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# **Sodium flux during hemodialysis and hemodiafiltration treatment of acute kidney injury: Effects of dialysate and infusate sodium concentration at 140 and 145 mmol/L**

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## **KEYWORDS**

acute kidney injury, fluid volume balance, hemodiafiltration, hemodialysis, ionic dialysance, sodium flux, sodium mass removal

# Abstract

## Background:

A higher sodium (Na) dialysate concentration is recommended during renal replacement therapy (RRT) of acute kidney injury (AKI) to improve intradialytic hemodynamic tolerance. but it may lead to Na loading to the patient. We aimed to evaluate Na flux according to Na dialysate and infusate concentrations at 140 and 145mmol/L during hemodialysis (HD) and hemodiafiltration (HDF).

## Methods;

Fourteen AKI patients that underwent consecutive HD or HDF sessions with Na dialysate/infusate at 140 and 145mmol/L were included. per dialytic flux of Na was estimated using mean sodium logarithmic concentration including diffusive and convective influx. We compared the flux of sodium between HD140 and 145, and between HDF140 and 145.

## Results:

Nine HD140, ten HDF140, nine HD145, and 11 HDF145 sessions were analyzed. A Na gradient from the dialysate/replacement fluid to the patient was observed with dialysate/infusate Na at 145 mmol/L in both HD and HDF ( $p = 0,01$ ). The comparison of HD145 to HD140 showed that higher Na dialysate induced a diffusive Na gradient to the patient (163 mmol vs. -25 mmol,  $p = 0,004$ ) and that of HDF145 to -140 (211 vs. 36mmol,  $p = 0,03$ ) as well. Intradialytic hemodynamic tolerance was similar across all RRT sessions.

## Conclusions:

During both HD and HDF, a substantial Na loading occurred with a Na dialysate and infusate at 145mmol/L. This Na loading is smaller in HDF with Na dialysate and infusate concentration at 140mmol/L and inverted with HD140. Clinical and intradialytic hemodynamic tolerance was fair in regardless of Na dialysate and infusate.

## BACKGROUND

Acute kidney injury (AKI) is common in critically ill patients and is associated with a significant morbi-mortality. About 5% to 6% of these patients will develop a severe AKI that requires renal replacement therapy (RRT).<sup>1,2</sup> Despite technological progress, RRT remains a critical issue in ICU settings, and its use independently increases the mortality, bringing it to 30%-50%.<sup>2</sup>

Several complications may be associated with RRT including vascular access-associated infections, bleeding and, the most prevalent, hemodynamic instability (related to RRT: HIRRT). HIRRT complicates both intermittent and continuous modalities and has been reported to occur in more than 20% of patients.<sup>3,4</sup> Nonetheless, continuous RRT has gained wide application in ICUs, often supplanting intermittent modalities because of the belief that it is better tolerated in hemodynamically unstable patients.<sup>6-10</sup> A similar hemodynamic

tolerance would be, however, obtained with intermittent compared with continuous techniques. If certain recommendations are followed including cooler dialysate, longer duration of RRT sessions and most importantly high dialysate sodium." In fact, a Na dialysate >145 mmol/L has been associated with a better hemodynamic tolerance in ICU patients treated by IHD,<sup>12</sup> but it would induce a Na overload to the patient. Given that natremia is mostly less than 145 mmol/L, the osmotic gradient between blood and dialysate induces a Na transfer from dialysate to the patient and a fluid load,

In chronic hemodialyzed patients, the elevation of the dialysate Na levels prevented intradialytic hypotension, but it may also promote hypernatremia, thirst, hypertension, and increased interdialytic weight gain.<sup>13-15</sup> Data on AKI patients treated by RRT are scarce. However, fluid overload has been associated with altered lung function and increased mortality.<sup>16,17</sup> We hypothesized that RRT contributes to a patient load independent of fluid balance; and evaluated Na transfers according to different Na dialysate and infusate concentrations (140 and 145 mmol/L) with both intermittent HD and HDF in AKI patients.

