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

Guillaume Geri, David Grimaldi, Thierry Seguin, Lionel Lamhaut, Nathalie Marin, Jean-Daniel Chiche, Frédéric Pène, Adrien Bouglé, Fabrice Daviaud, Tristan Morichau-Beauchant, et al.

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

3 Running title : High-permeability hemodialysis in post-resuscitation shock (HYPERDIA)

4  
5 Guillaume Geri (1,2,3), David Grimaldi (1), Thierry Seguin (4), Lionel Lamhaut (2,3,5),  
6 Nathalie Marin (1), Jean-Daniel Chiche (1,2), Frédéric Pène (1,2), Adrien Bougle (1), Fabrice  
7 Daviaud (1), Tristan Morichau-Beauchant (1), Michel Arnaout (1), Benoit Champigneulle (1),  
8 Lara Zafrani (1), Simon Bourcier (1), Yen-Lan Nguyen (1), Julien Charpentier (1), Jean-Paul  
9 Mira (1,2), Joël Coste (2,6), Christophe Vinsonneau (7), Alain Cariou (1,2,3)

10  
11 [1]Medical Intensive Care Unit, Cochin University Hospital, APHP, Paris, France  
12 [2]Paris Descartes University, Sorbonne Paris Cité–Medical School, Paris, France  
13 [3]Sudden Death Expertise Centre, INSERM U970 (team 4), Paris Cardiovascular Research  
14 Centre, Paris, France  
15 [4]Medical-surgical Intensive Care Unit, Toulouse-Rangueil Hospital, Toulouse, France  
16 [5]SAMU 75, Necker University Hospital, APHP, Paris, France  
17 [6]Biostatistics and Epidemiology Unit, Hôtel Dieu, APHP, Paris, France  
18 [7] Intensive Care Medicine, Germon et Gauthier Hospital, Béthune, France

19  
20 **Corresponding author:**

21 Dr. Alain Cariou - Medical Intensive Care Unit – Cochin Hospital - APHP  
22 27 rue du Faubourg Saint-Jacques - F-75679 Paris Cedex 1, France  
23 Telephone: 33 1 58 41 25 01 - E-mail: [alain.cariou@aphp.fr](mailto:alain.cariou@aphp.fr)

24

25 **Abstract** (288 words)

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

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

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

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

50

51 Registration: NCT00780299

52

53 Key words: cardiac arrest; post-resuscitation shock; continuous veno-venous hemodialysis;  
54 ischemia-reperfusion; cardio-pulmonary resuscitation

55

56 Funding: The study was funded by the French Ministry of Health. Baxter Edwards provided  
57 the Septex™ membranes that were used in the HCO-CVVHD group but had no access to data  
58 management, analysis and manuscript writing.

59 Disclosures: none

60

61 Previous presentations:

62 Oral presentation at Reanimation 2018 (SRLF - January 2018, Paris, France)

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

64

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## 68 **Introduction**

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

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

93 10]. Importantly, these haemofilters allowing HCO-CVVHD do not require special  
94 equipment as they can be used with devices that are commonly used in intensive care  
95 units (ICU) for continuous RRT.

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

99

## 100 **Methods and design**

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

### 107 *Study setting and participants*

108 The study was performed in the medical ICU of Cochin University hospital, which  
109 serves as a cardiac arrest centre in the southern Paris area (France). During the study  
110 period, all consecutive patients who were admitted after a witnessed CA were  
111 screened for participation. They were eligible if the following inclusion criteria were  
112 present: adults (> 18 yo), still comatose (defined by a Glasgow Coma Scale less than  
113 or equal 7); CA presumed to result from a cardiac cause; and if patients had a post-  
114 resuscitation shock, i.e., a need for continuous vasopressor infusion (epinephrine or  
115 norepinephrine) with a dose higher than 1 milligram per hour. Patients meeting any of  
116 the following non-inclusion criteria were not included in the trial: CA cause associated  
117 with an increase of hemorrhage risk (traumatic brain injury, subarachnoidal

118 hemorrhage, ischemic stroke, diffuse hemorrhage), Glasgow Coma Scale higher than  
119 7, moribund patient with a life expectancy lower than 24 hours, life expectancy lower  
120 than 28 days related to a underlying chronic disease, logistic inability to start the  
121 treatment within the first 6 hours after ROSC, anticoagulants contraindication,  
122 heparin-induced thrombocytopenia, severe thrombocytopenia lower than 20G/L,  
123 neutropenia related to a hematologic malignancy, Acquired ImmunoDeficiency  
124 Syndrome (AIDS) with CD4 T lymphocytes lower than 0.050G/L,  
125 immunosuppressive treatments (except corticosteroids), pregnancy, weight higher than  
126 100 kilograms, absence of national statutory health insurance coverage, inclusion in  
127 another interventional trial or any administrative supervision

