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Clinical paper

Hemodynamic efficiency of hemodialysis treatment with high cut-off membrane during the early period of post-resuscitation shock: The HYPERDIA trial

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Abstract

Background: After resuscitation of cardiac arrest (CA), an acute circulatory failure occurs in about 50% of cases, which shares many characteristics with septic shock. Most frequently, supportive treatments are poorly efficient to prevent multiple organ failure and death. We evaluated whether an early plasma removal of inflammatory mediators using high cut-off continuous veno-venous hemodialysis (HCO-CVVHD) could improve hemodynamic status and outcome of these patients.

Patients and methods: We performed a randomized open-label trial. Patients with post-cardiac arrest shock (defined as requirement of norepinephrine or epinephrine infusion > 1 mg/h) were included. The experimental group received 2 distinct sessions of HCO-CVVHD during the first 48 h following ICU admission. The control group received continuous veno-venous hemofiltration (CVVH) with standard membranes if needed. The primary endpoint was the delay to shock resolution asssessed by the length of catecholamine infusion. Number of vasopressors-free days at day 28, arterial blood pressure measures every 6-hours, daily fluid balance and mortality (ICU and day-28) were evaluated as secondary endpoints.

Results: 35 patients were included: 17 (median age 68.4, 59% male) in the HCO-CVVHD group and 18 (median age 66.3, 83% male) in the control group. Baseline characteristics did not differ between the two groups. Day-28 mortality rate was 64.7% and 72.2% in the HCO-CVVHD and control group, respectively (p = 0.72). Probability of vasopressors discontinuation over time was similar in the two groups (p for logrank test = 0.67). Number of day-28 catecholamine-free days was 25.1 [0, 26.5] and 24.5 [0, 26.2] in the HCO-CVVHD and control group, respectively (p = 0.65). No difference was observed regarding the daily-dose of vasopressors, arterial pressure profile and fluid balance.

Conclusion: In cardiac arrest patients, HCO-CVVHD did not decrease the lenght of post-resuscitation shock and had no significant effect on hemodynamic profile.

Registration: NCT00780299.

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Introduction

Despite several advances in management of cardiac arrest (CA), a large subset of patients with return of spontaneous circulation (ROSC) will present a post-CA shock, which may result in refractory multiple organ failure and death.[1,2] This syndrome typically occurs within the first hours after ROSC as a consequence of the whole-body ischemia-reperfusion process.[3,4] Previous clinical investigations have depicted hemodynamic features, which combine vasodilation and myocardial dysfunction.[5,6]

Post-resuscitation shock is associated with an important release of inflammatory mediators and cytokines (endotoxin, TNF-alpha, interleukines) to the blood and an exacerbation of the systemic inflammatory response, in a way quite similar to what is observed in sepsis and septic shock.[7] Considering this pathophysiology, it has been suggested that an early blood removal of inflammatory mediators could be associated with an improvement in hemodynamic compromise and outcome. However, inflammatory mediators are relatively large molecules and conventional haemofilters used for renal replacement therapies (RRT) are unlikely to achieve their clearance. A better clearance of these molecules can be obtained using alternative extracorporeal blood purification therapies. In a previous clinical study, high-volume hemofiltration (HVHF), which potentially offers an effective blood purification of circulating inflammatory mediators, was found of potential benefit in patients with post-CA shock.[8] However, these results were not replicated and did not translate into standard management, mostly because HVHF is difficult to manage in routine practice and because it requires special equipment. Another approach is offered by specially designed haemofilters that permit high cut-off veno-venous hemodialysis (HCO-CVVHD) resulting in removal of pro-inflammatory cytokines.[9,10] Importantly, these haemofilters allowing HCO-CVVHD do not require special equipment as they can be used with devices that are commonly used in intensive care units (ICU) for continuous RRT.

When designing the HYPERDIA study, we hypothesized that HCO-CVVHD could improve the hemodynamic status of patients with post-CA shock, as compared with standard management.

