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Intradialytic Tolerance and Recovery Time in Different High-Efficiency Hemodialysis Modalities

Agnieszka Zakrzewska [1,†], Jan Biedunkiewicz [2,†], Michał Komorniczak [1], Magdalena Jankowska [1], Katarzyna Jasiulewicz [1], Natalia Płonka [1], Bogdan Biedunkiewicz [1], Sylwia Małgorzewicz [3], Agnieszka Tarasewicz [1], Ewelina Puchalska-Reglińska [4], Janusz Siebert [5], Alicja Dębska-Ślizień [1] and Leszek Tylicki [1,*]

[1] Department of Nephrology, Transplantology and Internal Diseases, Medical University of Gdańsk, Smoluchowskiego 17, 80-214 Gdańsk, Poland
[2] Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Medical University of Gdańsk, 80-214 Gdańsk, Poland
[3] Department of Clinical Nutrition, Medical University of Gdańsk, Dębinki 7, 80-211 Gdańsk, Poland
[4] Dialysis Unit, 7th Naval Hospital in Gdańsk, 80-305 Gdańsk, Poland
[5] Department of Family Medicine, University Center for Cardiology, Medical University of Gdansk, 80-211 Gdansk, Poland
* Correspondence: leszek.tylicki@gumed.edu.pl
† These authors contributed equally; first co-authors.

Abstract: There are several forms of maintenance high-efficiency hemodialysis (HD) including hemodiafiltrations (HDF) in different technic modes and expanded HD using dialyzers with medium cut-off membranes. The aim of the study was to assess the intradialytic tolerance and length of dialysis recovery time (DRT) in these modalities. This is an exploratory, cross-over study in maintenance HD patients with low comorbidity and no clinical indications for the use of high-efficiency HD, who were exposed to five intermittent dialysis in random order: high flux hemodialysis (S-HD), expanded HD (HDx), pre-dilution HDF (PRE-HDF), mix-dilution HDF (MIX-HDF) and post-dilution HDF (POST-HDF). 24 dialysis sessions of each method were included in the analysis. Dialysis parameters including blood flow rate, dialysis fluid flow rate and temperature, and pharmacological treatment were constant. Average total convection volume for post-HDF, pre-HDF and mix-HDF were 25.6 (3.8), 61.5 (7.2) and 47.1 (11.4) l, respectively. During all therapies, patients had similar hydration status monitored using bioimpedance spectroscopy and similar variability over time in systemic blood pressure, cardiac output, and peripheral resistance monitored using impedance cardiography. The lowest frequency of all intradialytic adverse events were observed during HDx. Delayed DRT was the shortest during PRE-HDF. Patients were also more likely to report immediate recovery while receiving PRE-HDF. These differences did not reach statistical significance, however the study results suggest that, intradialytic tolerance and DRT may depend on the dialysis method used. This support the need of taking into account patient preferences and quality of life while individualizing high efficiency therapy in HD patients.

Keywords: hemodialysis; hemodiafiltration; expanded hemodialysis; quality od life

1. Introduction

For some time now, hemodialysis (HD) using high-flux membranes is the standard of chronic dialysis treatment in many countries. Although randomized studies have inconclusive results, a systematic review from the Cochrane Database including 33 studies and 3820 patients found that high-flux HD (S-HD) can reduce cardiovascular mortality as compared to low-flux HD [1]. Technological advances over the past few decades have contributed to major developments in HD therapy and the introduction of high-efficiency dialysis therapies into clinical practice. Significant technological changes in dialyzer membrane permeability and ultrafiltration-controlled delivery systems permitted more efficient removal of larger - medium-sized water-soluble toxins. There are several forms of high-efficiency dialysis treatment, which include among others: hemodiafiltration

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(HDF) in pre-dilution (PRE-HDF), post-dilution (POST-HDF) and mixed dilution (MIX-HDF) mode and the so-called expanded HD (HDx) using dialyzers with medium cut-of membranes (MCO) [2–4]. The observational studies and some secondary analyses of randomized trials have indicated that high-volume online HDF may improve patient survival in comparison to S-HD, regardless of whether pre-dilution or post-dilution mode is used [5,6]. Quite recently, CONVINCE (Comparison of high-dose HDF with high-flux HD) trial confirmed that the use of high-volume PODT-HDF resulted in a lower risk of death from any cause than conventional S-HD [7]. Pending the results of other controlled studies in this area, these methods are being used increasingly, especially in patients with high comorbidity, long duration of dialysis therapy and contraindications to kidney transplantation [8]. Some experts recommended the use of high-volume online HDF in patients whose Age Adjusted Charlson Comorbidity Index (AACCI) is ≥ 8 [9]. Particularly clinical benefits have been demonstrated in patients with hemodynamic instability, poorly controlled blood pressure (BP), polyneuropathy, calcium-phosphate disorders, pruritus or erythropoietin resistance, among others [2,10]. All those studies concentrate on hard point outcomes. However, patient related outcome measures and patient preference as a drive in the choice of the modality should be also taken into account [8]. There is little clinical experience in the use of high-efficiency HD methods in patients with low comorbidity and better prognosis.

