Influence of acidaemia and hypoxaemia on CVVH haemocompatibility in a porcine model

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Abstract

Background. Reduced haemocompatibility and early filter failure during continuous venovenous haemofiltration (CVVH) can be attributed to various aspects from filter engineering to rheological problems. Still, little is known about the impact of acidaemia and hypoxaemia on the haemocompatibility of a CVVH. In a porcine model, we investigated blood and coagulation parameters, filter performance and blockage of filter capillaries to assess the impact of acidaemia and hypoxaemia on haemocompatibility.

Methods. Pigs were assigned to three groups (n = 6). One group received mixed acidaemia (pH 7.2) by acid infusion (0.2 M of lactic acid and 0.2 M HCl diluted in normal saline) and low tidal volume ventilation (6–8 mL/kg⁻¹), one group underwent an additional hypoxaemia (pH 7.2; PaO₂ <70 mmHg) and another was treated with normal saline and normoventilation (control group; pH 7.4). To accelerate biocompatibility reactions, CVVH was operated with reinfusion of the filtrate to the venous line for 3 h based on standardized heparinization.

Results. Acidaemia led to a contradictory pattern with respect to prothrombin time (prolongation), activated partial thrombin time and activated clotting time (acceleration). In comparison to normal pH homeostasis, acidaemia led to increasing activation markers such as terminal complement complex marker sC5b-9, thrombin–anti-thrombin complexes (TAT) and D-dimers. Additional hypoxaemia intensified activation with regard to TAT and complement complex marker sC5b-9. Platelet counts suffered from acidaemia and a tendency for higher rates of blocked hollow fibres was found.

Conclusion. Acidaemia led to deteriorated haemocompatibility reactions to a CVVH circuit. The coagulation pattern developed towards complications for the coagulatory state.

Keywords: acidosis; coagulation; continuous venovenous haemofiltration; haemocompatibility; hypoxaemia

Introduction

Early filter failure, low blood flow rates/filter clearance and a deterioration of the coagulation system are common problems during the use of renal replacement therapies (RRT) in the case of acute renal failure (ARF) or multiple organ failure [1–5].

There is one common pathophysiology in most critically ill patients requiring RRT, which is acidosis even when the
Acidaemia and CVVH compatibility in pigs

**Table 1. Drugs and procedures used for anaesthesia and general ventilation**

<table>
<thead>
<tr>
<th>Drug/procedure</th>
<th>Drug or procedure used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication (i.m.)</td>
<td>Azaperone, 3 mg/kg⁻¹</td>
</tr>
<tr>
<td>Total i.v. anaesthesia</td>
<td>Propofol, 7–10 mg/kg⁻¹ (for intubation)</td>
</tr>
<tr>
<td>Volume management</td>
<td>Jonosteril acetate® during instrumentation 24 mL/kg⁻¹ h⁻¹</td>
</tr>
<tr>
<td>Ventilation used for native baseline</td>
<td>Ventilator 711® (Siemens, Germany); volume-controlled mode</td>
</tr>
</tbody>
</table>

**Table 2. Instrumentation**

<table>
<thead>
<tr>
<th>Vascular access</th>
<th>Catheter</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left external jugular vein</td>
<td>4-Fr central venous catheter (Arrow, Erdingen, Germany)</td>
<td>Central venous access; acid infusion</td>
</tr>
<tr>
<td>Right external jugular vein</td>
<td>8.5-Fr sheath (Arrow, Erdingen, Germany) pulmonary artery catheter (Criti-Cath™); SP5127 S-TIP TD; Becton Dickinson, Heidelberg, Germany)</td>
<td>Haemodynamic monitoring</td>
</tr>
<tr>
<td>Right femoral vein</td>
<td>Double-lumen catheter (13 Fr, 20 cm length, tip-hole catheter; Gambro, Hechingen, Germany)</td>
<td>Connection with the CVVH system</td>
</tr>
<tr>
<td>Right femoral artery</td>
<td>Arterial catheter (Combidyn®; B. Braun, Melsungen, Germany)</td>
<td>Invasive blood pressure</td>
</tr>
</tbody>
</table>