Methods and design

The HYPERDIA trial was a prospective, monocentric, randomized, controlled trial aiming to assess the feasability, safety, clinical and biological efficacy of HCO-CVVHD in patients with post-CA shock as compared with standard management. The hypothesis was that the duration of the hemodynamic compromise would be shorter with HCO-CVVHD (intervention group) as compared with standard strategy (control group).

Study setting and participants

The study was performed in the medical ICU of Cochin University hospital, which serves as a cardiac arrest centre in the southern Paris area (France). During the study period, all consecutive patients who were admitted after a witnessed CA were screened for participation. They were eligible if the following inclusion criteria were present: adults (> 18 yo), still comatose (defined by a Glasgow Coma Scale less than or equal 7); CA presumed to result from a cardiac cause; and if patients had a post-resucitation shock, i.e., a need for continuous vasopressor infusion (epinephrine or norepinephrine) with a dose higher than 1milligram per hour. Patients meeting any of the following non-inclusion criteria were not included in the trial: CA cause associated with an increase of hemorraghe risk (traumatic brain injury, subarachnoidal hemorrhage, ischemic stroke, diffuse hemorrhage), Glasgow Coma Scale higher than 7, moribund patient with a life expectancy lower than 24 h, life expectancy lower than 28 days related to a underlying chronic disease, logistic inability to start the treatment within the first 6 h after ROSC, anticoagulants contraindication, heparin-induced thrombocytopenia, severe thrombocytopenia lower than 20 G/L, neutropenia related to a hematologic malignancy, Acquired ImmunoDeficiency Syndrome (AIDS) with CD4 T lymphocytes lower than 0.050 G/L, immunosuppressive treatments (except corticosteroids), pregnancy, weight higher than 100 kg, absence of national statutory health insurance coverage, inclusion in another interventional trial or any administrative supervision

Randomization

If eligible, patients were randomly assigned in a 1:1 ratio to intervention or standard group (Fig. 1). Randomization was performed using a computer-generated assignment sequence via a dedicated website (telemedicine cleanweb.aphp). Time zero was defined by randomization time.

Physicians in charge were aware of the intervention assignement because it was not possible to blind them for HCO-CVVHD. However, hemodynamic management was similar in the 2 groups, and data managers and staticians were blinded to the randomization result.

Outcomes

The main endpoint was the lenght of time between inclusion and shock resolution, assessed through the duration of vasopressors infusion. Complete weaning of vasopressors was considered if the infusion was not resumed after 1 h of weaning.

Secondary outcomes included arterial pressure, the dose of vasoactive/vasopressor agents expressed by the inotropic score [(dopamine dose × 1) + (dobutamine dose × 1) + (adrenaline dose × 100) + (noradrenaline dose × 100) + (phenylephrine dose × 100) wherein all doses are expressed as μg/kg/min] [11] and cumulated fluid infusion over the first 72 h and adverse events up to day-28 or death. All cause deaths and refractory MOF-related deaths were assessed at day-7 and day-28. Blood measurement of cytokines, markers of endothelial dysfunction and apoptosis were collected over the first 72 h.

Follow-up was stopped at either patient's death or day-28.

Biological assessment

We evaluated 6 biomarkers broadly chosen for they role in leukocyte adhesion (ICAM-1/CD54) as well as in pro- (TNF-α, IL-1a, IL-1b, IL-6) and anti-inflammatory pathways (IL-10). Patients' plasma levels were

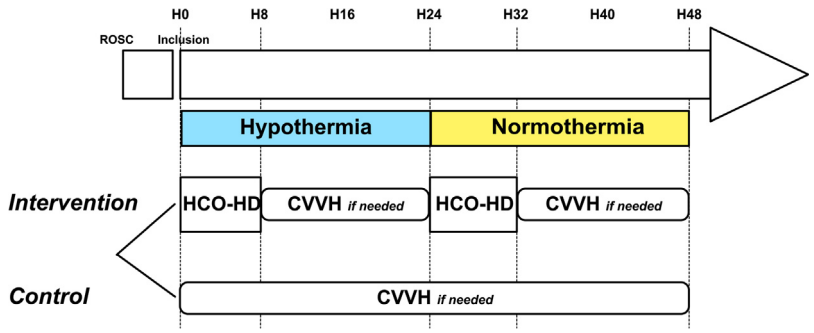

Fig. 1 – Study design.

