Chapter

Extracorporeal Blood Purification with the Oxiris Membrane in Septic Shock

Franco Turani and Sara Martini

Abstract

Septic shock with AKI is associated with a high mortality. We evaluated whether continuous renal replacement therapy (CRRT) using a membrane (oXiris) with adsorbing properties could improve cardio-renal response and modulate endotoxin and cytokine levels. 105 patients requiring CRRT for septic shock-AKI received CRRT with an oXiris filter. The main cardio-renal parameters, SOFA total score, SOFA organ score, endotoxin and cytokine levels were measured at baseline (T0) and 72 h after the start of CRRT (T1). Norepinephrine infusion rate, blood lactate levels, and thromboelastographic parameters were monitored. At T1, the renal function improved ($p < 0.01$) urinary output increased ($p < 0,.01$) with the cardiac response and the decrease of norepinephrine infusion. SOFA total decreased to 8.4 ± 3 from 12 ± 2 ($p < 0.001$). Endotoxin decreased also at T 1 ($p < 0.01$) with a reduction of Il 6 and procalcitonin. Lactate level ranged from 3.37 ± 3.2mto 1.67 ± 1.8 mmol/l ($p < 0.01$). CRRT with the oxiris filter improves the cardio renal response response in septic patients with AKI. This is associated with a modulation of endo-toxemia, of cytokines and the stability of the coagulation parameters.

Keywords: blood purification, AKI, septic shock, Oxiris membrane, citrate anticoagulation

1. Introduction

Sepsis and septic shock are one of the 10 causes of death worldwide, and the second cause in Intensive Care Unit. Moreover, in many septic patients (e.g., 40%), acute kidney injury rapidly develops, increasing the risk of mortality (from 50 to 80%) and the complications [1]. Despite the clinical importance of AKI during sepsis, many physiological aspects are not completely known, and its treatment is currently inadequate. Only recently, new studies have challenged the hemodynamic nature of AKI during sepsis, which may occur even if the renal blood flow (RBF) is maintained [2].

In the context of sepsis, considering as a dysfunctional immunological response, probably many pro-inflammatory mediators and endotoxin may interact with the kidney at different levels (tubular cells, mesangial cells, glomerular cells) and induce AKI [3]. The kidney itself may exacerbate this inflammatory response and cross talk with other organ (lung, heart) to induce a multiorgan failure [4]. This may occur also

in the recent viremia Covid-19, in which an uncontrolled inflammatory response is described by many AA and septic shock with a multiorgan failure may ensue.

Extracorporeal blood purification, combining renal replacement therapy with the adsorption of many mediators, may be useful to modulate the septic immunological response and halt the renal cross talk with other organs.

Many devices are widely used, with different adsorbing capacity, but with inconclusive results [5].

The AN69-based oXiris membrane is modified with a positively charged charged polyimine ethylene layer capable of adsorbing negatively charged endotoxin molecules and IL6, IL10, and other mediators. Broman et al. have shown that Oxiris membrane may adsorb endotoxin and IL6 better than AN 69 st. in the first 24 h of treatment of patients with abdominal sepsis [6].

In this prospective study, we evaluated the changes of endotoxin during 76 h of CRRT in patients with different sources of sepsis. The changes of IL6, IL10, and procalcitonin are also studied, with the assessment of the coagulation in an attempt to confirm the effect of oXiris on endotoxin and other mediators in septic patients with AKI in a time period study longer than 24 h.

2. Methods

2.1 Study design

Non-interventional, observational, multicenter, prospective study.

2.2 Study cohort

The setting was a 11-bed secondary referral medical-surgical intensive care unit (ICU) at the Aurelia Hospital in Rome, Italy, and the 15-bed Cardiothoracic Intensive Care at the European Hospital in Rome. All patients were treated according to the normal ICU protocol and current severe sepsis guidelines [7].