Materials and methods

**Study design**

In total, 18 male pigs were assigned to three groups with six animals each. All animals underwent CVVH. The control group (CG) was handled with normoventilation and physiological pH homeostasis. One group underwent normoxia and mixed acidaemia [normoxia/acidaemia group (NAG)] and another group received hypoxaemia and mixed acidaemia [hypoxaemia/acidaemia group (HAG)] (for details, see below).
Animals and housing conditions

We used healthy, juvenile male, castrated pigs (German landrace × large white), weighing 37–42 kg. Animals were held under standard conditions along the guidelines for laboratory animal care of the European and German Societies of Laboratory Animal Sciences. The experiments were performed at the Department of Experimental Medicine (facilities are certified by ISO 9001:2000). The study protocol was approved by the University Animal Care Committee and the federal authorities for animal research in Berlin, Germany.

Anaesthesia and volume management

Prior to the experiment, food was withheld for 12 h, but animals had free access to water until premedication. Premedication and anaesthesia was performed as stated in Table 1 and previously described in detail [25]. The normal range of young pigs' body temperature (38.0–39.0°C) was kept with a Warm Touch™ (Tyco Healthcare, Neustadt, Germany). Instrumentation (see Table 2) and all measurements were based on the animals being in the supine position.

Instrumentation

Vascular access was performed as indicated in Table 2. The urinary bladder was directly catheterized with a balloon catheter (Wiruthan®, CH 12; Rüsch, Kernen, Germany) through a short paramedian laparotomy (40 mm). Standard suture techniques were used to close the abdomen.

Acidaemia protocol

Target values for mixed acidaemia were a pH of 7.19–7.24 and PaCO₂ of 80–85 mmHg. The additional target value for hypoxaemia was PaO₂ of ≥ 70 mmHg (and SvO₂ > 65%) in the respective group. Mixed acidaemia was achieved by infusion of an acid solution (0.2 M of lactic acid and 0.2 M hydrochloric acid, diluted in normal saline) and a change from normoventilation to low tidal volume ventilation (6–8 mL/kg−1 h−1).

• In the NAG, mixed acidaemia was started with a central venous bolus infusion of the acid solution (1.8 mmol/kg−1 h−1 of acid). Bolus infusion lasted about 75 min and was followed by a standardized, continuous acid infusion of 2.1 mmol/kg−1 h−1 with a pump (Schiwa-Matic 9000®; Schiwa GmbH).

• In the HAG, FiO₂ was reduced to 0.4 and tidal volume was reduced to 6–8 mL/kg−1. In that group, reduced oxygen supply induced metabolic acidosis and acid infusion was individually adjusted to set target values for acidaemia. This resulted in an acid infusion of 0.6 mmol/kg−1 h−1.

• The CG received an equal volume of 2.1 mL/kg−1 h−1 of normal saline instead of the acid solution and normoventilation was maintained at all times.

In order to standardize the volume of acid infusion and tidal volumes, tris(hydroxymethyl)aminomethane (Tris 36.34% Braun®, B. Braun, Melsungen, Germany) was used for titration of the targeted pH values when the pH decreased below the threshold (7.19) due to circulatory deterioration of the animals, causing metabolic acidemia (Figure 1).

Continuous venovenous haemofiltration

An AK10® machine equipped with medical-grade poly-vinyl-chloride (PVC) tubes and polyamide membrane filters (Polyflux 140H®) was connected to the 13-Fr dual-lumen, tip-hole catheter, 20 cm long (all CVVH materials were from Gambro, Hechingen, Germany). The CVVH was operated by recirculation of the filtrate into the venous bubble trap for 3 h. Based on a former study [25], this procedure served to accelerate possible reactions of haemocompatibility. Anticoagulation was performed with continuous intravenous (i.v.) infusion (60 IU/kg−1 h−1) of unfractionated heparin (Liquemin®, Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany). The activated clotting time (ACT; Hemochron 400®, AD Krauth, Cardiovascular Vertriebsgesellschaft, Hamburg, Germany) was initially adjusted to 150–200 s.