measured at baseline and at 8, 24, 32, 48 and 72 h using human Magnetic Luminex screening assay (R&D Systems, Inc. Minneapolis, MN, USA). All analytes were measured in duplicates according to the manufacturer's protocol using a Bio-Plex 200 Luminex instrument and Bio-Plex software (Bio-Rad, Hercules, CA), as described previously.[12] A single assay lot was used and all specimens for any given individual were run on the same plate. Analyte- and plate-specific lower limits of detection (LLOD) were calculated as concentrations 2.5 standard deviations above the background for each analyte on each plate. Results [median, Q1–Q3] are expressed in pg/mL.

Intervention

In the intervention group, a double-lumen dialysis catheter was inserted in a large vein. After verification of catheter position, a first 8-hours session of HCO-CVVHD was performed as soon as possible and a second session was repeated 24 h after inclusion. For each session, a Septex© hemofilter (Gambro-Baxter, Meyzieu, France) was used in combination with a Prismaflex machine (Prismaflex©, Gambro Industries, Meyzieu, France). This set can take care of items that are 5–50 kilodaltons in size. The initial settings were blood flow 150 mL/min, dialysate flow 2500 mL/h and ultrafiltration flow 0 mL/h. Between the 2 HCO-CVVHD sessions, standard CVVHF could be performed if necessary, based on standard indication for RRT and with a targeted dialysis dose of 35 mL/kg/h. Heparin was used as anticoagulant.

In the 2 groups, CVVHF could be used if RRT was deemed necessary by physicians in charge, based on standard indication for acute renal failure. CVVHF was chosen because it requires the same machine and because its use in unstable patients has already been demonstrated feasable. If used for RRT, the same modalities of CVVH were employed in the 2 groups regarding hemofilters, device (Prismaflex©, Gambro Industries, Meyzieu, France) and targeted dialysis dose (35 mL/kg/h). In case of uncontrolled metabolic acidosis (defined with a pH lower than 7.20), physicians in charge were also allowed to switch the patient toward intermittent dialysis.

Hemodynamic management

The same strategy was used for hemodynamic management in the 2 groups. An invasive monitoring of arterial pressure was performed in all patients through a radial or femoral catheter. Fluid responsiveness was evaluated by passive leg raising according to current recommandations.[13] The decision to use epinephrine and norepinephrine as vasopressor agents was left to the discretion of the physician in charge of the patient. Transthoracic echocardiography was encouraged to assess myocardial function. In case of myocardial dysfunction with persistent low perfusion symptoms, dobutamine could be added. Catecholamines were continuously infused using a central venous line and the dose was changed using a 0.25 mg/h step-to-step in order to maintain the mean arterial pressure above between 65 and 75 mmHg.

The management of the early phase of post cardiac arrest shock is detailed in the Supplementary Appendix.

Concomitant treatments

Physicians were asked to follow the most recent guidelines regarding initial resuscitation and ICU management at the time the study was performed.[14] When used, therapeutic hypothermia was started immediately at ICU admission (or continued if initiated pre-hospital) during the first 24 h in order to obtain a target temperature between 32 °C and 34 °C. Normothermia between 37 °C and 37.5 °C was then achieved using passive rewarming (0.3 °C/h) and maintained during the next 48 h. In patients with a high suspicion of acute coronary syndrome as the cause of CA, early coronary angiograms were routinely performed at hospital admission and were followed, when indicated, by immediate percutaneous coronary interventions.

Ethical issues, patients' consent and trial registration

The study received ethics committee approval by CPP Ile de France III, Paris-Tarnier Cochin, Paris (France) (approval number 2574). The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and adhered to French regulatory requirements. When possible, written informed consent was obtained from patient surrogates before study enrollment. According to French law, in the case of impaired decision-making capacity without any surrogate at the time of inclusion, the patient's written informed consent could be obtained after enrollment.