The study population consisted of patients with sepsis/septic shock defined by Sepsis 3 conference with AKI, defined by KDIGO criteria. (Sepsis 3 Kdigo) Inclusion criteria were also considered: Endotoxin activity assay ≥0.6 and/or IL6 ≥ 150 pg/mL, noradrenaline infusion, MAP, and P/F ratio < 200 with mechanical ventilation or NIV. Patients with an age < 18 years 80 > and/or being pregnant, if present chronic renal failure (or previous treatment with CRRT), endotoxin or interleukins in the normal range, Glasgow Coma Score (GCS) < 8 due to hemorrhagic or ischemic events, and the need of extracorporeal membrane oxygenation (ECMO) were not eligible to receive CRRT and Oxiris treatment.

2.3 Study procedure

After receiving consent, Oxiris filter (Baxter, Il_USA) was assembled on the Prismaflex System or Prismamax (Il_USA), and CRRT was started on CVVHDF mode.

All treatments were performed by the same experienced nurses under the supervision of the investigators. Vascular access was obtained with use of double-lumen venous catheters through echographic visualization of femoral or Iinternal giugular vein. The circuit was prepared according to the manufacturer's guidelines

Qb ml/min	150 ± 20
Qd ml/h	1000 ± 600
Qr pre dilution ml/h	0
Qr post dilution ml/h	800 ± 250
Q PBP citrate infusion ml/h	1400 ± 250
Filtration fraction (%)	25 ± 6

Table 1.
CVVHDF with oXiris filter: initial prescription.

Anticoagulation	N. patients	Hours of treatment
Heparin ev	10	26 ± 5
Citrate 10 mmol/L	10	32 ± 8
Citrate 18 mmol/L	70	56 ± 16
No anticoagulation	11	18 ± 6

Table 2.
CVVHDF with oXiris filter: anticoagulation of the circuit.

by rinsing the device with 1000 ml of physiological saline solution with 5000 UI of heparin.

In **Tables 1** and **2**, the initial prescription of CRRT with oXiris membrane and the protocols of anticoagulation we used are shown.

2.4 Measurement

Endotoxin activity was measured using a commercial kit for whole blood neutrophil-dependent chemiluminescence (EAA Endotoxin Activity Assay; Spectral Diagnostics, Inc., Toronto, Ont., Canada). Arterial blood samples for EAA assay were drawn before the treatment (T0), after 72 h of CRRT with the Oxiris membrane (T1). The plasma levels of IL-6 and IL 10 were measured using enzyme-linked immunosorbent assay kits, according to the manufacturer's instructions (R&DSystems, Minneapolis, MN, USA). PCT was detected by enzyme-linked fluorescence assay (MINIVIDAS; bioMérieux, Marcy-l'Étoile, France).

Hemodynamic and respiratory data were continuously recorded on the electronic patient record system. Transthoracic echocardiography was performed by a cardiologist blind to the protocol, and the images was stored and analyzed off-line.

Thromboelastography analysis was performed at basal time and at the end of the treatment.

The Thrombelastograph® (TEG® 5000, Haemonetics Inc., Braintree MA) analyzer, the TEG6s system (Haemonetics, Braintree, MA, Niles, IL) have been used.

2.5 End points

Primary end points

1. Improvement of renal failure with the decrease of SOFA renal to 50% of the basal level

2. Increase of urinary output of 50% vs. basal level, improvement of the fluid balance, and increase of P/F ratio

3. Resolution of the arterial hypotension and decrease of the vasoactive drugs with the changes of SOFA cardio to 50% of the basal level

4. Decrease of SOFA total to 40% of the basal level

Secondary end points

1. Decrease of endotoxin to <0.6 and IL6 to 40% of the basal level

2. Decrease of procalcitonin and PAI-1 to 40% of the basal level

3. Stability of the coagulation profile, included thromboelastographic parameters and changes of PAI-1

4. Improvement of filter thrombogenicity, evaluated by Platelet map thromboelastography

2.6 Data collection

All clinical data are stored on the clinical informatic platform CLINIC DATA PRO (System Line—Empoli, Italy). All microbiological, immunological, and coagulation data are stored on the laboratory informatic platform—MODULAB GOLD ITALY (WERFEN UK). The data of 25 patients were transmitted and stored on the clinical platform REDCUP Villa.

2.7 Ethical consideration

The study protocol was approved by the Ethics Committee of the Azienda Ospedaliera San Camillo – Forlanini (reference No. 418 CE Lazio 1/2019) and registered at clinicaltrials.gov (NCT03914586). Written informed consent was obtained from each patient or next of kin.