#### 128 *Randomization*

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

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

#### 137 *Outcomes*

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

142 Secondary outcomes included arterial pressure, the dose of  
143 vasoactive/vasopressor agents expressed by the inotropic score [(dopamine dose x 1) +  
144 (dobutamine dose x 1) + (adrenaline dose x 100) + (noradrenaline dose x 100) +  
145 (phenylephrine dose x 100) wherein all doses are expressed as  $\mu\text{g}/\text{kg}/\text{min}$ ] [11] and  
146 cumulated fluid infusion over the first 72 hours and adverse events up to day-28 or  
147 death. All cause deaths and refractory MOF-related deaths were assessed at day-7 and  
148 day-28. Blood measurement of cytokines, markers of endothelial dysfunction and  
149 apoptosis were collected over the first 72 hours.

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

### 151 *Biological assessment*

152 We evaluated 6 biomarkers broadly chosen for their role in leukocyte adhesion  
153 (ICAM-1/CD54) as well as in pro- (TNF- $\alpha$ , IL-1a, IL-1b, IL-6) and anti-inflammatory  
154 pathways (IL-10). Patients' plasma levels were measured at baseline and at 8, 24, 32,  
155 48 and 72 hours using human Magnetic Luminex screening assay (R&D Systems, Inc.  
156 Minneapolis, MN, USA). All analytes were measured in duplicates according to the  
157 manufacturer's protocol using a Bio-Plex 200 Luminex instrument and Bio-Plex  
158 software (Bio-Rad, Hercules, CA), as described previously [12]. A single assay lot  
159 was used and all specimens for any given individual were run on the same plate.  
160 Analyte- and plate-specific lower limits of detection (LLOD) were calculated as  
161 concentrations 2.5 standard deviations above the background for each analyte on each  
162 plate. Results [median, Q1-Q3] are expressed in pg/mL.

### 163 *Intervention*

164 In the intervention group, a double-lumen dialysis catheter was inserted in a  
165 large vein. After verification of catheter position, a first 8-hours session of HCO-



166 CVVHD was performed as soon as possible and a second session was repeated 24  
167 hours after inclusion. For each session, a Septex<sup>®</sup> hemofilter (Gambro-Baxter,  
168 Meyzieu, France) was used in combination with a Prismaflex machine (Prismaflex<sup>®</sup>,  
169 Gambro Industries, Meyzieu, France). This set can take care of items that are 5 to 50  
170 kilodaltons in size. The initial settings were blood flow 150 mL/min, dialysate flow  
171 2500 mL/h and ultrafiltration flow 0 mL/h. Between the 2 HCO-CVVHD sessions,  
172 standard CVVHF could be performed if necessary, based on standard indication for  
173 RRT and with a targeted dialysis dose of 35mL/kg/h. Heparin was used as  
174 anticoagulant.

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

### 183 *Hemodynamic management*

184 The same strategy was used for hemodynamic management in the 2 groups.  
185 An invasive monitoring of arterial pressure was performed in all patients through a  
186 radial or femoral catheter. Fluid responsiveness was evaluated by passive leg raising  
187 according to current recommendations [13]. The decision to use epinephrine and  
188 norepinephrine as vasopressor agents was left to the discretion of the physician in  
189 charge of the patient. Transthoracic echocardiography was encouraged to assess  
190 myocardial function. In case of myocardial dysfunction with persistent low perfusion

191 symptoms, dobutamine could be added. Catecholamines were continuously infused  
192 using a central venous line and the dose was changed using a 0.25 mg/h step-to-step in  
193 order to maintain the mean arterial pressure above between 65 and 75mmHg.

194 The management of the early phase of post cardiac arrest shock is detailed in  
195 the supplementary appendix.

#### 196 *Concomitant treatments.*

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

#### 206 *Ethical issues, patients' consent and trial registration*

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

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

### 216 *Statistical analysis*

217 Analyses were conducted according to the intention to treat principle. Discrete  
218 and continuous variables were summarized by frequencies and percentages (calculated  
219 among available data) and by their median and interquartile range, respectively.  
220 Baseline characteristics were compared according to treatment groups using exact  
221 Fisher's test and Wilcoxon-Mann-Whitney test for categorical and continuous  
222 variables, respectively. Univariate Kaplan-Meier curves were plotted to compare  
223 catecholamines infusion duration according to study arm. All tests of significance  
224 were two-sided with a maximal type I error risk of 5%.

225 HYPERDIA was a pilot study and very few data was available in order to  
226 calculate the sample size since no clinical study had been previously performed in this  
227 way. Based on experts' opinion, it was estimated that 40 patients (2 x 20) would be  
228 necessary to show a significant difference for the main endpoint. Considering a  
229 median duration of catecholamines infusion of 2 days (interquartile range 1-4) as  
230 reported in a previous clinical study, this sample size would be able to demonstrate a  
231 55% difference between the 2 groups with an alpha risk of 0.05 and 80% power.