The HYPERDIA trial has been prospectively registered at ClinicalTrials.gov (NCT00780299).

Statistical analysis

Analyses were conducted according to the intention to treat principle. Discrete and continuous variables were summarized by frequencies and percentages (calculated among available data) and by their median and interquartile range, respectively. Baseline characteristics were compared according to treatment groups using exact Fisher's test and Wilcoxon-Mann-Whitney test for categorical and continuous variables, respectively. Univariate Kaplan-Meier curves were plotted

to compare catecholamines infusion duration according to study arm. All tests of significance were two-sided with a maximal type I error risk of 5%.

HYPERDIA was a pilot study and very few data was available in order to calculate the sample size since no clinical study had been previously performed in this way. Based on experts' opinion, it was estimated that 40 patients (2×20) would be necessary to show a significant difference for the main endpoint. Considering a median duration of catecholamines infusion of 2 days (interquartile range 1–4) as reported in a previous clinical study, this sample size would be able to demonstrate a 55% difference between the 2 groups with an alpha risk of 0.05 and 80% power.

Results of the HYPERDIA trial are presented according to the CONSORT statement.[15]

Results

Patients' enrolment started in June 2013 and terminated in November 2015, on demand of the sponsor and before completion of the pre-planned sample size, because exhaustion of the financial academic support. Among the 317 CA patients admitted during the study period, 157 patients were screened for eligibility and 35 were finally randomized, with 17 patients allocated to the intervention and 18 patients allocated to the control group (Fig. 2). Baseline characteristics were similar in both study groups (Table 1). Patients were mostly males without significant past medical history. An early coronary angiography was performed in 27/35 (77.1%) cases and allowed a percutaneous coronary intervention in 4 (23.5%) and 5 (27.8%) patients of the intervention and the control arms, respectively. Chest and brain CT-scans were performed in 17 and 18 patients, respectively. Pulmonary embolism was evidenced in 2 patients in the control group.

Feasibility and safety

Regarding feasibility of the intervention, 16 over 17 patients effectively received the first session of HCO-CVVHD (one patient died before receiving the treatment). HCO-CVVHD was stopped before completion of the first session in 1 case because of refractory metabolic acidosis. Twelve patients received the second session of HCO-CVVHD at H24 (4 patients died within the first 24 h) and this second session was prematurely stopped in 2 cases (1 technical problem and 1 refractory metabolic acidosis). No ultrafiltration was performed in either groups.

In the control group, 12 and 4 patients received RRT using CVVH at day-1 and day-2, respectively (Supplementary e-Fig. 2).

Regarding adverse events, we observed 6 circuit coagulations and no other serious adverse event.

Clinical outcome

The median delay to complete weaning of vasopressors did not differ between the 2 groups, as illustrated by the course of infusion shown in Fig. 3 (log-rank p value = 0.673). This median time to catecholamine weaning was 37.3 [iqr 23.8, 69.5] and 71.1 [iqr 38.6, 86.4] hours in ICU survivors of the intervention and control groups, respectively. This delay was 31.6 [iqr 16.2, 50.4] and 11.2 [iqr 8.7, 15.9] hours in patients of the intervention and control group who died in the ICU. The median number of catecholamine-free days at D28 was 25.1 [iqr 0, 26.5] and