2.8 Statistical analysis

Sample size calculation was based on changes in EAA level detected using the EAA test in a previous study on oXiris in patients with AKI and septic shock [BPUF]. Using a Student's paired t-test with a two-sided $\alpha = 0.05$, it was calculated that 90% power would be obtained with a sample size of 60 patients, based on a decrease in endotoxin levels from 0.78[0.98–0.65] EU/ to 0.58 [0.13–0.41] EU/ml. To compensate for potentially larger variation in endotoxin levels, we estimated that 80 patients with complete datasets should be included.

Continuous variables are reported as mean ± SD or median (first–third quartiles) and categorical variables as count and proportion. Comparisons of proportions were made using Chi-square test or Fisher exact test. Continuous variables were compared

using Student t-test or Wilcoxon rank-sum test and one-way anal-ysis of variance or Kruskal-Wallis test, as appropriate. Post hoc Tukey range test and Dunn's test for multiple comparisons were used. We performed stepwise (forward and backward) multivariable logistic regression analyses to identify factors associated with different types of infections.

We performed multivariate analyses to identify factors potentially associated with different infections: abdominal infection vs. thoracic infection. Covariates found to be associated with abdominal infection in the bivariate analysis with a p value of less than or equal to 0.20 were entered in stepwise (forward and backward) multivariable logistic regression analyses with significance alpha levels less than or equal to 0.05 for retention. Multicollinearity was assessed calculating a variance inflation factor of each variable and rules out if the variance inflation factor was lower than 4. Results are shown as ORs with 95% CIs, and model performance was assessed using the Hosmer-Lemeshow goodness-of-fit test statistic. These analyses were conducted with GraphPad Prism 7.02 (La Jolla, CA, USA).

3. Results

From January 2012 to September 2020, 143 patients with sepsis septic shock (Sepsis III definition) and AKI (AKIN classification) required ICU admission to Aurelia Hospital and European Hospital in Rome.

Among these patients, after the revision of the clinical data stored in the clinical informatic platform, 42 patients have been excluded from the study, as they did not fulfill the inclusion criteria (**Figure 1**).

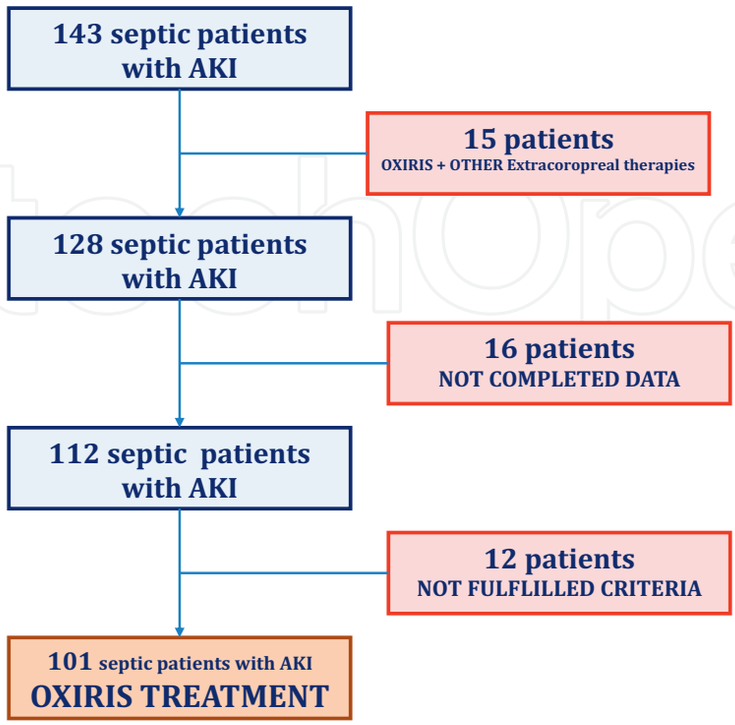

Figure 1.
Enrollment of the patients in the study. From 143 patient referred to the two intensive care AURELIA HOSPITAL and EUROPEAN HOSPITAL finally 101 patients were enrolled in the study.