## 2 | METHODS

In our Department of Intensive Care Medicine (Lapeyronie University Hospital, Montpellier, France), we routinely use online intermittent hemodialysis (HD) and hemodiafiltration (HDF) for the treatment of AKI. Usually, dialysate Na concentrations are set at values varying from 140 to 150 mmol/L as recommended.<sup>18</sup> We performed a prospective crossover study to evaluate Na flux according to two Na dialysate and infusate concentrations -140 and 145 mmol/L- during intermittent HD and HDF sessions. This work represents a preliminary study of a prospective randomized study NADIRA -Evaluation of hemodynamic effects of Na dialysate and infusate concentration variations during on-line HDF- which was approved by the institutional review board Comité de Protection des Personnes N° ID-RCB/AudraCT 2017-A0170449. Our local institutional review board waived the need of informed consent for this study.

### 2.1 | Population

Baseline patient characteristics were recorded, and the severity of illness was determined using the simplified acute physiologic (SAPS) 11 and SOFA scores. During the ICU stay, patients consecutively admitted to ICU with AKI were eligible for the study. They were included when RRT was initiated,<sup>19</sup> and prior RRT natremia above 135 and less than 145 mmol/L. Exclusion criteria included pregnancy, age <18 years old, previous chronic renal failure (glomerular filtration rate <30 ml/min/1.73 m<sup>2</sup> as estimated by CKD EPI). AKI of obstructive, glomerular, or vascular etiology. treatment limitation or presumed survival <48h. Fourteen patients were included and every patient was submitted to 4-h online intermittent HD or HDF. The need for invasive mechanical ventilation and the use of vasoactive drugs during ICU stay were recorded.

### 2.2 | Renal replacement therapy parameters

Online-HD/F was performed using an RRT generator (Fresenius 5008, Fresenius Medical Care, Bad Homburg, Germany) with a standard 1.8 m<sup>2</sup> Polysulfone hemodiafilter HF80. Countercurrent dialysate flow was routinely set at 200 ml/min; online infusate flow in predilution mode at 60 ml/min and blood flow at 200 ml/min. Dialysate and infusate

temperature was adjusted to 36°C. The Na dialysate and infusate concentrations were set at 145 and 140mmol/L. We distinguished four types of RRT sessions: online HD or HI)F with Na dialysate and infusate at 140 mmol/L, and at 145 mmol/L. The net-ultrafiltration rate was maintained at 0 ml/h. I.IDF, or HD session followed HD or HDF session after a washout period of 12 h. During the washout period, serum Na concentrations were maintained in normal range (135-145 mmol/L) and the order of sessions was changed simultaneously. During RRT treatment, any perfusion or bolus infusion was not permitted unless an intradialytic hypotension occurred.

### 2.3 I Biological parameters

Blood samples were drawn from the arterial port of the venous catheter immediately before, and at the end of each online HD/F session for measurements of Na, urea, creatinine, albumin, and protein. At the end of treatment, blood samples were collected by standard stop-flow technique." Plasma Na concentrations were measured using an indirect potentiometry method.

### 2.4 I Renal replacement therapy dose -quantification

Kt/V were determined by using Daugirdas second generation` Single pool urea model equation (spKt/v)<sup>20</sup>:

$$\text{spKt/V} = -\ln\left(\frac{C_{\text{urea\_post}}}{C_{\text{urea\_pre}}}\right) - 0.008 \times \text{td} + \left(\left(4 - 3.5 \times \frac{C_{\text{urea\_post}}}{C_{\text{urea\_pre}}}\right) \times \left(\frac{W_{\text{pre}} - W_{\text{post}}}{W_{\text{post}}}\right)\right) \quad (1)$$

where pre- and post-correspond to pro- and post-treatment conditions, respectively, td is time duration session in minutes,  $C_{\text{urea}}$  is urea concentration in mmol/L, and W is body weight in kg.

Equilibrated Kt/V (eqKt/V) was calculated as<sup>21</sup>

$$\text{eqKt/V} = (\text{Kt/V})_{\text{sp}} - \left(0.6 \times (\text{Kt/V})_{\text{sp}} / \text{td}\right) + 0.03 \quad (2)$$

During each RRT session, instantaneous ionic clearance ( $K_{\text{ocM}}$ , ml/min) as well as total ionic clearance ( $K_{\text{locM}} = K_{\text{ocM}} \times \text{time duration Session in minutes}$ ) were calculated from the measurement of ionic dialysance by the OCM module, standard on the dialysis monitor.