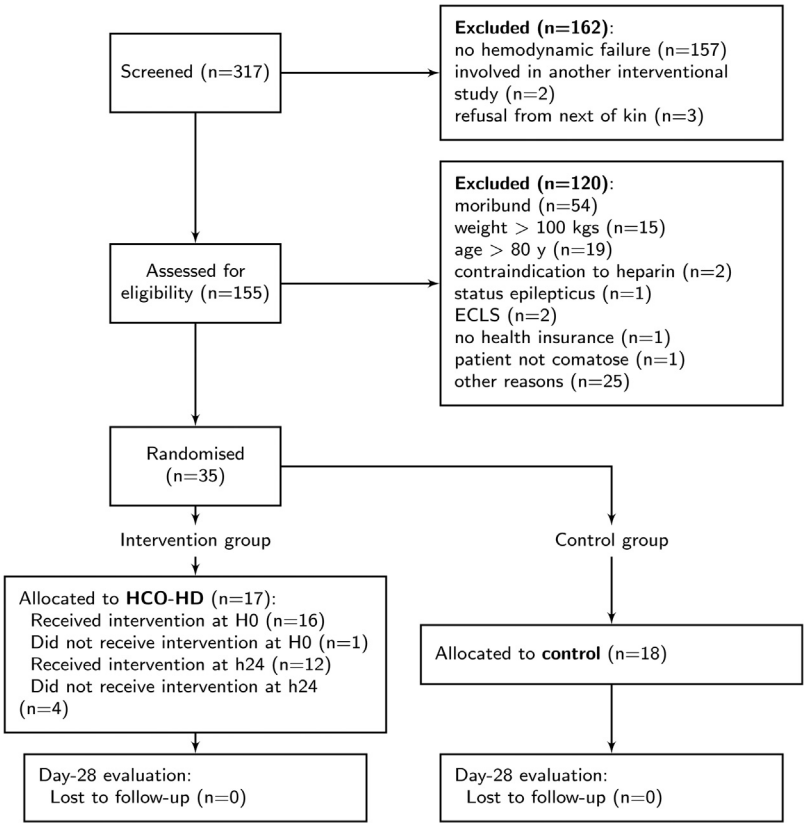

Fig. 2 – CONSORT flowchart of the study.

Table 1 – Baseline characteristics according to the study groups.

Variable	HCO-CVVHD n = 17	Controls n = 18
Demographics		
Age, y	68.4 [59.1,72.7]	66.3 [64.9,72.1]
Male gender	10 (58.8)	15 (83.3)
Weight, kg	75 [70, 86]	82 [72, 90]
Height, cm	173 [165, 180]	175 [170, 180]
Past medical history		
Myocardial infarction	0 (0)	1 (5.6)
Acute coronary syndrome	0 (0)	1 (6.7)
Pulmonary embolism	0 (0)	1 (6.7)
Atrial fibrillation	2 (13.3)	5 (33.3)
Conduction disorder	0 (0)	2 (13.3)
Cardiovascular risk factors		
Current smoking	5 (29.4)	9 (50)
Dyslipidemia	6 (40)	3 (30)
Arterial hypertension	8 (47.1)	8 (44.4)
Diabetes	3 (17.7)	3 (16.7)
CA characteristics		
Witnessed CA	16 (94.1)	18 (100)
Bystander CPR	12 (70.6)	12 (66.7)
Initial rhythm		
Shockable	4 (23.5)	8 (44.4)
Unshockable	11 (64.7)	9 (50)
Unknown	2 (11.8)	1 (5.6)
Time from collapse to CPR	3 [0,5]	4.5 [0,10]
Time from collapse to ROSC	25 [19,28]	34 [22,40]
In-hospital diagnostic procedures		
Coronary angiography	13 (76.5)	14 (77.8)
Chest CT scan	9 (52.9)	8 (44.4)
Brain CT scan	8 (47.1)	10 (56.6)
ICU admission characteristics		
Body temperature, median [IQR]	35 [34,36]	35 [34,35]
Time from collapse to ICU admission	164 [122,203]	153 [96,218]
SAPS II	2 [1,2]	2 [1,3]
LOD	8 [7,11]	9 [7,11]
Lactate	2.7 [1.4, 4.2]	1.9 [1.1, 3.6]
SOFA score	12.5 [11,15]	11 [11,12]

No significant difference was observed between the 2 groups.
CA: cardiac arrest; CPR: cardiopulmonary resuscitation; ROSC: restoration of spontaneous circulation; CT: computed tomography; ICU: intensive care unit; IQR: interquartile; SAPS: simplified acute physiology score; LOD: logistic organ dysfunction; SOFA: sequential organ failure assessment.

24.5 [iqr 0, 26.2] days in the intervention and control groups, respectively (p = 0.634). Similar results were obtained after exclusion of the patient in the intervention group who did not receive the treatment.