After the experiment, filters were rinsed with 2 L of normal saline and cut open. The whole fibre bundle was visually examined for the percentage of blocked filter capillaries [26] by two investigators independently from each other.

Laboratory analyses

All samples for blood and coagulation analyses were drawn from the central venous catheter and immediately processed. The coagulation parameters [activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen concentration, anti-thrombin III activity (ATIII) and D-dimer level, all from citrated plasma] were determined using laboratory standard methods at the local Institute for Clinical Chemistry, Charité—Universitätsmedizin Berlin. Platelet counts (from EDTA blood) and...
thrombin–anti-thrombin complex (TAT, from citrated tubes) were determined at the Institute for Veterinary Diagnostic GmbH, Berlin. The sC5b-9/terminal complex of the complement system was analysed from EDTA blood at the Institute for Clinical Immunology, Heidelberg University, Germany. The sC5b-9 concentration was measured by enzyme-linked immunosorbent assay (monoclonal antibody to sC5b-9; Diatec AS, Oslo, Norway), SC5b-9 complexes were detected by rabbit anti-C5 (Dako, Hamburg, Germany), followed by peroxidase-labelled third antibody (Dianova, Hamburg, Germany).

Analysis of molecular coagulation parameters
To differentiate between the effects of haemodilution on coagulation parameters (due to volume support and infusion of acid) and the effects of acidemia and hypoxaemia, we made adaptive calculations. We set total plasma protein and haematocrit as a passive parameter with respect to the haemodilution effect. To describe the grade of haemodilution, we calculated protein and haematocrit for the different time points in percent from the respective native baseline values. Figures 3 and 4 show the values of the coagulation factors and platelets at the beginning and at the end of the CVVH period. Presentation of the respective parameter is in percent from its native baseline value as are the values provided for total protein and haematocrit in the same figures. This is thought to ease a direct insight in parameter changes exceeding the effects of haemodilution. A statistical comparison was made for the change in protein vs change in fibrinogen, TAT, D-dimer, etc. A higher change than seen in total protein means a loss of the respective parameter, while a lower change means a synthesis count-acting the drop of concentration due to dilution. Concerning the results of the platelet counts, we opposed changes to the haematocrit (native baseline values of all blood and coagulation parameters are depicted in Table 3).