232 Results of the HYPERDIA trial are presented according to the CONSORT statement  
233 [15].

### 234 **Results**

235 Patients' enrolment started in June 2013 and terminated in Novembre 2015, on  
236 demand of the sponsor and before completion of the pre-planned sample size, because  
237 exhaustion of the financial academic support. Among the 317 CA patients admitted

238 during the study period, 157 patients were screened for eligibility and 35 were finally  
239 randomized, with 17 patients allocated to the intervention and 18 patients allocated to  
240 the control group (**Figure 2**). Baseline characteristics were similar in both study  
241 groups (**Table 1**). Patients were mostly males without significant past medical history.  
242 An early coronary angiography was performed in 27/35 (77.1%) cases and allowed a  
243 percutaneous coronary intervention in 4 (23.5%) and 5 (27.8%) patients of the  
244 intervention and the control arms, respectively. Chest and brain CT-scans were  
245 performed in 17 and 18 patients, respectively. Pulmonary embolism was evidenced in  
246 2 patients in the control group.

#### 247 *Feasibility and safety*

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

255       In the control group, 12 and 4 patients received RRT using CVVH at day-1  
256 and day-2, respectively (**e-Figure 2**).

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

#### 259 *Clinical outcome*

260       The median delay to complete weaning of vasopressors did not differ between  
261 the 2 groups, as illustrated by the course of infusion shown in **Figure 3** (log-rank p

262 value=0.673). This median time to catecholamine weaning was 37.3 [iqr 23.8, 69.5]  
263 and 71.1 [iqr 38.6, 86.4] hours in ICU survivors of the intervention and control  
264 groups, respectively. This delay was 31.6 [iqr 16.2, 50.4] and 11.2 [iqr 8.7, 15.9]  
265 hours in patients of the intervention and control group who died in the ICU. The  
266 median number of catecholamine-free days at D28 was 25.1 [iqr 0, 26.5] and 24.5 [iqr  
267 0, 26.2] days in the intervention and control groups, respectively (p=0.634). Similar  
268 results were obtained after exclusion of the patient in the intervention group who did  
269 not receive the treatment.

270         Regarding hemodynamic patterns, the inotropic score did not differ over time  
271 between the 2 groups, as well as mean arterial pressure and cumulated fluids (**Figure**  
272 **4** and **eTable 1**).

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

#### 275 *Biological markers*

276         No difference was observed at any time points between the 2 groups for all  
277 pro- and anti-inflammatory cytokines over the first 72 hours (**Figure 5**).

278

#### 279 **Discussion**

280         Even if based on a solid rationale, the present study failed to show a clinical  
281 benefit in using HCO-CVVHD in patients with post-cardiac arrest shock, as compared  
282 with standard management. We did not observe a significant change in hemodynamic  
283 profile and even if underpowered, the trial did not indicate any other potential positive  
284 signals regarding clinical outcome. In septic shock, HCO-CVVHD has been proved  
285 efficient to remove pro-inflammatory cytokines as IL-6, TNF-alpha and IL-1ra [9, 10],

286 even by using intermittent session of HCO-CVVHD as done in the present study [16].  
287 This removal of pro-inflammatory cytokines has been associated with hemodynamic  
288 improvement [17, 18]. Despite similarities between septic shock and post-resuscitation  
289 shock, we did not evidence any difference regarding hemodynamic improvement in  
290 successfully resuscitated cardiac arrest patients treated or not with HCO-CVVHD.  
291 This finding may raise several hypothesis.

292         The first reason could come from serum levels of cytokines, especially pro-  
293 inflammatory cytokines, that were dramatically lower in our population as compared  
294 with levels reported in septic shock patients [17, 19, 20]. This may be explained by the  
295 very transient rise in cytokines that characterised the post-resuscitation syndrome.  
296 Provoked by the whole-body ischemia-reperfusion, this phenomenon is known to  
297 provoke a brief cytokinic storm. But we can hypothesize that such a cytokinic storm  
298 may have prolonged effects despite a quick decrease of blood levels of pro-  
299 inflammatory cytokines. Considering the very short half-life of these molecules, it is  
300 possible that the HCO-CVVHD intervention was done too late to provide a clinical  
301 effect. For instance, it has been shown that the IL-6 half-life in septic patients was  
302 about 2 to 4 hours and that its blood level was divided by 1,000 in 3 hours [21]. This  
303 may explain the relatively low level of pro-inflammatory cytokines that we observed  
304 and the lack of effect of the intervention. These quite low levels may thus not be  
305 impacted by an epuration technique as the concentration gradient would be too low  
306 and a potential decrease impossible to detect. Alternatively, this lack of efficiency  
307 could be due to membrane fouling, which is common in this setting. It has been  
308 demonstrated that the sieving profile of the HCO membranes shifts towards lower  
309 molecular weights during operation due to this inevitable phenomenon. This  
310 membrane fouling is related to the adhesion of proteins to the membrane surface,

311 which acts as a barrier that further affects the transmembrane clearance because of  
312 pore occlusion [22, 23]. Assuming that this phenomenon may occur even if blood  
313 cytokine levels are low, this may also explain that we did not observe any difference  
314 in cytokine clearance between the 2 groups. Moreover, regards to the low levels of  
315 circulating cytokines, we cannot exclude that a standard CVVHF membrane was as  
316 efficient as the HCO-CVVHD membrane, leading to the lack of difference we  
317 observed.