2. Materials and Methods

2.1. Study design

This is an exploratory, open, cross-over (one-center) study in maintenance HD patients who were exposed to five high-efficiency intermittent dialysis modalities in random order: (i) S-HD, (ii) HDx, (iii) PRE-HDF, (iv) MIX-HDF, (v) POST-HDF. Each patient underwent three sessions in each of these modalities during one week. The second and third sessions of the week entered the final analysis. Patients and dialysis unit staff were not blinded to treatment allocation. The aim of the study was to compare patients' tolerance of dialysis methods in a group of patients with low comorbidity who have no clinical indications for the use of high-efficiency dialysis. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethical Committee at the Medical University of Gdansk (no. NKBBN/479-759/2022; 18 November 2022).

2.2. Patients

The inclusion criteria were as follows: adult patients, eligible for kidney transplantation, treated chronically with HD 3 x per week for at least 6 months; dialysis single-pool Kt/V for urea (spKt/Vurea) > 1.2; patient's weight in the range of 60-85 kg; AACCI < 8; achievement of a blood flow of > 350 ml/min through a fistula or arteriovenous catheter. Exclusion criteria include life expectancy < 6 months, severe incompliance to the HD procedures and accompanying prescriptions, emergency hospitalization within 30 days before entering the study, diabetes, active inflammation, active cancer, hemodynamic instability during HD sessions, poorly controlled BP, uremic polyneuropathy, uremic pruritus, dialysis amyloidosis and erythropoietin resistance. Also, patients needed to have no contraindication for bioimpedance measurement and be able to record dialysis recovery time (DRT).

2.3. Dialysis prescription and equipment

All dialysis therapies were performed on Fresenius 5008 dialysis machine with AutoSub Plus system (Fresenius Medical Care, Bad Homburg, Germany). SHD and HDF treatments were performed with high-flux FX 100 dialyzers (effective surface area: 2.2; UF coefficient 73 ml/h x mmHg; Fresenius Medical Care; Germany). HDx sessions were performed using Terranova 400 MCO dialyzer (effective surface area: 1.7 m2 , UF coefficient 48 ml/h x mmHg; Baxter, Canada). Dialysis sessions time was set at 4 hours for all modalities. Temperature of dialysate was set at 36.5 C degree. Blood flow rate and dialysate flow rate were set to 350 and 500 mL/min, respectively. Ultrafiltration (fluid removal) profiling and sodium profiling were not used. The electrolyte composition of dialysis fluid was: Na 138-140 mmol/l; K 2.0-3.0 mol/l; HCO3 32 mmol/l; Ca 1.25-1.5 mmol/l; Mg 0.5 mmol/l;

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Cl 110 mmol/l; glucose 1.0 g/l. The fliud removal of each session was set according to individual patient's interdialytic weight gain. All patients received standard heparin as a bolus and continuous infusion in accordance with current practice. Sterile and nonpyrogenic substitution fluid for HDF was produced online by ultrafiltration of the ultrapure dialysate. Substitution fluid rate and convection rate during HDF modalities were optimized automatically using the AutoSub Plus system based on pressure pulse attenuation and cross-membrane pressure assessment (Fresenius Medical Care; Germany). The basic principle of AutoSub Plus is to avoid excessive hemoconcentration in the dialyzer and maximization of the ultrafiltration flow [11]. For a given patient, dialysis settings were kept unchanged during all treatment modalities, e.g. post-dialysis weight, dialysis session length, composition of the dialysis fluid, blood and dialysis fluid flow, dialysis fluid temperature, anticoagulation dose. The patient's concomitant medications were continued in an unchanged manner.

2.4. Outcomes

During all sessions adverse events (AEs), DRT, hemodynamic parameters and hydration state were recorded. The results from the middle and the last dialysis sessions in week were used in the analysis.