Regarding hemodynamic patterns, the inotropic score did not differ over time between the 2 groups, as well as mean arterial pressure and cumulated fluids (Fig. 4 and Supplementary eTable 1).

Overall day-7 mortality was 68.7%: 11/17 (64.7%) and 13/18 (72.2%) in the intervention and control groups, respectively (p = 0.725).

Biological markers

No difference was observed at any time points between the 2 groups for all pro- and anti-inflammatory cytokines over the first 72 h (Fig. 5).

Discussion

Even if based on a solid rationale, the present study failed to show a clinical benefit in using HCO-CVVHD in patients with post-cardiac arrest shock, as compared with standard management. We did not observe a significant change in hemodynamic profile and even if underpowered, the trial did not indicate any other potential positive signals regarding clinical outcome. In septic shock, HCO-CVVHD has been proved efficient to remove pro-inflammatory cytokines as IL-6, TNF-alpha and IL-1ra,[9,10] even by using intermittent session of HCO-CVVHD as done in the present study.[16] This removal of pro-inflammatory cytokines has been associated with hemodynamic improvement.[17,18] Despite similarities between septic shock and post-resuscitation shock, we did not evidence any difference regarding hemodynamic improvement in successfully resuscitated cardiac arrest patients treated or not with HCO-CVVHD. This finding may raise several hypothesis.

The first reason could come from serum levels of cytokines, especially pro-inflammatory cytokines, that were dramatically lower in our population as compared with levels reported in septic shock patients.[17,19,20] This may be explained by the very transient rise in cytokines that characterised the post-resuscitation syndrome. Provoked by the whole-body ischemia-reperfusion, this phenomenun is known to provoke a brief cytokinic storm. But we can hypothesize that such a cytokinic storm may have prolonged

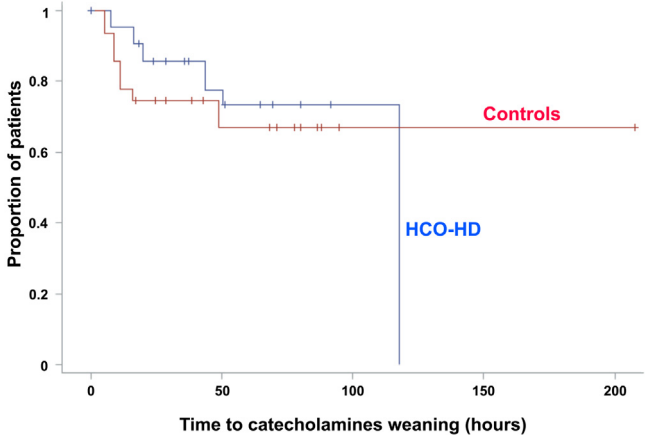

Fig. 3 – Univariate Kaplan Meier curve of time to catecholamines weaning in the two study groups.

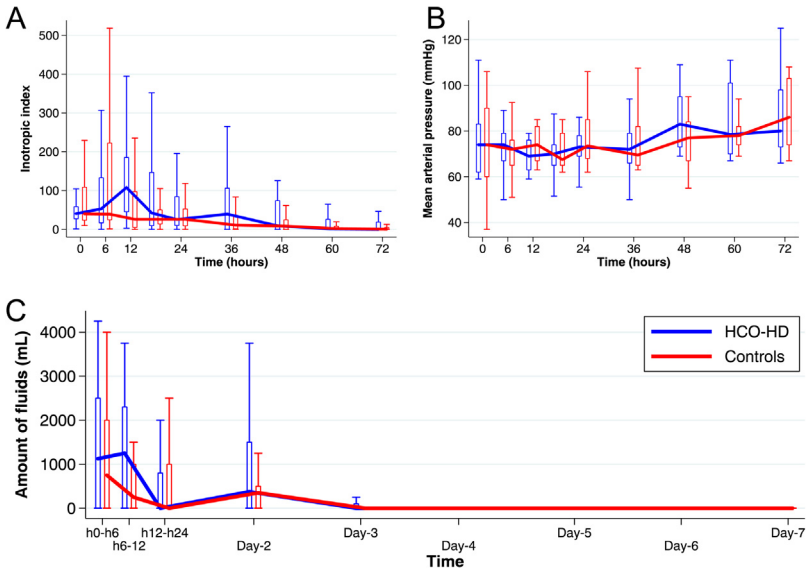

Fig. 4 – Hemodynamic profile over time in both study groups. Inotropic index (plot A), mean arterial pressure (plot B) and total amount of fluids (plot C) according to the study group are shown. No statistical difference was observed between the two groups over time in the three outcomes.