In total, 101 patients with sepsis/septic shock and AKI (AKIN criteria) received CRRT with oXiris filter and completed the study. In **Tables 3** and **4**, the main basal anthropometric and clinical data are reported. All patients received intensive care treatment in accordance with the Survive Sepsis Campaign Bundle. The initial prescription was continuous venovenous hemodiafiltration (CVVHDF), as reported in **Table 1**. Data on anticoagulation are shown in **Table 2**.

For the 101 patients included in the study, we analyzed the protocol data at basal time (T0) and after 72 h of treatment (T1). All patients included in the study were also stratified on AKIN criteria, and the changes between these groups were also evaluated.

3.1 Primary end points

During the 72 h of treatment, urinary output increased and creatinine improved (**Table 5**). SOFA renal decreased (**Figure 2**). Urinary output increased to 57% and was associated with the increase of P/F ratio and fluid balance (**Tables 5** and **6**).

In **Table 6**, the main hemodynamic changes during the treatment are shown. MAP increased and norepinephrine dosage dropped to low value. This is associated with the changes of SOFA cardio.

SOFA total decreased, too, as a result of this global clinical improvement (**Figure 2**).

3.2 Secondary end points

At T0, EE activity was 0.64 ± 0.15. 8.5% of patients had low EAA activity (*< 0.39 unit*), 28% medium EAA activity (*0.40–0.59 unit*), and 63% of patients high EAA activity *(> 0.60 unit*), confirming the massive release of endotoxin in septic patients with AKI.

Number of patients	**101**
M/F	68/33
Age/year	68 ± 9
Weight (kg)	85 ± 15
Height (cm)	170 ± 6
BSA	2.2 ± 0.6

Table 3.
The main anthropometric data at study entry.

APACHE II	23 ± 4
SOFA total	12.6 ± 3
AKIN Classification	
AKI 3 patients	36
AKI 2 patients	27
AKI 1 patients	38

Table 4.
Basal clinical data at study entry.

	T0	T1
Creatinine mg/dl	2.3 ± 1	1.15 ± 0.5***
UOP mL/24 h	1074 ± 825	1826 ± 1173***
HCO3 meq/l	21 ± 2	24 ± 3
Lactate mmol/l	2.3 (1.6–3.2)	1.1 (0.8–1.8)**

*** *p< 0.001*
** *p< 0.01*

Table 5.
Renal and metabolic changes during CRRT with the membrane oXiris.

	T0	T1
MAP mmHg	63 ± 12	79 ± 13***
Noradrenaline µicr/kg/min	0.12 ± 0.1	0.05 ± 0.01***
P/F ratio	215 ± 80	288 ± 73*
Arterial elastance	1.2 (1.1–1.4)	1.9 (1.3–2.05)
Ventricular elastance	0.7 (0.6–0.9)	1.2 (1.1–1.4)

*** *p< 0.001*
** *p< 0.01*
* *p<0.05*

Table 6.
Hemodynamic and respiratory changes during CRRT with the membrane oXiris.

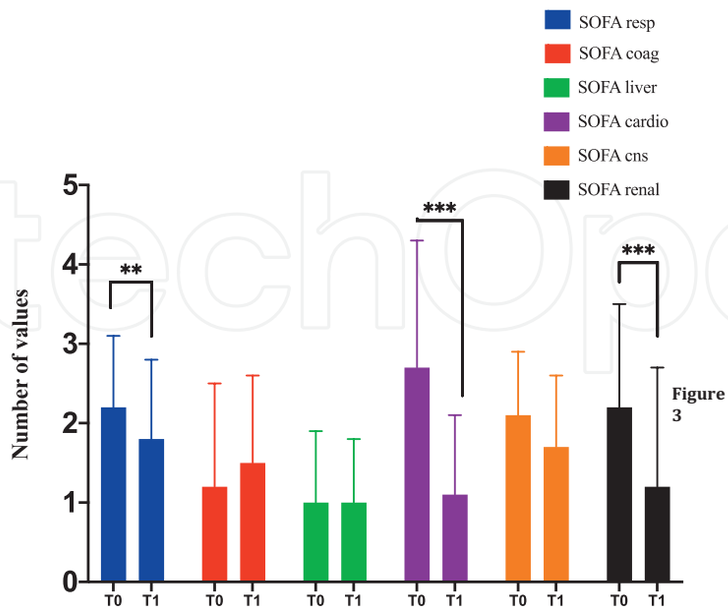

Figure 2.
SOFA changes during CRRT with oXiris filter. SOFA changes are shown. SOFA resp., SOFA card, SOFA renal improve. To = basal time. T1 = after 72 h of oXiris treatment.