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

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

335 against cytokine removal, whatever the technique employed, in the setting of post  
336 cardiac arrest shock.

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

355

## 356 **Conclusion**

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



359

360 **Funding and support**

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

364 **Competing interests**

365 GG, DG, TS, LL, NM, JDC, FP, AB, FD, TMB, MA, BC, LZ, SB, YLN, JC, JPM, JD  
366 and CV have no conflict of interest.  
367 AC received fees from Bard for lectures.

368 **Authors' contribution**

369 AC, TS and CV designed the trial. GG, DG, LL, NM, JDC, FP, AB, FD, TMB, MA,  
370 BC, LZ, SB, YLB, JC, JPM collected the data. AC, GG and JC designed the statistical  
371 analysis. AC and GG drafted the manuscript. CV and TS reviewed the manuscript.  
372 AC, GG and JC had full access to the final trial dataset.

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444 **List of figures**

445

446 **Figure 1 Study design**

447

448 **Figure 2. CONSORT flowchart of the study**

449

450 **Figure 3. Univariate Kaplan Meier curve of time to catecholamines weaning in**  
451 **the two study groups.**

452

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

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458 **Figure 5. Cytokinic profile over time in both study groups.** No difference at each  
459 time point was observed for all the cytokines.

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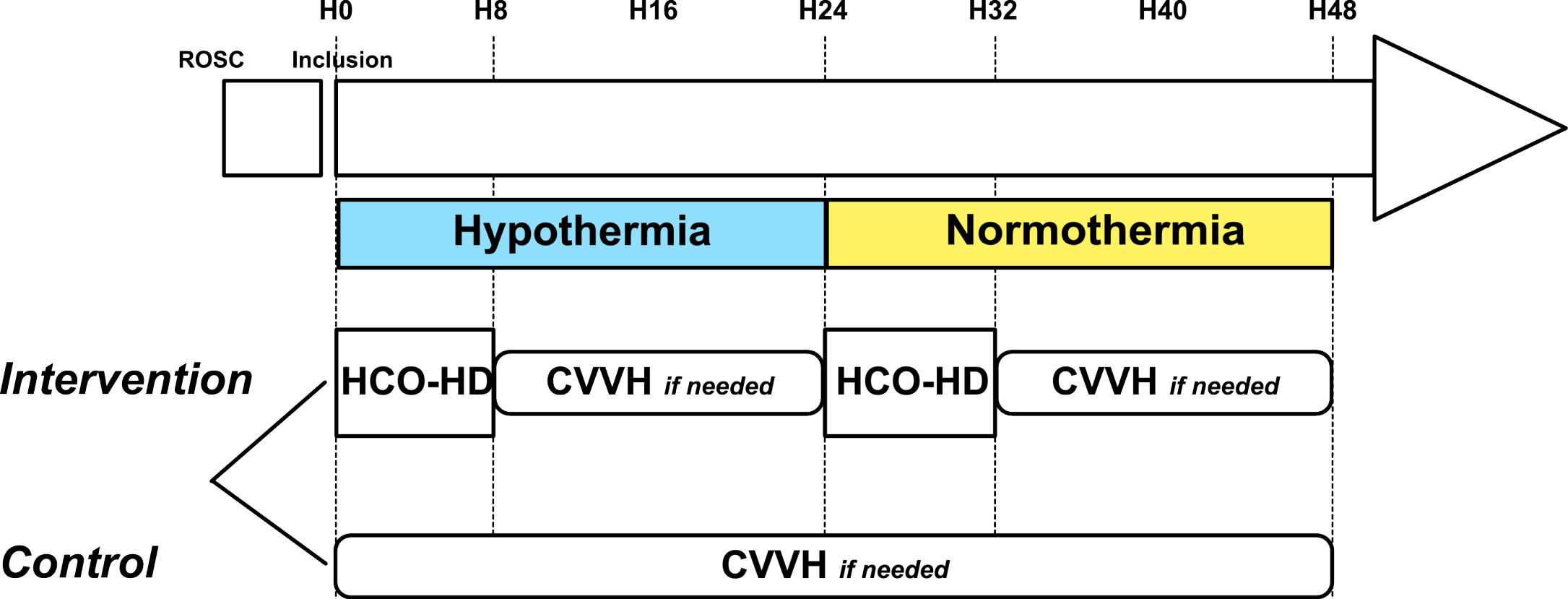
463 **Table 1. Baseline characteristics according to the study groups**