2.4.1. Adverse events

The frequency of symptomatic hypotension, AEs potentially related to BP/fluid shifts, AEs not classically related to BP/fluids shifts and intradialytic clotting events were recorded. Symptomatic hypotension was defined as a decrease in systolic BP ≥ 20 mm Hg requiring reduction or cessation of ultrafiltration and/or need for intravenous fluid bolus or head-down tilt of dialysis chair. AEs potentially related to BP/fluid shifts were defined as breathlessness, cramp (normal BP), dizzy/lightheaded, fall, headache, venous pressures erratic, clotted needle, or restless legs. AEs not classically related to BP/fluids shifts were defined as aches in bones, arm pain, back pain, bleeding, constipation, diarrhea, feeling cold, feeling down, feeling hot, generally unwell, heavy legs, increased lethargy, infection (given antibiotics), itch, leg pain, nausea, stomach pains, sweating, swollen abdomen, and vomiting. Intradialytic clotting events were defined as either an increase in venous pressure requiring additional anticoagulant dosing or clotting of the extracorporeal circuit [12].

2.4.2. Dialysis recovery time

At each dialysis session, the patient was asked the duration of DRT to baseline function following their antecedent dialysis session. The patients' responses were converted to a number of minutes as follows [13]:

i. Answers given in minutes were recorded directly.
ii. Answers in hours were multiplied by 60.
iii. Variants of "half a day," including the "next day," were given a value of 720 min.
iv. Variants of "one day" were given a value of 1440 min.
v. Variants of "more than a day" were given a value of 2160 min (36 h).

Given that the distribution of DRT was bimodal with a peak at zero, it was analyzed by separate crossover analysis: percentage of immediate DRT (equal 0 minutes) and delayed DRT in minutes.

2.4.3. Hemodynamic monitoring

For real-time hemodynamic measurements the CardioScreen 2000 (Medis. Medizinische Messtechnik GmbH, Germany) device was used. CardioScreen 2000 is a feasible and accurate method for non-invasive hemodynamic measurements using methods of impedance cardiography which utilizes a physiological adaptive signal analysis (PASA) algorithm. Hemodynamic measurements obtained by PASA algorithm were correlated highly significant to measurements obtained by the thermodilution method [14]. The following parameters were measured or calculated: systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), Cardiac Index [CI], Systemic Vascular

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Resistance Index [SVRI]. Hemodynamic parameters were measured in resting position 10 minutes prior to dialysis, during dialysis (at the following time points: 15, 30, 60, 120, 180, 240 minutes) and 10 min after dialysis. In order to aggregate the changes in time during the entire dialysis session, the area under the curve (AUC) of BP, CI, SVRI were calculated using the trapezoid method.

2.4.4. Hydration state

Body composition and hydration state had been assessed by a portable whole body bioimpedance spectroscopy device (BCM; Fresenius Medical Care, Bad Homburg, Germany). The measurements were obtained before and after dialysis session in resting position. The extracellular water (ECW), intracellular water (ICW) and total body water (TBW) were calculated from a fluid model [15].

2.5. Statistics

Continuous data is reported as means (± standard deviation, SD) or medians (inter-quartile ranges, IQR). The Shapiro-Wilk test was used to determine the distribution of continuous variables. Categorical data is reported as percentages of the total. The Wilcoxon signed-rank test or ANOVA was used in the analysis comparing the results of the variables repeatable more than twice. Two-sided $p<0.05$ was considered to be statistically significant. The statistical analysis was performed using the program Statistica 13.3 (TIBCO Software Inc.; Palo Alto, CA, USA). Given that the distribution of DRT was bimodal with a peak at zero, it was analyzed by separate analysis with 2 models (immediate DRT as categorical variable and delayed DRT as continuous variable).

3. Results

3.1. Characteristics of patients

12 patients met inclusion criteria and were enrolled to the study, 11 men (91.67%) and 1 women (8.33%), in mean age of 52.5 ± 15.47 years. Hypertension was diagnosed in 10 (83.3%) patients. A description of the study group is presented in Table 1.

Table 1. Characteristics of the study group.