At T1, EAA decreased to 0.5 ± 0.1 *unit (p < 0.01 vs T0)* Il6, Il 10, and procalcitonin mirrored these changes (**Table** 7).

	T0	T1
IL6 pg/ml	437 (206–1137)	91 (28–188)***
IL 10 pg/ml	14 (7–132)	8 (6–42)
Procalcitonin ng/ml	45 (14–58)	12 (10–18)***
EAA unit	0.64 ± 0.15	0.51 ± 0.1**

*** $p < 0.001$
** $p < 0.01$

Table 7.
Immunological changes during CRRT with the membrane oXiris.

Parameters	T0	T1
Platelets (10^3 µl)	159 ± 124	127 ± 83
Fibrinogen (mg/dl)	507 ± 248	493 ± 248
D/dimer (ng/ml)	2402 ± 1136	2135 ± 1037
PAI-1 (ng/ml)	76 ± 31	25 ± 28*

* $p<0.05$.

Table 8.
Coagulation parameters during CRRT with oXiris filter.

Coagulation parameters were stable, with nonsignificant decrease of platelets and no changes of TEG parameters (**Table 8**).

PAI – I decreased, too, confirming an antithrombotic effect of RRT with oxiris membrane, as indicated by platelet TEG in patients with citrate anticoagulation.

3.3 Adverse events

Clotting of the filter (5/20) and minor bleeding (8/20) were the most common events in patients with heparine anticoagulation. Patients with citrate anticoagulation developed acid-base disturbance (metabolic acidosis 7/70, lactic acidosis 5/70), clotting of the filter (10/70), and two episodes of HIT not related completely to the CRRT treatment. In the patients treated without anticoagulation, clotting of the filter was a common event (6/11).

4. Discussion

4.1 Key findings

The main findings of this study are:

1. AKI during sepsis/septic shock is associated with a pro-inflammatory response (IL6, Procalcitonin, Endotoxin), it's equally present in all the AKIN groups and drives a multiorgan dysfunction.

2. CRRT with the adsorbing filter oXiris may improve this condition: its use has a positive effect either on the cardio-renal function and the immunological response.

3. Despite the involvement of the coagulation system during sepsis/septic shock, CRRT with the oXiris filter seems to prevent the worsening of the coagulation and DIC.

4. This effect may result from an antithrombotic of the oXiris filter, mainly when anticoagulation with citrate is used.

AKI is a severe complication of sepsis: it's a common finding in 40–50% of septic patients and correlates with a high mortality. However, no effective therapy is currently available, and recent studies challenged the notion that AKI during sepsis depends on renal perfusion and systemic hypotension. New evidences suggest that a dysregulated immunological and inflammatory response induces microcirculatory alterations not responding to the usual intensive care treatment.

Data of our study confirm these results: IL6 is high at basal levels and probably has a direct toxic on the kidney and induce a vasoplegic response, which is also detrimental for the renal function.

Shimatsu et al. found that high quartiles of IL6 increased the risk of anuria and AKI, whereas Payen et al. found that plasma cytokine's profile differed according to AKI severity [8].

In adjunct to IL6, we also evaluated procalcitonin and endotoxin: they were elevated in all the AKIN groups. Procalcitonin increases during bacterial infection and during sepsis, may induce a toxic effect on the kidney, and is associated, too, with AKI development and mortality in critically ill patients, in line with our results. Very recently, Ronco et al. have shown that a combination of [TIMP-2] Å ~ [IGFBP7] and PCT improved the predictive ability for AKI occurrence. Unfortunately, in our study we did not measure biomarkers and we cannot confirm these data [9].

Nevertheless, the serial measurements of cytokines and procalcitonin and the changes of the renal function reinforce the Ronco's hypothesis that there is an association between inflammation and AKI development.