Dialysis monitors measured effective treatment time (tHD or tHIF).  $K_{\text{locM}}/V$  was calculated by the dialysis monitors after entering patient age, gender, and anthropometric characteristics using the Watson formula.<sup>22</sup>

## 2.5 I Na transfer estimation

We estimated Na mass removal and transfer using blood based simple kinetic modeling assessment.<sup>23</sup> The patient was arbitrarily designated as the reference, that is, in case of positive transfer there is a transfer of sodium from the dialysate/replacement liquid to the patient and conversely in case of a negative transfer.

Measurement of Na mass transfer using blood-side-based calculation on pre- and post-session serum sampling values.

Mean ionic dialysance measured by the dialysance machine ( $K_{ocM}$ ) was used as a surrogate of sodium dialysance.

The logarithmic mean of Na plasma concentration (pNa) over the session was calculated as

$$pNa(\text{mmol/L}) = (\text{Na}_{\text{pre}} - \text{Na}_{\text{post}}) / \ln(\text{Na}_{\text{pre}} / \text{Na}_{\text{post}}) \quad (3)$$

where  $\text{Na}_{\text{pre}}$  and  $\text{Na}_{\text{post}}$  correspond to natremia before and after the RRT session, respectively. Na diffusive mass transfer (NaDT) was calculated as the Product of ( $\text{Na}_{\text{dialysate}} - \text{pNa}$ ) by its effective clearance ( $K_{ocM}$ , ml/min) and duration of the session (tHD, min) as:

$$\text{NaDT}(\text{mmol}) = (\text{Na}_{\text{dialysate}} - \text{pNa}) \times K_{ocM} \times \text{tHD} / 1000. \quad (4)$$

Na convective mass transfer (NaCT) must take into account Na flux during substitution (NaFluxsub) and ultrafiltration (NaFluxUF).

NaCT was calculated as follows:

$$\text{NaCT} = (\text{NaFluxsub} - \text{NaFluxUF}) \times \text{tHF} = \left[ (\text{Q}_{\text{sub}} \times \text{Na}_{\text{infusate}}) / 1000 - (\text{Q}_{\text{sub}} + \text{K}_{\text{uf}}) \times \text{DifNa} / 1000 \right] \times \text{tHF} \quad (5)$$

Given that none of our patients had any ultrafiltration, NaCT included only Na flux during substitution.

Consequently, NaCT was calculated as

$$\text{NaCT} = \frac{\text{Qsub}(\text{ml}/\text{min}) \times (\text{Na}_{\text{infusate}} - \text{DifNa})}{1000 \times \text{tHF}(\text{min})} \quad (6)$$

where  $\text{Qsub}$  = substitution Volume (L) x 1000//tHF (min) and  $\text{DifNa} = 0.97 \times \text{pNa}$  owing that only 97% of Na diffused because of colligative forces induced by Gibbs-Dorman effect.

During the HD session, total sodium mass transfer (NetNaMT) is equal to NaDT and during the HDF session to the sum of NaDT and NaCT.

## 2.6 I Clinical evaluation of renal replacement therapy sessions

Clinical tolerance of RRT was investigated by collecting at baseline and every 30min during each session: pulse, temperature, and mean arterial blood pressure. An intradialytic hypotensive event was defined by a 20% reduction of mean arterial blood pressure or by an increase in vasoconstrictive agents' dose. Rates of blood, fluid substitution, and dialysate flows were also monitored every hour.

## 2.7 I Statistical analysis

Results are expressed as mean  $\pm$  SD or median and interquartile range [IQR], depending on data distribution, for continuous variables and as frequency and percentages for categorical variables. Qualitative values were compared using chi-square test. Quantitative variables were compared using the Student I-test or the nonparametric Wilcoxon test or Mann-Whitney test. Comparative statistical analysis between the four groups was performed using the Kruskal-Wallis test. A p value of  $<0.05$  was considered as statistically significant. Statistical analysis was performed using R Software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