Gender (Men/Women)	11/1
Causes of ESRD (n/%)	
Autosomal Dominant Polycystic Kidney Disease	4 / 33.4
Glomerulonephritis (primary or secondary)	3 / 25.0
Hypertensive nephropathy	2 / 16.7
Renal malformation	1 / 8.3
Interstitial nephropathy	1 / 8.3
Other	1/ 8.3
Age (years)	52.5 (15.5)
AACI (points)	4.5 (2.2)
Dialysis vintage (months)	42.5 (31.04)
Body Mass Index (kg/m^2)	23.8 (3.6)
Weight (kg)	73.7 (14.2)
spKt/V_{urea}	1.5 (0.3)
Hemoglobin (g/dl)	10.9 (0.9)
Albumin (g/l)	33.1 (4.9)

ESRD: end-stage renal disease ; AACI: Age Adjusted Charlson Comorbidity Index.

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3.2. Dialysis parameters

Dialysis session time, blood flow rate, dialysate flow rate were constant during all modalities. All patients achieved the minimum level of convection for high volume post-HDF with substitution volume > 21 l. Mean (standard deviation) total convection for post-HDF, pre-HDF and mix-HDF were 25.6 (3.8), 61.5 (7.2) and 47.1 (11.4) l, respectively. The fluid removal, SBP, DBP, TBW, ECW and ICW did not differ between tested treatments. Detailed dialysis parameters and patients' hydration status results are presented in Table 2.

3.3. Hemodynamic parameters.

SBP and DBP at the beginning (first minute) and at the end dialysis (240 minute) session did not differ between treatments. AUC of SBP, DBP and MAP measurements obtained during dialysis over time did not differ between treatments as well. CI was decreasing ($p<0.001$ for all methods) while SVRI was increasing ($p<0.001$ for all methods) during all methods used. AUC of CI and SVRI measurements obtained during dialysis over time did not differ between the treatments. Detailed results are presented in Table 3, Figures 1 and 2.

Table 2. Delivered dialysis parameters, systemic blood pressure and hydration status parameters..

	S-HD	**HDX**	**PRE-HDF**	**MIX-HDF**	**POST-HDF**	**p**
Time min	240	240	240	240	240	NA
Blood flow ml/min	350	350	350	350	350	NA
Dialysate flow ml/min	500	500	500	500	500	NA
Ultrafiltration ml	2.12 (0.74)	2.33 (0.62)	2.45 (0.8)	2.29 (0.74)	2.19 (0.52)	p=0.6
Total convection l	NA	NA	61.5 (7.2)	47.1 (11.4)	25.6 (3.8)	NA
SBP $_{predialysis}$ mmHg	147.7 (27.5)	144.1 (20.3)	147.7 (26.6)	147.3 (20.3)	144.3 (22.4)	p=0.95
DBP $_{predialysis}$ mmHg	88.5 (18.8)	88.3 (16.9)	89.9 (20.4)	89.9 (16.4)	86.1 (18.0)	p=0.93
TBW $_{predialysis}$ l	39.76 (8.04)	41.64 (11.65)	39.05 (6.84)	40.15 (7.32)	39.7 (8.4)	p=0.93
TBW $_{postdialysis}$ l	38.17 (8.03)	40.46 (12.51)	37.5 (6.97)	38.56 (7.29)	37.44 (8.24)	p=0.85
ECW $_{predialysis}$ l	19.1 (3.2)	19.9 (3.3)	20.1 (3.5)	19.3 (3.5)	18.9 (3.2)	p=0.74
ECW $_{postdialysis}$ l	17.2 (3.1)	17.43 (3.1)	17.38 (2.9)	18.2 (5.7)	16.7 (2.9)	p=0.77
ICW $_{predialysis}$ l	21.31 (5.6)	23.3 (7.5)	22.2 (5.1)	20.7 (4.2)	20.8 (5.4)	p=0.62
ICW $_{postdialysis}$ l	21.33 (5.7)	24.5 (8.8)	24.2 (6.5)	21.2 (4.7)	20.7 (5.5)	p=0.17

Note: Ultrafiltration: the fluid removal during the session; total convection: the total volume of convection during the session, which is the sum of the patient's dehydration volume and the volume of the replacement fluid administered; SBP: systolic blood pressure; DBP: diastolic blood pressure; TBW: total body water; ECW: extracellular water; ICW: intracellular water.

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Table 3. Systemic blood pressure and area under the curve (AUC) of hemodynamic parameters.