Statistical analysis
Data were analysed using Sigma Stat 3.1 for Windows. Results are demonstrated in box plots as the median and 25th and 75th percentiles. Since some data failed normal distribution, all comparisons were performed us-
Fig. 3. Measurements of coagulation factors at the CVVH circuit start; fibrinogen concentration, TAT, D-dimers, sC5b-9 terminal complement complex and platelet counts. Data are presented as a percentage of the corresponding native baseline values. To discriminate between haemodilution and active reaction of a particular factor, changes in coagulation factors are compared to changes in total plasma protein. The latter serves as a ‘passive solute’ being sensible to haemodilution. Changes in platelet counts were compared to changes in haematocrit as a ‘passive parameter’. Thus, every group is represented by two box plots: total plasma protein/haematocrit (arrow) and coagulation factor/platelets. Striped boxes indicate total plasma protein concentration, broken frame indicates haematocrit; \(^*P < 0.05\) vs total protein concentration within group; \(^#P < 0.05\) between groups.
Fig. 4. Measurements of coagulation factors after 3 h of CVVH recirculation; fibrinogen concentration, TAT, D-dimers, sC5b-9 terminal complement complex and platelet count. Adaptive calculations of parameters are similarly made as in Figure 3. Data are presented as a percentage of the corresponding native baseline values; every group is represented by two box plots: total plasma protein concentration/haematocrit (arrow) and coagulation factor/platelets. Striped boxes indicate total plasma protein, broken frame indicates haematocrit; *P < 0.05 vs total protein concentration within group; #P < 0.05 between groups.
Native baseline values for parameters concerning coagulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NAG</th>
<th>HAG</th>
<th>CG</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT [s]</td>
<td>27.4 (21.0/49.7)</td>
<td>31.0 (23.2/37.1)</td>
<td>42.7 (37.8/46.6)</td>
<td>40.8 (35.0/48.3), n = 100</td>
</tr>
<tr>
<td>PT [s]</td>
<td>102.5 (93.0/106.0)</td>
<td>93.0 (86.0/101.0)</td>
<td>92.5 (88.0/94.0)</td>
<td>100 (95/106), n = 100</td>
</tr>
<tr>
<td>ACT [s]</td>
<td>109.5 (97.0/126.0)</td>
<td>104.0 (97.0/107.0)</td>
<td>97.5 (90.0/102.0)</td>
<td>127.5 (110.0/145.0), n = 100</td>
</tr>
<tr>
<td>Total plasma protein [mg/dl]</td>
<td>44.3 (42.4/47.8)</td>
<td>44.6 (38.5/47.0)</td>
<td>43.1 (38.7/45.3)</td>
<td>50.0 (48.0/54.0), n = 100</td>
</tr>
<tr>
<td>Fibrinogen concentration [mg/dl]</td>
<td>141.5 (139/151)</td>
<td>166* (153/187)</td>
<td>149 (111/172)</td>
<td>152.5 (137.5/172.5), n = 100</td>
</tr>
<tr>
<td>D-dimer [μg/dl]</td>
<td>0.09* (0.09/0.14)</td>
<td>0.11* (0.10/0.12)</td>
<td>0.18 (0.15/0.29)</td>
<td>0.16 (0.11/0.23), n = 100</td>
</tr>
<tr>
<td>TAT complexes [μg/dl]</td>
<td>5.7 (4.0/8.9)</td>
<td>6.5 (5.6/8.5)</td>
<td>3.8 (3/6.7)</td>
<td>15.8 (8.0/29.1), n = 86</td>
</tr>
<tr>
<td>sC5b-9 complement complex [U/ml]</td>
<td>0.0</td>
<td>49.7 (36.7/81.1)</td>
<td>33.1 (18.7/175.8)</td>
<td>75.0 (29.0/195.0), n = 35</td>
</tr>
<tr>
<td>Platelet count [Gpt/L]</td>
<td>436.5 (205/606)</td>
<td>352.5 (312/424)</td>
<td>328.5 (281/396)</td>
<td>311.5 (237.5/373), n = 100</td>
</tr>
<tr>
<td>Red blood cell count (RBC) [Tpt/L]</td>
<td>5.3 (5.1/5.7)</td>
<td>4.9 (4.6/5.3)</td>
<td>5.0 (4.6/5.2)</td>
<td>4.8 (4.5/5.3), n = 100</td>
</tr>
<tr>
<td>Haematocrit [L/L]</td>
<td>0.26 (0.23/0.29)</td>
<td>0.26 (0.24/0.28)</td>
<td>0.27 (0.22/0.27)</td>
<td>0.26 (0.24/0.27), n = 33</td>
</tr>
</tbody>
</table>

Native baseline values of our study groups: total plasma protein concentration, haematocrit and coagulation factors; reference values: a number of up to 100 animals obtained from the same breeding programs were set as ‘laboratory reference values’. Values are presented as median (25th/75th percentile), *P < 0.05 vs CG.

Results

The groups showed no differences in native baseline values of measured coagulation and plasma parameters, except for D-dimers and fibrinogen concentration (Table 3). D-dimer concentration remained significant or in tendency on higher levels in the CG than in the acidaemic groups (HAG, NAG) from the beginning of the experiment. Fibrinogen concentrations were highest in the HAG animals, but—as in case of D-dimers—the patterns of serum levels were parallel in all groups throughout the experiment.