Interestingly more than 80% of patients, in our study, had endotoxin ≥0.6 ng/mL, a cutoff value, which correlates with a predictive positive response to BP in Euphrates trial.

In our study, as in Euphrates RCT, we enrolled patients with different infections (GRA– and GRAM+) or none (**Table 9**). Endotoxiemia, therefore, seems a global response during sepsis and AKI, not depending only on Gram-negative infections, but also on Gram + bacteria and probably by bacterial translocation, as recently pointed out by Honore' et al. [10].

The IL10 changes follow the changes of all other mediators, confirming that a pro- and anti-inflammatory response may coexist in the early phase of the sepsis.

Pathogen	**Number**
Gram-negative	40
Gram-positive	20
Mixed gram negative and positive	25
No microbiological data	15
Fungi	5

Table 9.
Pathogens isolated in the study population.

This dysregulated immunological response translated in a multiorgan dysfunction with high basal lactate levels, the need of vasopressor therapy, and of mechanical ventilation in more than 80% of patients.

CRRT with Oxiris filter had many effects on this condition. First of all, this treatment improved the renal function: creatinine decreased and urinary output increased with improvement of SOFA renal (**Figure 1**).As expected, cardiocirculatory function improved: MAP increased with the decrease of noradrenaline infusion and SOFA cardiac (**Figure 1**).

These data are well explained in the context of the cardio-renal syndrome, in which oliguria, electrolytic disturbances, and uremia depress the cardiac function. However, the circulatory function during sepsis depends also on many inflammatory mediators. In this study, in effect, the improvement of the renal and the cardiac function is associated with the decrease of IL 6 and procalcitonin (**Table** 7).

Very recently, Zhay et al. showed a superiority of oxiris filter in confront of RRT with no adsorbing filter, with data on il6 endotoxin and cardio-renal response similar to our study. Notably, they showed also the changes of procalcitonin, as in our study. These data are recently confirmed by Xie et al., who stated that the changes of procalcitonin during the treatment may have a positive impact on the survival [9, 11, 12].

We observed also the changes of the endotoxin. This is in agreement with Kellum's in vitro study and Broman's and Zai's et al.'s clinical studies [7, 11].

Different from these studies, we used a chemiluminescence method to detect EAA changes during a longer time study. Whereas Broman and Zai evaluated EAA changes during 24- and 8-h treatment; in our study, EAA changes are evaluated at basal time and after 72 h of treatment.

Notably, endotoxin improved more in sepsis of abdominal origin then in thoracopulmonary sepsis, as previously shown by Cutuli et al. [13]. Probably in our study, as in Euphas 2, patients with abdominal infection have a more rapid decrease of endotoxin trough the source control of surgery. In this case, endotoxin declines rapidly also at extracellular and tissue level, promoting a more efficient adsorbing effect of the membrane **Figure 3**.

This important pro-inflammatory reaction, as expected, activates the coagulation response: platelets are in the lower normal range, PAI-1 is increased, and TEG analysis showed high or normal MA in more of 50% of patients, confirming that hypercogulation is a common trait during sepsis [14].

During the treatment, all coagulation parameters are stable or improve, as indicated by D/D, the stability of the platelet's numbers and decrease of PAI-1. Data of TEG, too, indicate a stability of all parameters.

We can hypothesize that some properties of the oXiris filter—heparine-coated layers, the adsorbing action of pro-inflammatory, and pro-coagulant mediators with the use of regional anticoagulation with citrate may modulate the coagulation cascade and prevent DIC.

However, heparin-coated membrane itself, as assembled on oXiris membrane, probably fails to prevent a full anticoagulation. Shetz et al., Seminars et al. reported that AN69 ST membrane and Oxiris membrane do not prolong filter survival without anticoagulation [15, 16].

Probably heparin-coated layers may be saturated very early, as the anticoagulant effect is likely localized to only areas of membranes where heparin is immobilized and exposed areas to polityleniminе are not spared by thombogenicity.