	S-HD	HDX	PRE-HDF	MIX-HDF	POST-HDF	p
SBP 1st minute mmHg	145.8 (24.6)	139.1 (17.2)	143.4 (22.6)	141.2 (18.0)	137.9 (21.9)	p=0.75
SBP 240 minute mmHg	142.5 (35.5)	142.2 (28.3)	138.7 (35.7)	140.6 (35.5)	138.8 (29.2)	p=0.98
DBP 1st minute mmHg	87.0 (17.5)	86.3 (14.3)	86.1 (16.7)	87.9 (16.6)	83.4 (15.8)	p=0.85
DBP 240 minute mmHg	85.7 (17.1)	89.1 (21.3)	84.9 (17.3)	85.3 (20.5)	87.3 (18.7)	p=0.91
AUC SBP	323 816.6 (72 781.6)	318 930.3 (61 252.4)	316 602.0 (68 292.8)	305 190.3 (76 556.9)	313 049.4 (80 028.1)	p=0.8
AUC DPB	194 716.4 (37 664.1)	192 651.0 (53 530.6)	194 253.7 (33 794.1)	190 661.9 (44 971.5)	191 900.7 (44 991.7)	p=0.88
AUC MAP	237 748.1 (46 888.6)	230 184.4 (59 405.4)	235 096.4 (42 932.1)	231 486.3 (53 996.6)	234 209.5 (47 871.5)	p=0.23
AUC CI	6559.2 (1439.5)	6770.9 (1271.3)	6512.5 (1256.4)	6093.9 (1282.4)	6680.9 (1652.9)	p=0.65
AUC SVRI	6 176 119.3 (1 325 662.8)	6 456 193.4 (1 473 702.1)	6 256 567.9 (999 108.8)	7 075 464.9 (1 930 210.7)	6 301 942.5 (1 337 688.1)	p=0.34

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; CI: cardiac index; SVRI: systemic vascular resistance index.

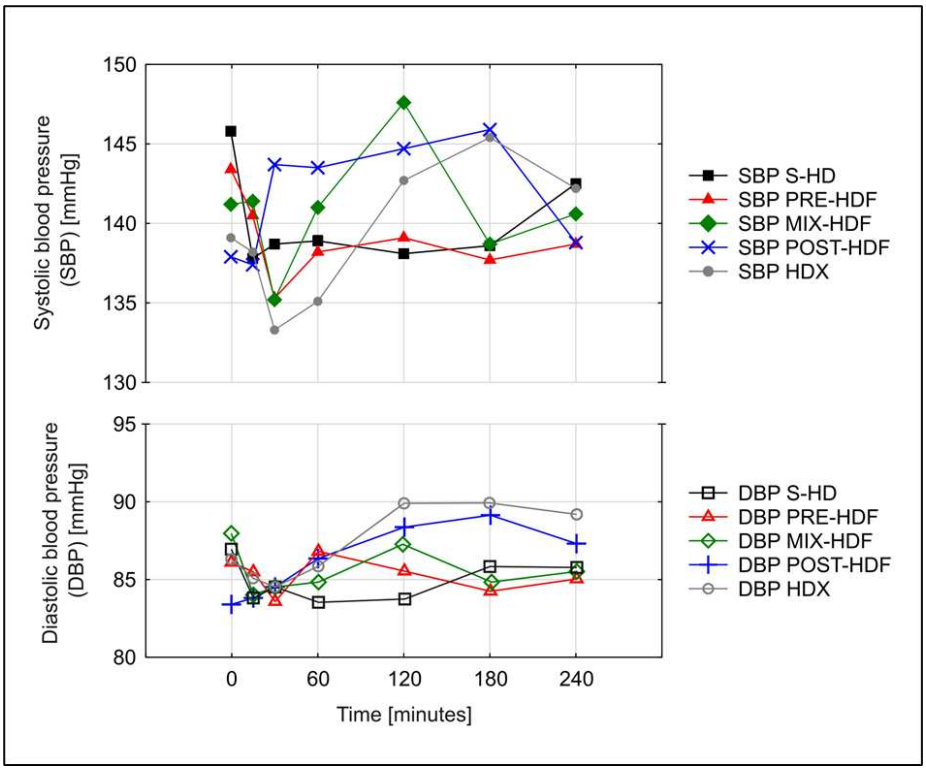

Figure 1. Changes over time in mean systolic (SBP) and diastolic blood (DBP) pressure during various dialysis treatments.