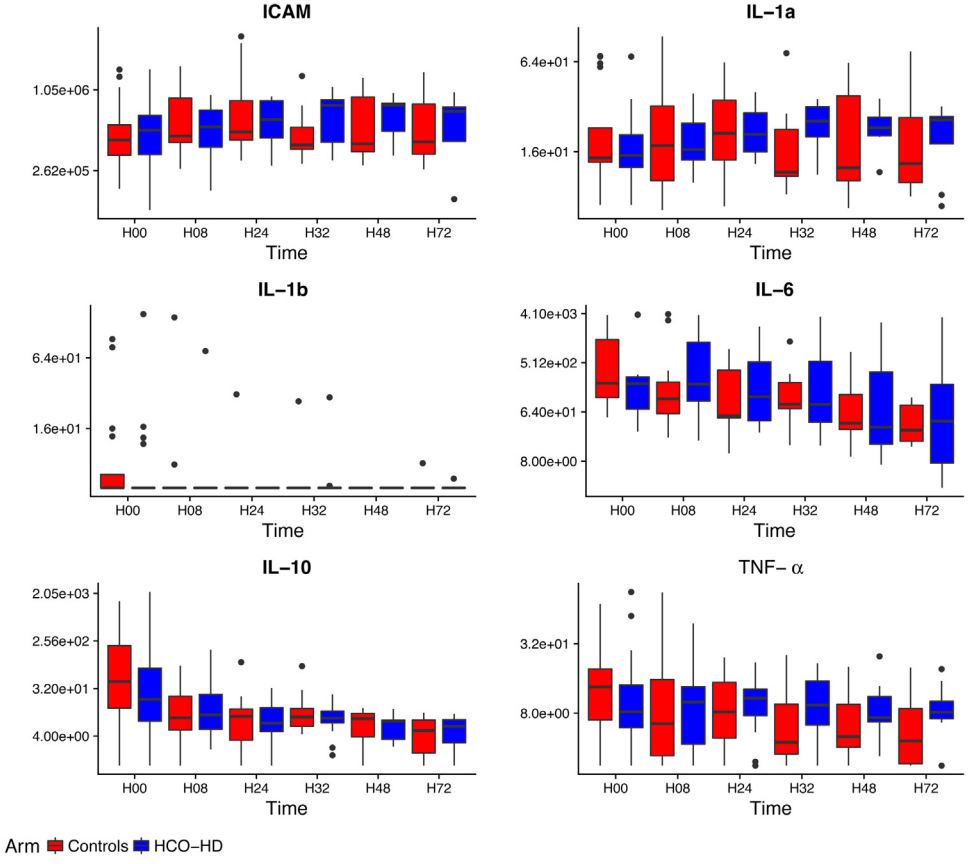

Fig. 5 – Cytokinic profile over time in both study groups. No difference at each time point was observed for all the cytokines.

effects despite a quick decrease of blood levels of pro-inflammatory cytokines. Considering the very short half-life of these molecules, it is possible that the HCO-CVVHD intervention was done too late to provide a clinical effect. For instance, it has been shown that the IL-6 half-life in septic patients was about 2–4 h and that its blood level was divided by 1000 in 3 h.[21] This may explain the relatively low level of pro-inflammatory cytokines that we observed and the lack of effect of the intervention. These quite

low levels may thus not be impacted by an epuration technique as the concentration gradient would be too low and a potential decrease impossible to detect. Alternatively, this lack of efficiency could be due to membrane fouling, which is common in this setting. It has been demonstrated that the sieving profile of the HCO membranes shifts towards lower molecular weights during operation due to this inevitable phenomenon. This membrane fouling is related to the adhesion of proteins to the membrane surface, which acts as a barrier that further affects the transmembrane clearance because of pore occlusion.[22,23] Assuming that this phenomenon may occur even if blood cytokine levels are low, this may also explain that we did not observe any difference in cytokine clearance between the 2 groups. Moreover, regards to the low levels of circulating cytokines, we cannot exclude that a standard CVVHF membrane was as efficient as the HCO-CVVHD membrane, leading to the lack of difference we observed.