Clotting times

ATIII demonstrated comparable decreases in all groups during haemodilution. Thus, heparinization could affect clotting times similarly in all groups. There was no significant change concerning the aPTT after the induction of acidaemia and hypoxaemia although the acid solution and volume support led to a clear haemodilution. In contrast, induction of acidaemia and haemodilution resulted in a decrease in PT percentage in the NAG and CG. Whole blood coagulation, measured with the ACT, did not significantly change within a group, but offered varying tendencies between groups. Acidaemia alone did not counteract haemodilutional effects on ACT as indicated by a tendency for prolonged ACT in the NAG and CG. Additional hypoxaemia, in contrast, rather counteracted the dilution and resulted in shorter ACT values (Figure 2).

Heparinization and connection to the CVVH, with a transient further haemodilution due to the system’s priming volume (300 mL), equalized clotting times between the groups. Interestingly, the standardized heparinization resulted in a smaller range between groups for the PT values, whereas a greater range was observed for the aPTT and ACT values. Furthermore, the CG with normal pH homeostasis showed the greatest prolongation of aPTT due to heparin until the end of the experiment. Regarding the induction of acidaemia, the aPTT was rather indicating an activation of the endogenous coagulation system. In contrast, the exogenous system, mirrored by PT, was rather deteriorated by acidaemia until the end of CVVH (P < 0.05 with respect to NAG and in tendency for HAG).

Coagulation parameters and platelets during the period of acidaemia and CVVH

At the CVVH start, total protein and haematocrit dropped from their native baseline values, which clearly indicated the haemodilution due to acid infusion, volume support and CVVH priming volume (Figures 3 and 4).

Fig. 5. This figure shows the percentage of blocked filter capillaries at the end of the experiment which based on a CVVH application with reinfusion of the filtrate to the venous bubble trap.
In control pigs (CG), fibrinogen values and D-dimers remained constant and were likely to be influenced by dilution only. But significant differences between the percentage of fibrinogen changes vs protein changes show that fibrinogen was affected by the induction of normoxic acidemia. D-dimers as indicator for fibrinolytic activity clearly increased under acidemia in both groups (NAG and HAG). During the normoxic acidemia, increases in plasmatic complement complex sC5b-9 were rather delayed as they reached significance only after 3 h of CVVH. This finding opposed the behaviour of the HAG and CG animals that were showing rapid increases in the complement complex followed by a decline already after 3 h.

Compared to the total protein concentration, TAT values were elevated within each group, but this was only significant in HAG animals. There were no significant differences in TAT values between the groups.

Both types of acidemia (NAG and HAG) clearly affected platelet counts from the very beginning of acidemia; there was no indication for sufficient platelet recruitment after 3 h. Interestingly, additional hypoxaemia (HAG) led to significantly lower haematocrit values after 3 h of CVVH, while the other groups tended to show increasing haematocrit values as a result of the abating haemodilution.

All changes in single parameters and clotting times occurring in the early stage of acidemia were found principally to be maintained until the end of the experiment.

Filter function
Filter function with respect to flow rates and transmembrane pressures did not change significantly between the groups. However, running CVVH under a normal pH homeostasis enabled operation of the filter nearly without any clogging, while acidemia tended to raise the number of blocked capillaries already after some hours (Figure 5).

Discussion
The purpose of this animal study was to assess the influence of acidemia and hypoxaemia/acidemia on the haemocompatibility of a CVVH circuit.

Main findings
Haemocompatibility of a CVVH circuit, was modulated by mixed acidemia of either type (with and without hypoxaemia).

- Platelet counts were impaired.
- Acidemia was both pro-coagulatory (activation of aPTT) and anti-coagulatory (PT) and also pro-fibrinolytic.
- Additional hypoxaemia intensified pro-coagulatory aspects and led to an early activation of complement.
- The CG with normal pH homeostasis rather demonstrated stable coagulation patterns mainly influenced by heparin and dilution.
- Within the short application period, filtration performance did not differ significantly between acidemia and normal state.