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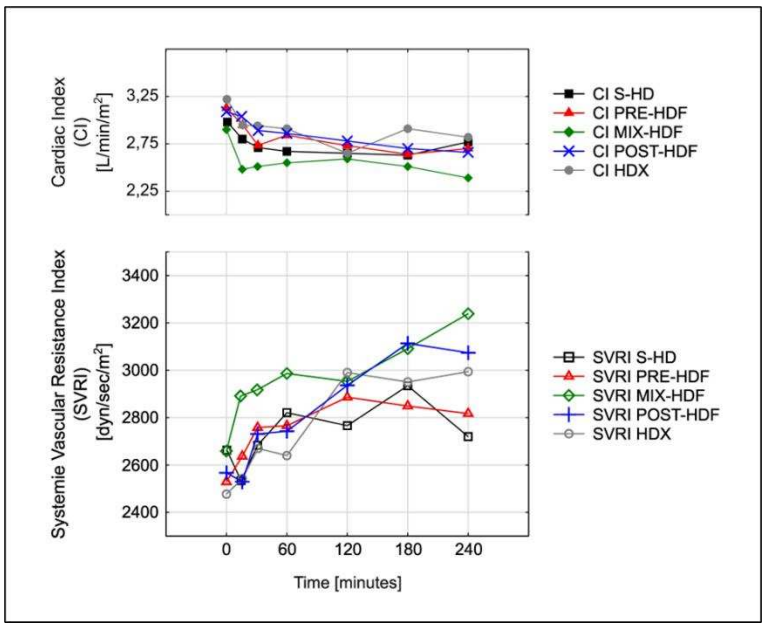

Figure 2. Mean area under the curve (AUC) of changes over time in cardiac index (CI) and systemic vascular resistance index (SVRI) during various treatments.

3.4. Adverse events and dialysis recovery time.

AEs were grouped to those that may or may not have been related to BP changes or fluid shifts and those related to clotting events. There were no incidents of symptomatic intradialytic hypotension during any treatment. The lowest frequency of all AEs was observed with HDx (25%), although the differences did not prove to be statistically significant. Delayed DRT was the shortest during PRE-HDF. Patients were also more likely to report immediate recovery while receiving PRE-HDF (62.5%). However, the differences did not reach statistical significance. Detailed results are presented in Table 4.

Table 4. Adverse events (% events per sessions) and dialysis recovery time (DRT).

	S-HD	HDX	PRE-HDF	MIX-HDF	POST-HDF	p
Symptomatic hypotension n	0	0	0	0	0	p=1.0
AEs potentially related to BP/fluid shifts n	0	1	1	2	4	p=0.39
AEs potentially not related to BP/fluid shifts n	7	4	5	5	2	p=0.47
Intradialytic clotting events n	1	1	2	2	4	p=0.51
All AEs n (%)	8 (33.3%)	6 (25%)	7 (29.2.%)	9 (37.5%)	10 (41.7%)	p=0.76
Immediate DRT n (%)	11 (45.8%)	12 (50%)	15 (62.5%)	9 (37.5%)	10 (41.7%)	p=0.10
Delayed DRT min	360.0 (180-720)	180 (120-390)	60 (30-600)	360 (180-360)	390 (60-720)	p=0.37

Note: AE: adverse event; values are given as number of events (percentage). Multiple the same episodes within 1 session were treated as a single event. All AEs: all AEs reported by patients and reported in the table, including clotting events; DRT: dialysis recovery time.

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4. Results

Despite substantial improvements in dialysis technology the survival of patients on HD is less than satisfactory. Crude 1-year mortality among prevalent HD patients has been reported to be 6.6% in Japan, 15.6% in Europe and 21.7% in the USA [16]. This was particularly visible during the COVID-19 pandemic, during which the fatality rate among infected HD subjects reached up to 30% [17]. However, maintenance HD patients have also a high burden of symptoms that negatively affect their quality of life [18]. It is important to note that patients may prioritize outcomes differently than those set by medical professionals. Post-dialysis fatigue, intra-dialytic hypotension, cramps and dizziness are the commonest symptoms reported by patients [19]. Post-dialysis fatigue and lack of energy interfere with daily life and are also a predictors of mortality [20]. Patients treated with standard HD report average DRT in the range of 2-4 hours, with approximately 25% reporting DRT greater than 6 hours [21,22]. In the FRENCHIE (French Convective versus Hemodialysis in Elderly) study that was designed to compare S-HD, and online HDF in terms of intradialytic tolerance, 25.9% of patients reported at least one AEs during dialysis session and 20.6% of patients had asymptomatic hypotension [23]. Thus, it is important to adopt objective measures of intradialytic stability. In this study we used the method of impedance cardiography for real-time hemodynamic measurements.