# 3 RESULTS

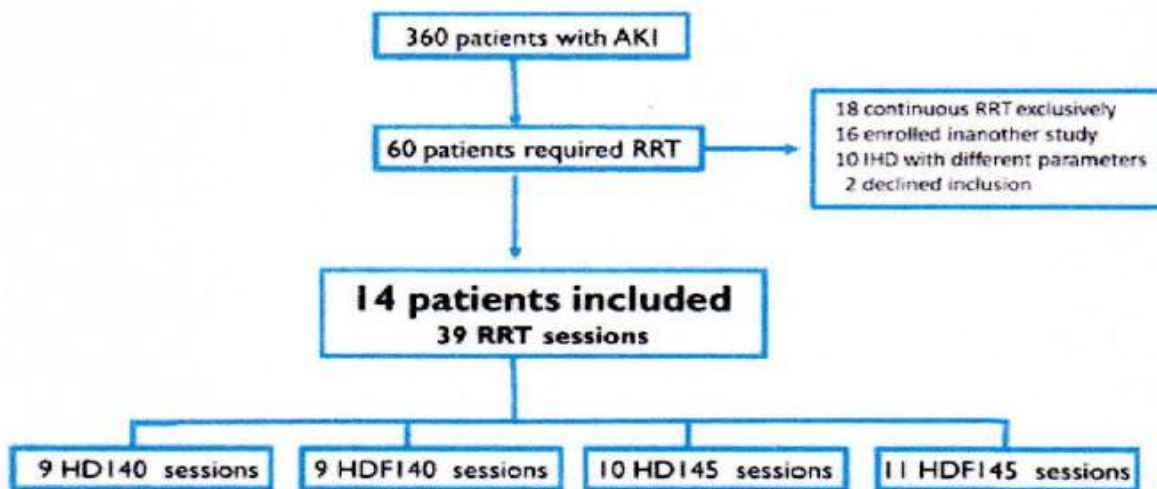
## 3.1 I Population

From December 2017 to July 2018, of the 60 KDIGO 3 AKI patients who received RRT, 14 with a median age of 66.5 years old entered the study (Figure 1). At admission, median SAPSII and SOFA score were at 61.5 and 9, respectively. Main clinical characteristics are reported in Table 1. Most of the patients were men (78.6%). Mechanically ventilated (11/14, 79%) and treated by vasoconstrictive agents (10/14, 71%). All patients were anuric. AKI was of septic origin in most of the patients (8/14, 57%).

## 3.2 Renal replacement therapy sessions, efficiency.

RRT included 19 HD and 20 HDF sessions. Each patient underwent at least two HD or HDF sessions with Na at 140 and 145 mmol/L. Treatment time session average was at  $4 \pm 0.1$  hours. Na dialysate and infusate were set at 140 mmol/L in 9 HD and 9 HDF sessions and at 145 mmol/L in 10 HD and 11 HDF sessions.  $\text{eqKt/V}$  and  $\text{Kt}_{\text{QCM}}/\text{V}$  varied from 0.86 to 1.01

and from 0.78 to 0.92, respectively, for all RRT sessions without any statistical differences in efficiency according to RRT modality and Na dialysate and infusate (Table 2),



**FIGURE I** Flow chart of the studied population.

AKI, acute kidney injury; HD hemodialysis; H DF. hcmodiafiltration; RRT, renal replacement therapy.

**TABLE 1** Clinical characteristics of the studied population

<i>n</i>	<b>14</b>
<b>Parameters</b>	
Sex (male), <i>n</i> (%)	11 (78.6)
Age (years), median [IQR]	66.5 [59.2–76.7]
BMI, median [IQR]	26.5 [23.5–30.1]
<b>Characteristics at inclusion</b>	
SAPSII, median [IQR]	61.5 [48.2–67.2]
SOFA, median [IQR]	9 [7–11]
Charlson Score, median [IQR]	3 [1–4]
<b>Diagnosis</b>	
Septic acute kidney injury, <i>n</i> (%)	8 (57.1)
<b>Treatment</b>	
Norepinephrine, <i>n</i> (%)	10 (71.4)
Mechanical ventilation, <i>n</i> (%)	11 (78.6)



TABLE 2 Efficiency of renal replacement therapy (RRT) sessions and natremia before ( $Na_{pre}$ ) and after RRT( $Na_{post}$ ) according to Na dialysate

	HD 140 <i>n</i> = 9	HDF 140 <i>n</i> = 10	HD 145 <i>n</i> = 9	HDF 145 <i>n</i> = 11	<i>p</i>
$Kt_{OCM}/V$	0.93 [0.87–0.99]	0.92 [0.86–1.01]	0.94 [0.90–0.96]	0.89 [0.82–1.01]	0.90
$eqKt/V$	0.79 [0.66–0.84]	0.92 [0.75–0.96]	0.78 [0.69–0.87]	0.79 [0.68–0.84]	0.53
$Na_{pre}$ (mmol/L)	139 [137–141]	137 [136–141]	139 [137–141]	139 [138–144]	0.38
$Na_{post}$ (mmol/L)	140 [138–142]	142 [141–142]*	140 [139–144]	143 [141–144]*	0.20

Note: *p*: differences between the four groups for  $Kt_{OCM}/V$ ,  $eqKt/V$ ,  $Na_{pre}$ , and  $Na_{post}$  (italics).

