anti-inflammatory properties of heparin [30].

LIMITATIONS OF THE STUDY

The primary limitation of this study was that the mock loop system was an artificial system and lacked organs and cells as sources for coagulation factory or cytokines. This study could only observe effects of the contact of preactivated septic blood to an oxygenator membrane without persisting supply of coagulation factors and proinflammatory mediators. A prolonged state of sepsis in the preliminary CLP model may result in DIC which is associated with sepsis [7]. Consequently, a stronger preactivation might rather be aggravated due to contact with a foreign surface in an ECMO system and result in clinically relevant pathologies than the septic blood in our experimental setting. The question whether or not the contact of the oxygenator membrane to stronger activated septic blood would further affect the coagulation status and therewith the oxygenator function remained unclear. Thus, on the basis of the recent data, it appears worthwhile to improve the experimental setting for in vivo or in vitro follow-up studies in the next step. Additionally, ECMO indication for ARDS patients showing signs of sepsis will remain an actual topic.

CONCLUSION

Septic blood withdrawn from a porcine CLP model was used for 12 h of in vitro extracorporeal circulation. In comparison to the blood withdrawn from healthy animals for the control experiments, it was preactivated and showed a mild procoagulant and proinflammatory state. Contrary to our hypothesis, the preactivated status of the septic blood was not further aggravated due to the contact with the oxygenator surface, and no increased clot formation or oxygenator resistance was observed. This result may be related to the limited half-life of coagulation factors, and lacking native sources for cytokines and coagulation factors to simulate a persisting and sufficient activation status within the artificial system.

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