Convective-based high-efficiency dialytic modalities including online HDF have been proposed as an alternative capable of relieving most intradialytic AEs and improving patient outcomes. HDF, used in various modes including POST-HDF, PRE-HDF, MIX-HDF, provides more effective removal of soluble middle molecular weight toxins and protein-bound compounds than conventional S-HD [4]. Other plausible biological mechanisms underlying potentially beneficial effects are: i/ better biocompatibility due to the combined use of biocompatible membranes and ultrapure/sterile fluids results in a reduction in systemic inflammatory response; ii/ favorable impact of HDF on intradialytic hypotensive episodes due to a higher sodium mass transfer and mode-specific thermal effects [24]. Large cohort studies, post-hoc analyzes of large randomized controlled trails, and a meta-analysis indicate that online HDF in the post-dilution mode receiving high convective volume exchange may result in patient mortality improvement [6]. Quite recently, CONVINCE trail provides the first convincing evidence that patients receiving high-volume HDF have improved survival compared with those receiving high-flux HD [7]. It appears to be a milestone that indicates the therapy of choice for patients treated with long-term dialysis [25]. However, the question of what therapy to offer patients with a potentially good prognosis or the prospect of transplantation remains unanswered.

Several previous studies investigating the influence of convection-based methods on intradialytic tolerance have yielded conflicting results. The FRENCHIE study compared high-flux HD and POST-HDF in terms of intradialytic tolerance in elderly chronic HD patients (over age 65) and reported a significantly differences between treatments with fewer episodes of intradialytic symptomatic hypotension and muscle cramps in POST-HDF [23]. Similar conclusions can be drawn from the results of the ESHOL trail [26]. However, in some studies, no improvement was observed in terms of intradialytic tolerance when switching therapy from S-HD to HDF *[19,27,28]* and some even indicate deterioration. For instance, in the cross-over study of Smith J. et al. POST- HDF was associated with an increased rate of symptomatic hypotension compared to S-HD (8.0% vs 5.3%) and intradialytic tendency to clotting (1.8% vs 0.7%) [12]. No significant improvement after changing treatment from high-flux HD to POST-HDF was also observed in some studies analyzing the quality of life *[29,30]*. The latter parameter is particularly difficult to objectify in patients with high co-morbidity index. Hence, we propose to study a group of patients that were eligible for kidney transplantation, relatively young and healthy. Such an approach, allowed us for excluding most factors that might influence AEs but the treatment modality (for example diabetic neuropathy, atherosclerosis, heart failure, or malnutrition).

To effectively perform high-volume POST-HDF, it is necessary to ensure high blood flow and good vascular access. It is also not a suitable method for patients with factors that increase blood viscosity (high hematocrit, cryoglobulinemia and gammopathies). PRE-HDF resolves this problem but requires about three times more replacement fluid than POST-HDF. This reduces the risks of clotting and protein deposition and allows much higher ultrafiltration rates up to 100% of the blood

flow rate which can be far lower than in POST-HDF [31]. The cooling effect of replacement solution in large volumes may help maintain hemodynamic stability as well [32]. Locatelli et al demonstrated 54% less intradialytic hypotension events in patients who were treated with PRE-HDF in comparison with a low-flux HD [33]. MIX HDF is the least frequently used in clinical practice, hence there is less tolerance studies on this method. In one of the few studies, symptomatic intradialytic hypotension episodes and other AEs occurred similarly in the MIX-HDF and PRE-HDF [34].