Abbreviations: HD, hemodialysis; HDF, hemodiafiltration.

\**p* < 0.05 differences between  $Na_{pre}$  and  $Na_{post}$  in groups HDF 140 and HDF 145.

TABLE 3 Na mass transfers during HD and HDF with Na dialysate at 140 and 145mmol/L as measured by modeled method

mmol/session	HD 140 <i>n</i> = 9	HDF 140 <i>n</i> = 10	HD 145 <i>n</i> = 9	HDF 145 <i>n</i> = 11	<i>p</i>
NaDT					
Median	-25.44	-15.87	162.70	128.00	0.005
Interquartile	[-49.18–92.70]	[-32.58–65.0]	[115.6–209.0]	[26.26–182.7]	
NaCT					
Median		51.66		91.01	0.06
Interquartile		[38.44–88.97]		[71.88–119.20]	
NetNaMT					
Median	-25.44	35.78	162.70	211.4	0.01
Interquartile	[-49.18–92.70]	[5.86–164.30]	[115.6–209.00]	[96.63–301.90]	

Note: *p*: differences for NaDT and NetNaMT between HD 140 and 145, and for NaDT, NaCT and NetNaMT between HDF 140 and 145 (italics).

Abbreviations: HD, hemodialysis; HDF, hemodiafiltration; NaCT, Na convective mass transfer; NaDT, Na diffusive mass transfer; NetNaMT, total sodium mass transfer.

### 3.3 I Na flux according to renal replacement therapy modality and Na dialysate and infusate concentrations

Protidemia remained unchanged after each session and glycemia was maintained below 8mmol/L before and after each session, thanks to an insulin Intravenous Infusion whenever necessitated. Median baseline natremia varied from 137 to 139 mmol/L and did not differ between groups (Table 2). After RRT, natremia increased to a median value of 140 (139–143) mmol/L. This increase was, however, significantly different only after HD and HDF at Na 145. A Na transfer from dialysate or infusate to the patient was observed in all modalities except for HD with Na dialysate at 140mmol/L (Table 3). Na flux to the patient was higher with Na 145 compared with Na 140 with both modalities. The comparison between HD and HDF145 showed that Na flux was significantly higher with HDF underlying that a Na overload occurred more importantly with convection mode (Table: 4). By contrast, Na flux to

the patient was canceled even inverted with HD140, whereas HDF140 still induced Na flux to the patient but significantly less than HD and HDF145 (Figure 2).