Dilution and acidemia
Dilution, as it occurs due to volume replacement after haemorrhage, is known to affect coagulation. In an animal study, dilution-based coagulopathy through withdrawal of 65% of the estimated blood volume followed by erythrocyte re-transfusion or colloidal substitution (Infukoll 6%) resulted in decreased PT, fibrinogen concentration, ATIII activities and platelet counts [27,28]. But the interpretation of these data is difficult as both haemorrhage and haemodilution naturally leads to a reduction in parameter concentration and prolonged coagulation times. Although we did not withdraw any blood volume, we had to deal with haemodilution as well due to acid infusion and volume support. For a better interpretation of our data, we ‘corrected’ the haemodilution by comparison of a single molecular and cellular parameter with total plasma protein concentration and haematocrit, respectively. Total protein and haematocrit were set as passive solutes only influenced by dilution, while coagulation parameters and platelets were assumed to react to the overall situation. By that, we got an approximate net impact of acidemia/hypoxaemia on coagulation factors.

Affection of fibrinogen concentration as a result of a normoxic acidemia during the CVVH circuit exposition period confirms the findings that hyperchloraemic acidosis lowers fibrinogen concentrations [13]. Acidosis was also shown to have no effects on fibrinogen synthesis rate but accelerates consumption, resulting in a deficit in fibrinogen availability [14].

Concerning the influence of acidemia, Martini et al. further reported a prolongation of functional clotting times like the PT, aPTT and ACT [13,14,29]. We also found deteriorating effects on PT and ACT due to acidemia. In contrast, our findings pointed to a rather activated aPTT during the CVVH application when acidemia was compared to the CG, which underwent similar haemodilution. In our case, the rather activating effects might be attributed to a modulation of the haemocompatibility behaviour when a CVVH circuit is operated on acidemic individuals. This phenomenon was intensified by additional hypoxaemia.

CVVH
Anticoagulation is usually required to prevent filter clotting even while bleeding complications occur. Compared to heparin and protamine strategies, CVVH without anticoagulation reached acceptable filter lifespan and appears feasible and safe in patients at high risk of bleeding (low platelets or prolonged plasmatic coagulation) [30,31].

The impact of an extracorporeal circuit with its artificial surfaces on coagulation activation has often been elucidated, but inconsistent results are reported. With respect to circumstances of normal acid–base state, it is described that the tissue factor/factor VIIa pathway of the plasmatic coagulation is activated by a CVVH circuit [32], whereas the intrinsic pathway of coagulation seems not to be activated by a CVVH circuit with regard to premature filter clotting [33,34]. But, based on acidemia, we found a contrasting result with activation of the aPTT values during the period of acidemia and exposition to the CVVH circuit. Thus, we observed trends for an activation of the intrinsic/contact pathway of coagulation.
Platelets and acidaemia

In our study, platelet counts were directly affected by both forms of acidaemia, confirming the findings of Martini et al. who reported depleted platelet counts due to acidosis. During haemofiltration, the impact of acidaemia on platelets may have been aggravated by mechanical destruction due to shear stress or thromboocyte sequestration in tissues. This would be in confirmation with previous studies identifying pump-driven extracorporeal circuits to result in platelet loss and dysfunction [35]. Taken together, loss of platelets due to acidaemia and the assumption of a potentially aggravated mechanical stress under acidaemia due to deteriorated haemorheology could explain an increased formation of a secondary protein layer and in turn more blocked filter capillaries in the acidaemic groups.

Complement and acidaemia

Complement activation is not only known from reperfusion syndrome after regional hypoxaemia, but also from acidosis. Previous in vitro studies showed acidosis (hydrochloric, lactic and respiratory hypercapnic acidosis) to trigger activation of the complement components C3a/C5a [36]. Further activation of the sC5b-9 complex was dose-dependent to lactic acid [37].