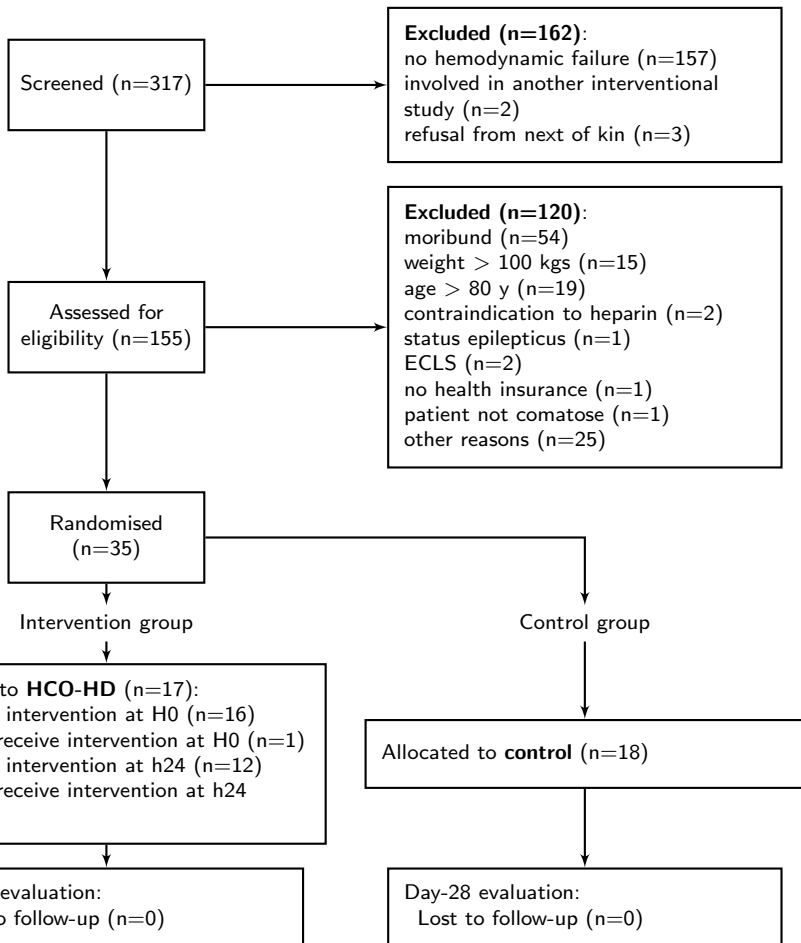
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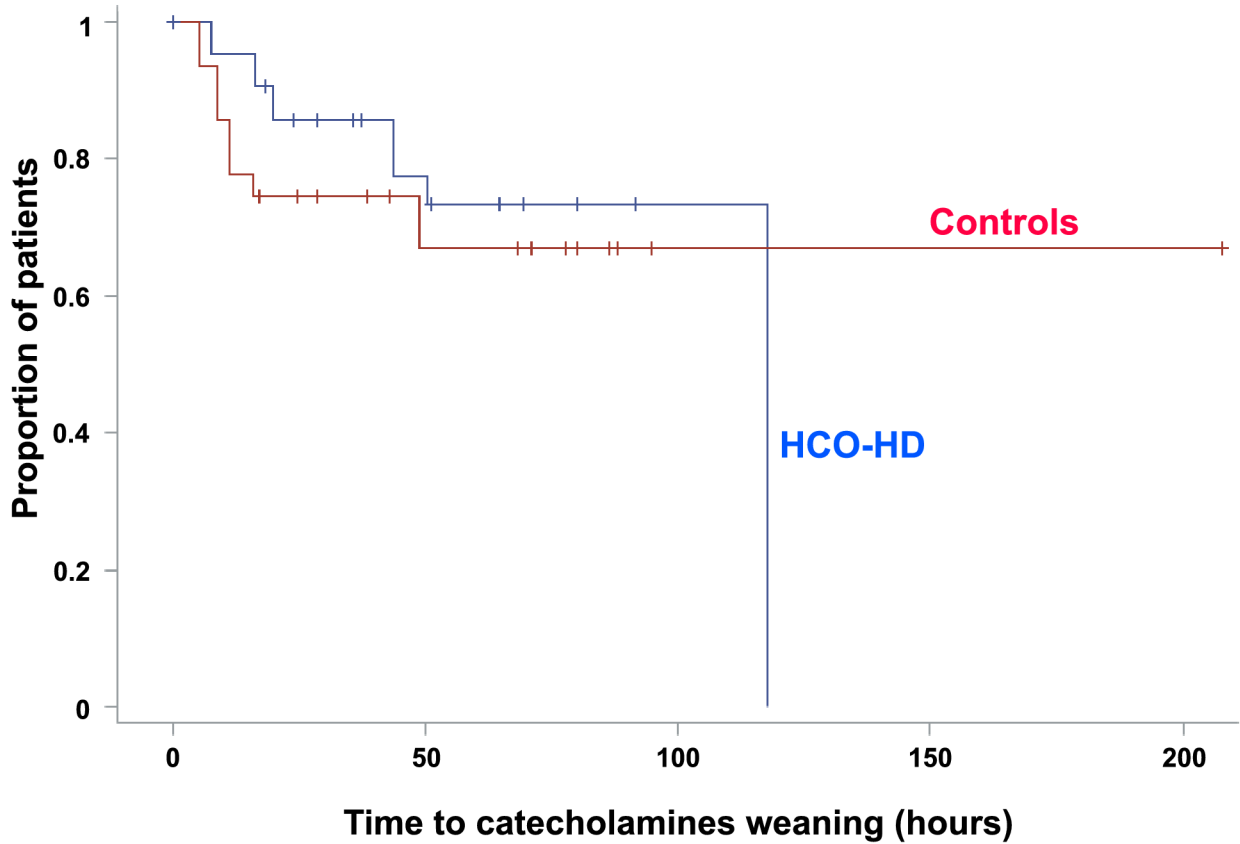
Variable	HCO-CVVHD n=17	Controls n=18
<b>Demographics</b>		
Age, y	68.4 [59.1,72.7]	66.3 [64.9,72.1]
Male gender	10 (58.8)	15 (83.3)
Weight, kg	75 [70, 86]	82 [72, 90]
Height, cm	173 [165, 180]	175 [170, 180]
<b>Past medical history</b>		
Myocardial infarction	0 (0)	1 (5.6)
Acute coronary syndrome	0 (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)
<b>Cardiovascular risk factors</b>		
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)