Second, one may argue that modalities for HCO-CVVHD were not optimal enough, but this hypothesis is difficult to defend. We performed two sessions of HCO-CVVHD, at randomization and 24 h after inclusion. Blood flow and reinjection doses were optimized and were similar to those previously used in septic shock patients. In previous studies testing HCO-CVVHD, dialysate flows were similar to what was used in the present study (i.e. 2500 mL/h), and the only important difference was that we only used short sessions of 8 h.[9,10] This may at least partly explain our findings and we don't know if a difference would have been evidenced using continous HCO-CVVHD instead of separate, discontinuous sessions.

Last, the pathophysiology of the post-cardiac arrest shock patients is multifactorial and is not only related to the release of cytokines. In a previous clinical trial, Laurent et al reported an effect of HVHF in post-cardiac arrest shock patients, while there was no difference in cytokines levels in controls.[8] Similar findings were recently observed in a rat model of cardiac arrest[24] where no improvement in mortality, neurological dysfunction and pro-inflammatory cytokines levels was observed in any of the hemofiltration groups (i.e. control group, standard volume CVVH and high volume hemofiltration). Taken together, these findings may plead against cytokine removal, whatever the technique employed, in the setting of post cardiac arrest shock.

The study suffers from several limitations. First, this is a monocentric study. However, the HYPERDIA study was a pilot randomized study and the monocentric design guaranteed management homogeneity. Second, the number of patients included in the study was small, which could lead to a lack of power despite a power calculation performed before the beginning of the trial. In line with the pilot study design, we cannot exclude that results would have been different in a multicentre study with a larger sample size. Nevertheless, there was no trend nor any signal suggesting a potential clinical benefit. Third, cardiac arrest patients included in the study might have been treated for one or several comorbidities we did not took into account; we thus could have missed a potential cofounder in this setting. However, the lack of imbalance thanks to the randomization does not support such a hypothesis. Fourth, we cannot rule out that the lack of difference would be partly related to the hemodynamic instability induced by the HCO-CVVHD treatment. However, we observed no significant difference between the two groups regards to the inotropic index, the mean arterial pressure and the total amount of fluids over time. Last, due to the nature of the intervention, it was obviously not possible to blind the investigators. However, we use a strict and similar algorithm regarding weaning of vasopressors in the 2 groups

Conclusion

In cardiac arrest patients, HCO-CVVHD did not decrease the lenght of post-resuscitation shock and had no significant effect on hemodynamic profile.

Funding and support

The study was completely funded by the French Ministry of Health. Baxter Edwards provided the Septex™ membranes that were used in the HCO-CVVHD group. The Assistance Publique Hôpitaux de Paris was the sponsor of the HYPERDIA trial.

Competing interests

GG, DG, TS, LL, NM, JDC, FP, AB, FD, TMB, MA, BC, LZ, SB, YLN, JC, JPM, JD and CV have no conflict of interest.

AC received fees from Bard for lectures.

Authors' contribution

AC, TS and CV designed the trial. GG, DG, LL NM, JDC, FP, AB, FD, TMB, MA, BC, LZ, SB, YLB, JC, JPM collected the data. AC, GG and JC designed the statistical analysis. AC and GG drafted the manuscript. CV and TS reviewed the manuscript.

AC, GG and JC had full access to the final trial dataset

Previous presentations

Oral presentation at Reanimation 2018 (SRLF– January 2018, Paris, France).

Oral presentation at LIVES 2018 (ESICM– October 2018, Paris, France).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.03.045.

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