### 3.4 I Clinical and hemodynamic tolerance of renal replacement therapy sessions

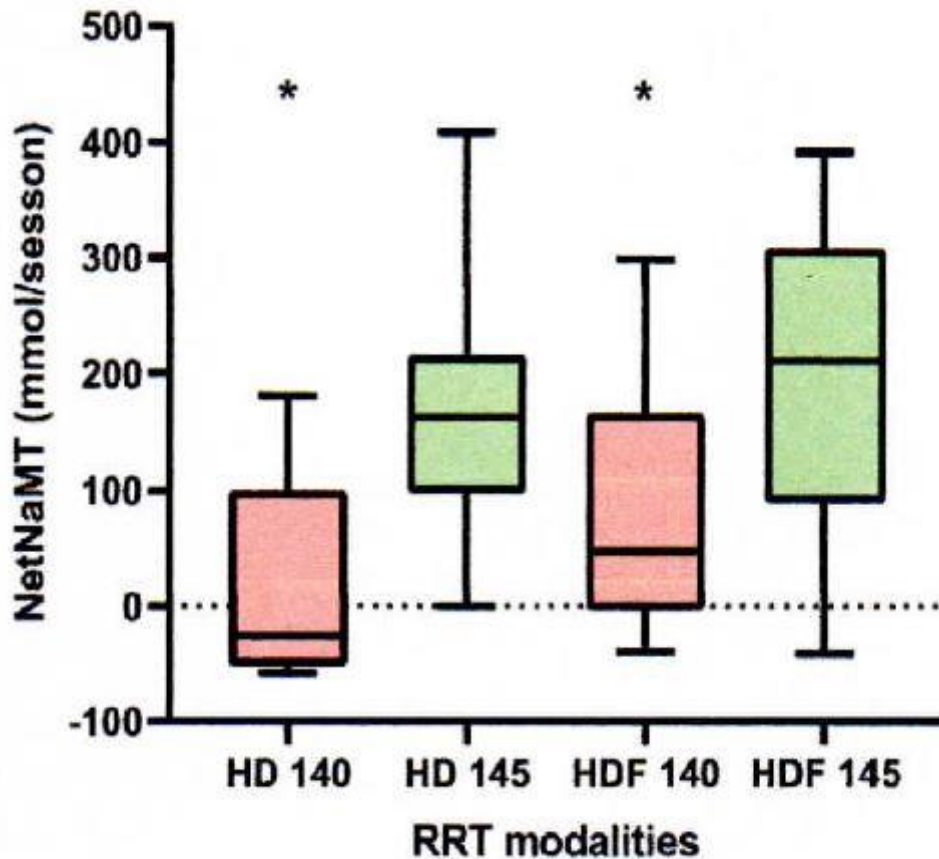
Body weight, blood pressure, and heart rate remained unchanged before and after each RRT session. Among the 39 RRT sessions, an intradialytic hypotensive event was observed in three patients during three sessions accounting for a mat-tolerated session's rate at 7%. The occurrence of these episodes was similar in all groups. Nine patients were discharged alive from the ICU that accounted for a mortality of 36%.

**TABLE 4** Comparison of Na mass transfers between HD and HDF sessions according to Na dialysate and infusate

<b>Hemodialysis</b>		
Na dialysate, mmol/L	140	145
HD sessions, <i>n</i>	<i>n</i> = 9	<i>n</i> = 9
NetNaMT, mmol/session		
Median	-25.44	162.70
Interquartile	[-49.18-92.70]	[115.6-209.00]
<b>Hemodiafiltration</b>		
Na dialysate and infusate, mmol/L	140	145
HDF sessions, <i>n</i>	<i>n</i> = 10	<i>n</i> = 11
NetNaMT, mmol/session		
Median	35.78	211.4
Interquartile	[5.86-164.30]	[96.63-301.90]
<i>p</i>	<i>0.004</i>	<i>0.067</i>

*Note:* *p*: difference between HD 140 and HDF 140; and between HD 145 and HDF 145 (italics).

Abbreviations: HD, hemodialysis; HDF, hemodiafiltration.



**FIGURE 2 Na mass transfers during HD and HDF according to Na dialysate and infusate.**

HD, hemodialysis; HDF, hemodiafiltration; RRT, renal replacement therapy. \* $p < 0.05$  between HD 140 and HD 145 and between HDF 140 and HDF 145. A positive transfer means a transfer of sodium from the dialysate/ replacement liquid to the patient, Conversely, a negative transfer takes place from (the patient's plasma to the dialysate/ replacement liquid).

## 4 DISCUSSION

We found that critically ill patients undergoing RRT received a sodium load with both HD and HDF when Na dialysate and infusate were set at 145 mmol/L. When Na dialysate and infusate were set at 140mmol/L, a Na transfer to the patient persisted but decreased significantly during HDF sessions to cancel out or even negated during HD. A fair intradialytic hemodynamic tolerance was observed regardless of modalities and Na dialysate and infusate concentrations.

AKI patients treated by RRT have an in-hospital global mortality rate of 40 to 60%.<sup>24</sup> Though RRT represents the cornerstone of the supportive management of severe AKI, its performances may have untoward effects including intradialytic hypotension that contribute to the morbimortality.<sup>24</sup> Indeed, intradialytic hypotension may occur in 30% to 70% of intermittent RRT sessions in ICU patients.<sup>3,25</sup> Continuous RRT modalities are presumed to induce less HIRRT however, it still occurs in 19% to 43% of patients.<sup>5</sup> Accordingly,

interventions to limit IIRRT might ultimately improve the persistently dismal outcomes of critically ill patients treated by RRT. Among all, the use of a high sodium dialysate concentration (>145 mmol/L) to limit osmotic shift and promote hemodynamic stability has been reported as an effective intervention.<sup>1,2,6,27</sup> However, it may induce a cumulative fluid balance which is an independent risk factor for increased mortality in septic shock and AKI.<sup>28,29</sup> Our aim in this study was to evaluate the amount of fluid load during an RRT session according to Na dialysate and infusate. We found that a Na dialysate and infusate set at 145 mmol that was above patient natremia induced a significant overload with both intermittent isovolumic HD and HDF.