<b>CA characteristics</b>		
<b>Witnessed CA</b>	<b>16 (94.1)</b>	<b>18 (100)</b>
<b>Bystander CPR</b>	<b>12 (70.6)</b>	<b>12 (66.7)</b>
<b>Initial rhythm</b>		
<b>Shockable</b>	<b>4 (23.5)</b>	<b>8 (44.4)</b>
<b>Unshockable</b>	<b>11 (64.7)</b>	<b>9 (50)</b>
<b>Unknown</b>	<b>2 (11.8)</b>	<b>1 (5.6)</b>
<b>Time from collapse to CPR</b>	<b>3 [0,5]</b>	<b>4.5 [0,10]</b>
<b>Time from collapse to ROSC</b>	<b>25 [19,28]</b>	<b>34 [22,40]</b>
<b>In-hospital diagnostic procedures</b>		
<b>Coronary angiography</b>	<b>13 (76.5)</b>	<b>14 (77.8)</b>
<b>Chest CT scan</b>	<b>9 (52.9)</b>	<b>8 (44.4)</b>
<b>Brain CT scan</b>	<b>8 (47.1)</b>	<b>10 (56.6)</b>
<b>ICU admission characteristics</b>		
<b>Body temperature, median [IQR]</b>	<b>35 [34,36]</b>	<b>35 [34,35]</b>
<b>Time from collapse to ICU admission</b>	<b>164 [122,203]</b>	<b>153 [96,218]</b>
<b>SAPS II</b>	<b>2 [1,2]</b>	<b>2 [1,3]</b>
<b>LOD</b>	<b>8 [7,11]</b>	<b>9 [7,11]</b>
<b>Lactate</b>	<b>2.7 [1.4, 4.2]</b>	<b>1.9 [1.1, 3.6]</b>
<b>SOFA score</b>	<b>12.5 [11, 15]</b>	<b>11 [11, 12]</b>