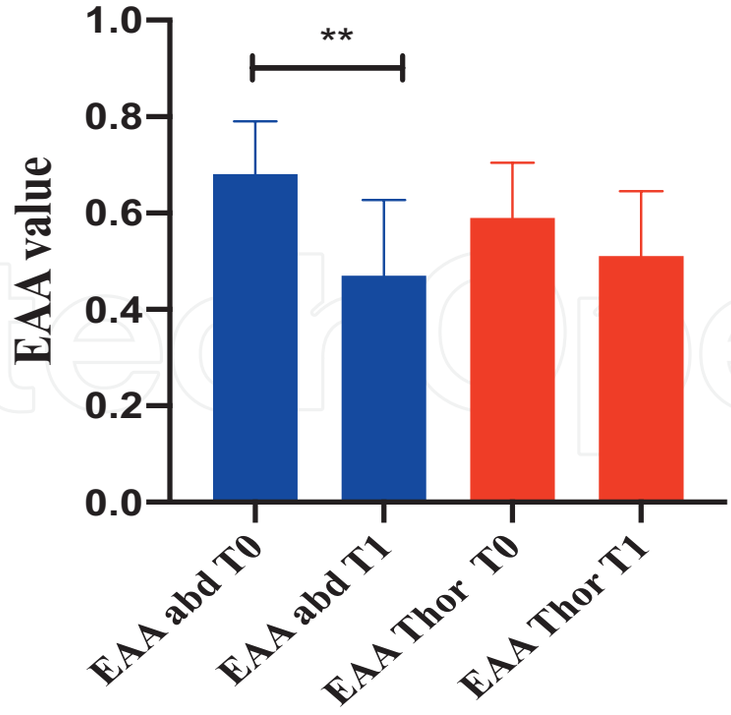

Figure 3.
*Endotoxin response during CRRT with oXiris filter in different infection patients. In patients with sepsis of abdominal origin (abd) endotoxin decreases more than in patients with sepsis of thoracopulmonary (thor) origin. **p < 0.01 in the group.*

Secondarily, during sepsis, activated monocite and other cells adhere to surface of extracorporeal circuit, inhibit fibrinolysis, and render clots resistant to heparin [17].

Third heparin has a weak activity on calcium concentration, whereas during sepsis, the most important pro-coagulant mechanism is induced by calcium release.

Finally, histones and other dams or pumps are strongly adsorbed by heparin layers, which may be early saturated and then inhibited to anticoagulate the membrane [18]. Thus, citrate protocol we used in this study seems a rational alternative to heparin [14].

The main advantage of citrate is that regional anticoagulation achieves optimal filter anticoagulation without affecting patient's coagulation. In this study, the coagulation parameters are stable, without induction of avert DIC.

In **Table 10**, the changes of TEG parameters during oXiris treatment are shown.

In **Figure 4**, the different changes of them during citrate and heparin anti coagulation are shown. In the heparin group MA and R were longer than citrate group, confirming that citrate achieves a better stability of the coagulation.

These data are in line with a very recent study by Osterman et al., who confirmed that coagulation profiles were stable during CRRT with citrate and no increase of prothrombotic status was found. Wiegele et al. confirmed these data [18].

We aimed, also, to control the in-filter changes of the coagulation to confirm whether citrate would be able to abolish the coagulation, as compared with heparin. Filter was fully anticoagulated by citrate, but not by heparin (**Figure 5**). This was little surprising, considering that heparin is widely used to anticoagulate all the extra corporeal circuits in many clinical contexts.

During sepsis, however, a pro-coagulant response is activated, either through calcium-dependent mechanism or inhibition of normal anticoagulant factors

Parameters	T0	T1
R (min)	9.65 ± 3	9.59 ± 4
K (min)	2.1 ± 0.5	3.7 ± 0.9
Ang (grade)	65 ± 7	62 ± 9
MA (mm)	65 ± 5	76 ± 59 ± 8
LY 30 (%)	3 ± 0.9	6.5 ± 0.9

Table 10.
TEG parameters during CRRT with oXiris filter.