Additionally, cross-talk between the complement and the coagulation cascade is known to happen under varying circumstances [38] and includes, e.g. platelet-mediated complement activation through P-selectin from platelet’s alpha granules or expression of binding sides for complement components on the platelets surface [39]. Further pro-coagulant activities of the complement system, such as direct platelet activation, modified phospholipid membranes of cells and tissue factor expression on various cell types [40], and direct activation of C5/C3 through thrombin [41] show the interaction of these cascade systems. Confirming these findings, combined acidaemia and hypoxaemia resulted in concomitant high TAT levels in parallel to elevated complement sC5b-9 levels and depleted platelet counts in our study. Thus, acidaemia combined with hypoxaemia deteriorates the haemocompatibility of a CVVH system.

Acidaemia-related coagulation disorders vs uraemia-attributed disorders

In renal failure, retention of organic compounds leads to an ‘endogenous intoxication’ [42]. In uraemia/uraemic syndrome, haemostasis is affected in various aspects. Platelet dysfunction (defect granule secretion, enhanced cAMP, abnormal Ca2+ mobilization) and altered platelet–vessel wall interaction (abnormalities in GPIIb/IIIa receptor binding activity, increased prostaglandine I2 (PGI2) or nitric oxide (NO)) result in increased bleeding, such as gastrointestinal and intracranial bleeding, while in contrast, patients suffer from thrombotic complications [42–45]. Interestingly, our study shows acidaemia to have similarly oppositional effects on haemostasis. Facing prolonged PT, pro-fibrinolytic activities and impaired platelet counts in our porcine model, acidaemia seems to produce an increased bleeding risk, while at the same time, pro-coagulatory trends in the intrinsic pathway could be observed. In fact, uraemic syndrome, which is more pronounced in chronic renal failure, is usually accompanied by acidaemia. Thus, the two components that can be assumed to impair the coagulation state cannot be discriminated for individual impact under clinical circumstances. We know that RRT treatment (removal of uraemic toxins) restores coagulation disorders and acid–base status. The order of how we mention these aspects is automatically assigning a ranking of the importance of impact on coagulation. However, acidosis is identified to be a fatal trigger for coagulation disorders by research on trauma and haemorrhagic shock [10,46,47]. With respect to the match of our results concerning acidaemia-related coagulation disorders with those described for uraemic syndrome, the impact of RRT on coagulation might be phrased in the reverse order: ‘RRT restores the acid–base state and—probably in turn—coagulation’.

Study design

This study has some limitations. Our results can just be attributed to a short term of acidaemia and CVVH application, while patients are exposed to these conditions for days or weeks. In our previous studies (in vivo and in vitro), we also operated the CVVH in a recirculation mode of giving the filtrate back into the venous bubble trap for several hours. This means the return of filtrate including activated coagulation and complement factors as a continuous source of further activation. This procedure already significantly affected haemocompatibility after a short time [4,25]. When biocompatibility already affects yield from short-term application under a particular mode, the effects obtained are likely to be more pronounced in a longer-lasting exposition. We used a quite artificial study setting inducing acidaemia in healthy animals. But this is the only way to get the net impact of acidaemia rather than the overall result of interfering pathophysiology. Demonstrating the net impact is giving both an explanation for paradox complications in the clinical application and a hint for a potential new strategy to reduce complications by a more determined correction of the acid–base disorders.

Conclusion

The study groups showed no significant differences concerning the filter performance, but the acidaemia affected the haemostatic system in different ways. Importantly, pro-coagulatory effects on the intrinsic pathway of coagulation occurred in acidaemic pigs in parallel to pro-fibrinolytic activities and deterioration of the extrinsic pathway (PT) and platelet counts. The latter is crucial because ACT and aPTT, which were rather activated by acidaemia, are the most common parameters chosen to monitor and regulate anticoagulation. Our findings might explain the paradoxical finding of simultaneously clotted haemofilters and bleeding in the patient. Facing permissive hypercapnia and tolerated acidosis in intensive care patients [21], additional investigations are desirable to improve CVVH protocols with respect to clinically relevant biocompatibility conditions.

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Conflict of interest statement. None declared.

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