In chronic hemodialyzed patients, a Na dialysate higher than natremia leads to a Na transfer to the patient according to the osmotic gradient.<sup>30</sup> Consequently, this Na overload increased progressively weight gain and Na inflation. In addition, it has been observed that the use of a Na dialysate >140mmol/L, generating a positive osmotic gradient from the dialysate to the patient, induced an interdialytic weight gain and a higher ultrafiltration volume during RRT sessions.<sup>31</sup> By contrast, the use of a Na dialysate lower than predialytic natremia will affect patient weight and contribute to a better pressure control.<sup>32</sup> A few data exist regarding to Na dialysate and infusate concentrations and potential overload in critically ill. In a study of 60 ICU patients receiving extended daily dialysis or CRRT (CVVHD and CVVHDF), both extended daily dialysis and CRRT contributed to a positive Na flux with a greater positive sodium flux with continuous modalities. The sodium load was affected by multiple factors especially the gradient between dialysate and serum Na.<sup>33</sup> Our results are in line with these observations. The major factor that causes the transfer of Na to the patient appears to be the positive gradient between the dialysate/replacement fluid sodium and the patient's serum Na at the start of the treatment leading to an extracellular fluid expansion. In addition, HDF contributed a higher load of Na to the patient compared with HD. Indeed, HDF cumulates the effects of both diffusion and convection and, therefore, a greater transfer of Na.

In critically ill patients, Na overload is a matter of concern since it may contribute to the morbi-mortality. During their ICU stay, the vast majority of patients experience an increased extracellular volume that will be reflected in an exacerbation of interstitial edema in various organs including the lung. In addition, hypervolemia would generate an increased pressure in the renal capsule by venous congestion that induces a decrease in renal plasma flow and glomerular filtration flow.<sup>34</sup> There is a proof of evidence of a deleterious effect of Na overload in the critically ill. AKI patients exhibited a greater Na overload than those without AKI.<sup>35</sup> A weight gain >10% during ICU stay increased significantly the mortality in critically ill patients.<sup>28,36</sup> Last, among AKI patients requiring RRT, the presence of a Na overload at the initiation of the treatment increases 90-day mortality<sup>36</sup> and would have a negative impact on the recovery of renal function.<sup>37</sup>

We must acknowledge some limitations to the study. First, our work shares the limitations of single-center studies. Our unit is indeed familiar with both hemodialysis and hemofiltration therapies which are not the general rule in ICU settings. In addition, citrate anticoagulation which may be currently used in ICU settings was avoided in this study to prevent any Na loading induced by citrate infusion. Second, the number of patients included may be considered small but a great number of RRT sessions was evaluated that allowed our investigations. The modeled method we used to calculate Na transfers was validated only in chronic hemodialysis settings but not in AKI. Nevertheless, we assume that such will be extrapolated in acute settings. In addition, we did not include the amount of Na due to

different perfusions including antibiotics, sedation, parenteral nutrition... Given the short course of the RRT session less than 4 h, this should not significantly impact our estimation.

## **5 CONCLUSIONS**

Our study showed that both intermittent HD and HDF with a Na dialysate and infusate set at 145 mmol/L will induce a Na overload to the patient. This Na overload will be lesser with HDF and even negative with HD when the Na dialysate and infusate were set at 140mmol/L. Convective modalities induced more Na overload than diffusive ones. At (hose different values of Na dialysate and infusate. We did not observe any differences in hemodynamic tolerance during RRT sessions. These results need further studies for confirmation, but they should prompt us to pay attention to Na transfers during RRT.

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### **CONFLICT OF INTEREST**

Bernard Canaud is part-time employee of Fresenius Medical Care acting as consultant. The remaining authors have nothing to disclose. The results presented in this article have not been published previously in whole or part.

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