The use of impedance cardiography enabled us an indirect insight into cardiac output, blood viscosity and autonomic activity, as sympathetic stimulation constricts peripheral arteries and increases vascular resistance. In line with previous observations CI was decreasing while SVRI was increasing during all methods used [35]. Of note the CI AUC and SVRI AUC were not statistically different between all modalities which indicates similar hemodynamic stability during the tested treatments. However, in Figure 2 we may observe that curves of SVRI are following a different pattern in POST-HDF, MIX-HDF and HDx versus PRE-HDF and S-HD. It is interesting to analyze them further, as we controlled for fluid removal, hydration indices (Table 2) and CI (Figure2). Post-HDF SVRI, is expected to increase following the increasing viscosity. However, this should not be the case in MIX-HDF and HDx. Hence, we may hypothesize that the explanation can be found in sympathetic activity stimulation. Indeed, SBP curves in Figure 1 show distinct instability in MIX-HDF and HDx modalities. Unlike the previous studies, our patients are characterized by strong cardiovascular stability. Based on measured hemodynamic indices, we might expect a higher rate of patient reported AEs in MIX-HDF and HDx. On the contrary, there were no significant differences in the incidence of various complications during dialysis procedures, and it even seems that the study patients tolerated HDx treatment best (Table 3). Small observational studies indicate that HDx may result in better treatment tolerance than standard HD with less dialysis hypotension and reduction DRT *[36,37]*. Other studies indicate that HDx use may be effective in reducing symptoms of restless leg syndrome, dialysis pruritus and improve quality of life *[38,39]*. It may be that removing a wider range of toxins, including large middle toxins, accounts for some of these benefits [40]. HDx allows for diffusion and convection to be combined inside a hollow fiber dialyzer with reduced fiber internal diameter equipped with MCO membranes with wider pores. These modifications induce a convection even up to 12.7 l per a 4 h session and improve the clearance of medium to high molecular weight uremic toxins in the range of 5–50 kDa with marginal albumin loss while maintaining the simplicity of the procedure comparable to standard HD [2]. Compared to HDF, HDx does not increase trans-membrane pressure, thus providing minimal stress to the filter. At the opposite extreme are POST-HDF sessions, during which at least one side effect was observed in almost 42% of patients. The largest number of clotting events is noteworthy, which is fully understandable considering the highest degree of hemoconcentration in the dialyzer, increase the viscosity of the blood before fluid substitution, which results in deposition of plasma proteins on the membrane surface, clogging of membrane pores, increased transmembrane pressure, and occlusion of dialyzer blood channels [31]. There are no similar studies comparing all high-efficiency dialysis modalities in this regard. Individual small studies comparing PRE-HDF in relation to POST-HDF and HDx in relation to POST-HDF did not show any differences in terms of dialysis tolerance *[41–43]*. Importantly, taking into account parameters of hemodynamic stability (Figure 1 and Figure 2) POST-HDF should be favored over other methods, explaining the long term benefits of this method in CONVINCE study.

Yet another interesting patient outcome measure that we tracked in our study was the length of DRT. The length of DRT is a recent and reliable method of post-dialysis fatigue assessment, an important patient's-reported complaint that affects their quality of life and restricts the ability to perform their daily activities [44]. Davenport et al. found that the DRT ≥1 hour may be present in more than 75% of HD patients [45]. Most importantly, evidence from the DOPPS study has suggested an association between longer DRT and increased mortality [22]. So far, no convincing evidence has been obtained that dialysis methods based on convection i.e. HDF shortens the length of DRT *[45,46]*. There were also no differences in DRT and self-reported intradialytic symptoms with differing convection volume during HDF [47]. Our results indicate that PRE-HDF may contribute to shortening

post-dialysis fatigue more effectively than other compared therapies. This improvement concerned both an increase in the percentage of patients who reported a return to well-being immediately after the dialysis, as well as a shortening of DRT in those for whom it required a longer time (Table 4).

Our exploratory study is, to our knowledge, the first to compare all above-mentioned highly effective dialysis therapies. Although we recruited a highly homogenous group of patients and strictly controlled for different dialytic indices, one may not rule out that the significance of showed differences would be reached in a larger study sample. Such studies albeit needed, seems very difficult to execute without compromising the quality. Our study has several strengths: i/ the choice of crossover design was made in order to abrogate the influence of interpatient variability; ii/ a detailed analysis of the variability of hemodynamic parameters over time was performed; iii/ the patients' hydration status was measured and did not differ during individual treatments; iv/ basic dialysis parameters have been unified for all treatment modalities; v/ the high-volume nature of HDF, known to provide the best long-term prognosis was assured during study. On the other hand, we are aware of limitations of our study. We have only one woman in the study group, that may rise a question about its homogeneity, given the differences in the body composition. However, exclusion of female participants is a recognized problem in many nephrological studies and we decided against it [48]. We are convinced that crossover design of the study should mitigate such a bias. Another important limitation is the small size of the study group. This allows only exploratory conclusions to be drawn. This is the cost that should be paid when eligibility criteria are set to control for many confounders.

In conclusion, the study did not find any significant differences in intradialytic AEs and DRT between S-HD, PRE-HDF, MIX-HDF, POST-HDF and HDx. However, the study results may suggest that tolerance of dialysis session and postdialysis fatigue may vary in some patients when using different modalities. This strongly indicates the necessity of individualizing such therapy. In that population of patients S-HD performed similarly to the other high performance but more sophisticated method of HD. Therefore rather patients without the perspective of transplantation should be prioritized in applying other than S-HD high performance methods to allow them better life expectancy and possible acceptable life quality.

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