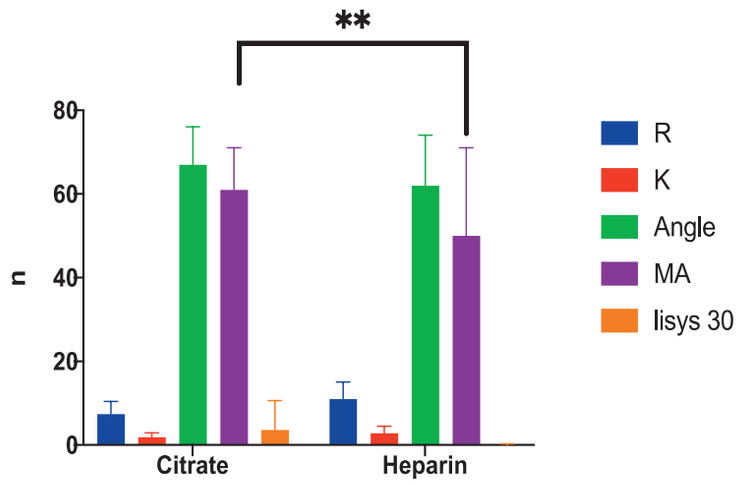

Figure 4.
*TEG changes during CRRT with oXiris filter from arterial sample. In citrate group, MA was higher than in heparin group, as a more firm coagulation is achieved ** p < 0.01 between the groups. R and K are expressed in min, ANG in grade, and MA in mm.*

(e.g., decrease of AT III). In this way, heparin response is blunted and thrombosis of circuits may occur, with failure of the treatments and worsening of the patient's condition [19].

These data are in line with Panigada et al., who reported that citrate infusion to maintain ca++ filter <0.25 mmol/L fullly anticoagulated the ECCO2 removal circuit and had TEG changes as in our study [20].

Ostermann et al., otherwise, have shown that citrate anticoagulation does not affect intra-circuit parameters and that all patients exhibited raised thrombin generation.

At variance with this study, we utilized the Haemonetic TEG, which employs a heparinized blood sample that is mixed with dried reagents within each of the four channels of the cartridge. We cannot hypothesize whether these different changes of TEG parameters depend on a different method, or reagents or a different properties of the dialytic membranes have been used.

Failure of the circuit depends not only on coagulation factors, by also on platelets, which are activated during sepsis and CRRT.

In this study, we evaluated also platelet's function by thromboelastography: this was downregulated in the filter during treatment with citrate, but not with heparin (**Figure 4**).

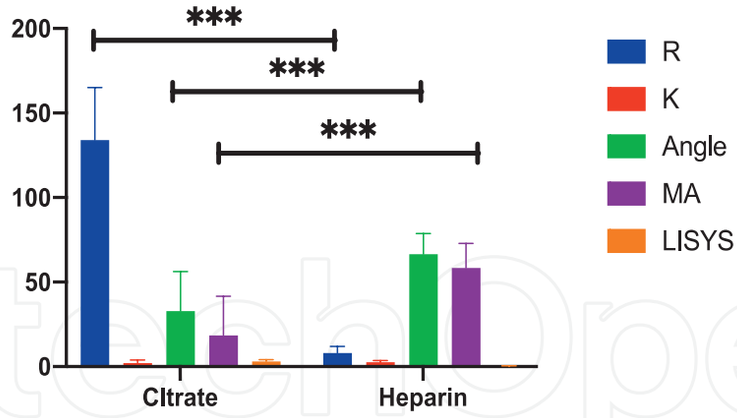

Figure 5.
*In filter changes during CRRT with oXiris filter. In citrate R was higher, angle and MA lower than heparin group, as a stronger filter anticoagulation. *** p < 0.001 between the groups. R and K are expressed in min, ANG in grade, and MA in mm.*

As platelets are activated via a calcium-dependent mechanisms, citrate probably decrease platelet activation in many ways, including inhibition of PF4, extracellulare vescicles, and particle microparticle, which are strongly pro-coagulant **Figure 5**.

Heparin, itself, may enhance platelet aggregation probably by P2Y receptor: the effect of Ca++ inhibition by and the action of heparin may explain the different TEG changes and confirm that citrate has a full anti coagulation, better than heparin [21].

These data are, again, at difference with Ostermann, who observed no change in platelets function, using PFA-100 analyzer. Panigada, too, did not show any effect of citrate on platelet function evaluated by aggregometry. Also in this case we can conclude whether these divergent data stem from different methods of study or from an effect of the oXiris membrane we used.

Conflict of interest

Dottor Franco Turani received a research grant by Baxter Healthcare, Chicago, USA.

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