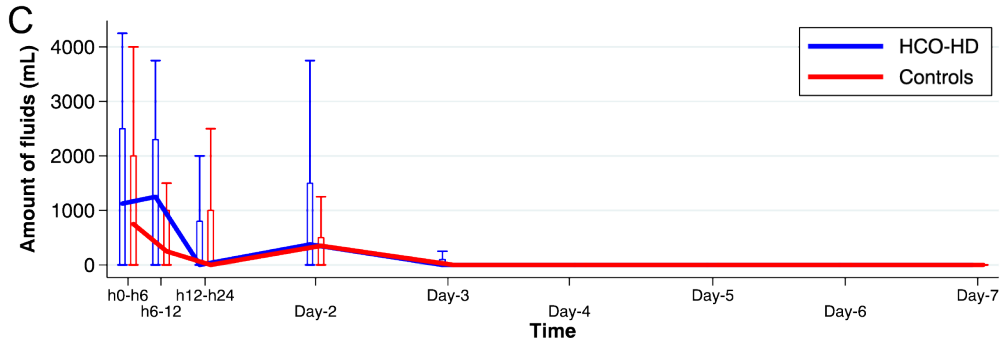
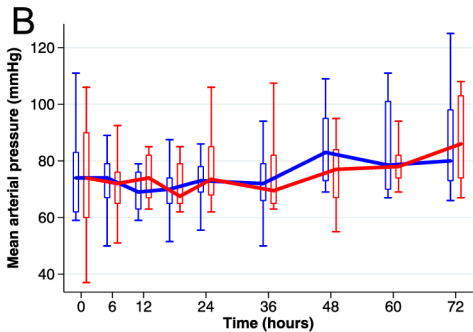
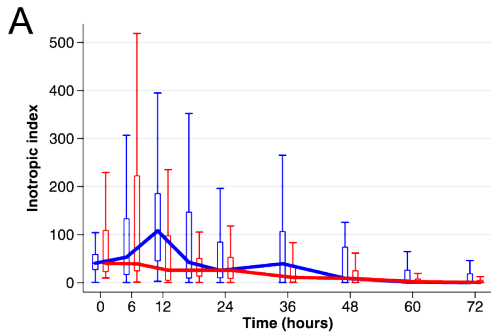
465 No significant difference was observed between the 2 groups.  
466 CA: cardiac arrest; CPR: cardiopulmonary resuscitation; ROSC: restoration of  
467 spontaneous circulation; CT: computed tomography; ICU: intensive care unit; IQR:  
468 interquartile; SAPS: simplified acute physiology score; LOD: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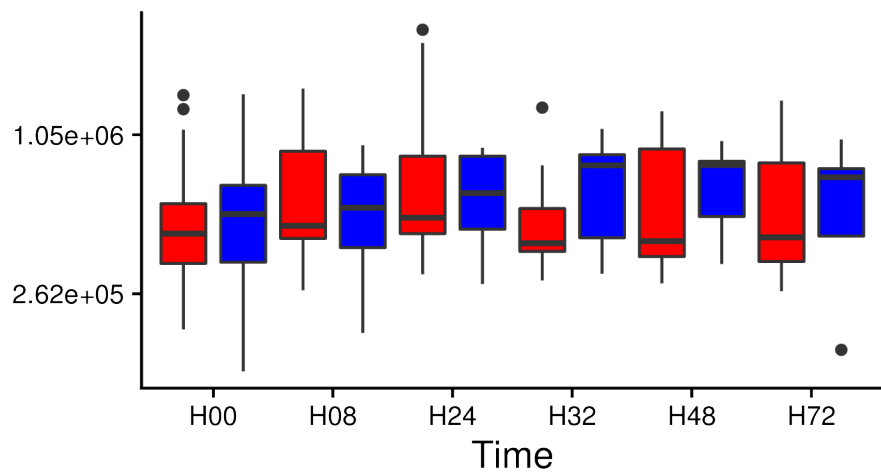
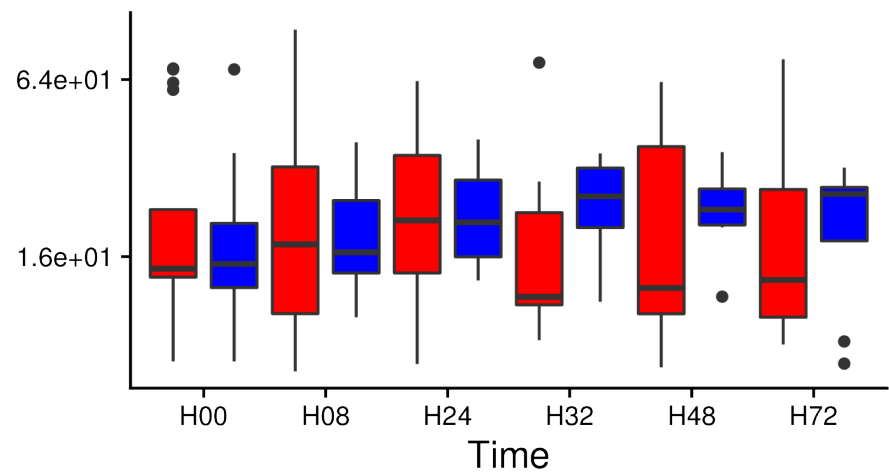
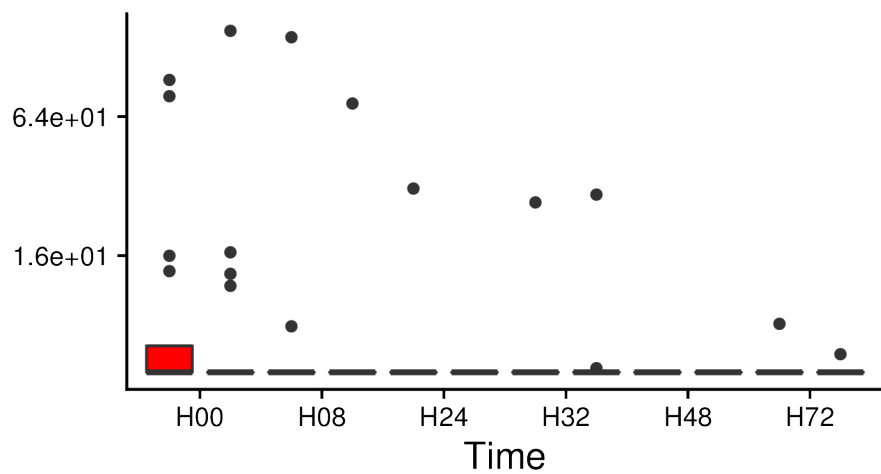
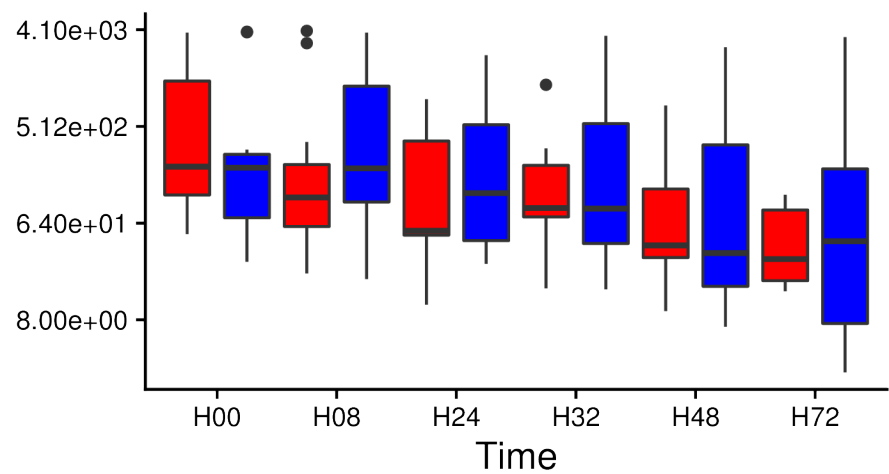
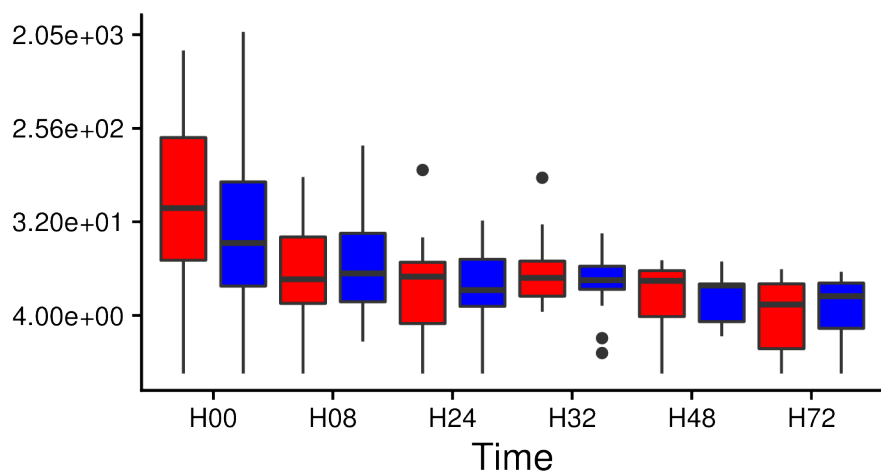
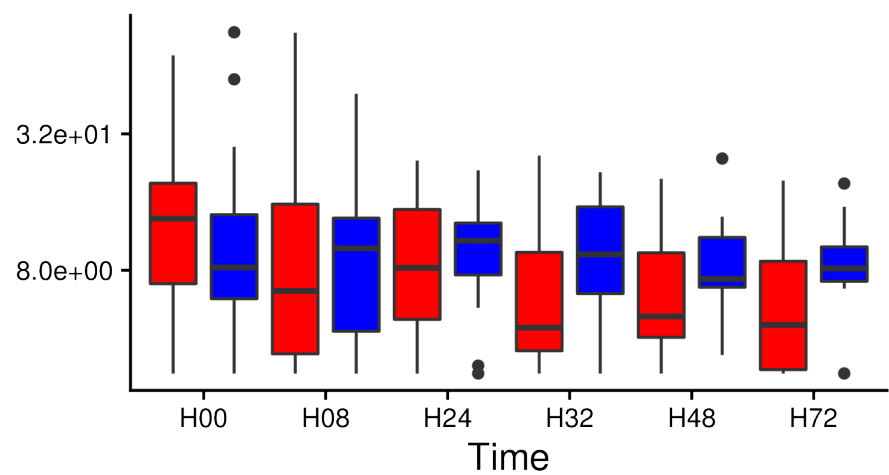










**ICAM****IL-1a****IL-1b****IL-6****IL-10****TNF- $\alpha$** 

Arm ■ Controls ■ HCO-HD