ACUTE INTHEMO STUDY

Acute Hemodynamic Effects and Uremic Toxin Removal in Conventional and Extended Hemodialysis and Hemodiafiltration

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ABSTRACT

Background: Intensive HD (short-daily HD and nocturnal HD) is associated with significant improvement of several clinical, biochemical and biological parameters. Potential explanations are the increased removal of uremic toxins or improved hemodynamic stability. The removal of uremic toxins can also be influenced by modality, also depending on molecular size and compartmental kinetics. Only one study so far has assessed the effect of extended HDF on uremic toxin removal, and none so far has compared this modality with extended HD.

Intervention: Thirteen stable conventional HD patients randomly completed a single study of 4-hour HD (HD4), 4-hour HDF (HDF4), 8-hour HD (HD8) and 8-hour HDF (HDF8), with a 2-week interval between the study sessions. Between the study sessions, the patients received routine conventional HD treatments.

Measurements: Blood pressure (BP) and heart rate (HR), Pulse Wave Analysis (PWA), cardiac output (CO), microvascular density by sublingual capillaroscopy, as well as relative blood volume (RBV) and thermal variables were measured. Clearance and removal of uremic toxins were also studied.

Results: Long treatments showed more stability of peripheral and central systolic and diastolic BP and CO, in line with decreased RBV slope in long dialysis. No differences in microvascular density were found. Energy transfer rates were comparable. Small molecule and phosphate removal were superior during long treatments. Beta2 microglobulin (B2M) and FGF23 reduction ratios were highest in HDF8.

Conclusion: Treatment time, and not modality was the determinant for the hemodynamic response. HDF significantly improved removal of middle molecules, with superior results in extended HDF.

METHODS

-Prevalent conventional HD patients: random order of mid-week HD4, HDF4, HD8, HDF8 with 2-week interval
-**Inclusion criteria**: no significant residual urine production, AVF allowing Qb=300 mL/min, informed consent, older than 18 years; **Exclusion** criteria: withdrawal of consent, acute illness
-Fresenius 5008 Therapy System, FX80 for HD, FX800 for HDF, Qb 300 mL/min, Qd 600 mL/min, Qs 83.3 mL/min, post-dilution HDF
-**Hemodynamic measurements** at start, and at times 30, 60, 120, 240, and (for HD8 and HDF8) 360 and 480 minutes. BP and HR: Task Force Monitor, RBV: Fresenius Blood Volume Monitor (BVM), sublingual microcirculation: Sidestream Dark Field, Glycocheck, PWA: Sphygmocor, CO: Transonic, Bioimpedance: Body Composition Monitor (BCM)
-**Thermal balance and energy expenditure**: Blood Temperature Monitor (BTM), calculates energy transfer (ET) rates in kJ/h
-**Blood / dialysate sampling and measurements**: blood at start, and at times 15, 30, 60, 10, 240, and (for HD8 and HDF8) 360 and 480 minutes; dialysate at the end from collection bag. Urea, creatinine, uric acid and phosphorus: Cobas 6000); B2M: Immulite 2000; FGF23: Immutopics
-**Calculations**:
*_Reduction Ratio_ (RR) = 1 – [post-dialysis/pre-dialysis concentration]
*_Total Solute Removal_ (TSR) = dialysate concentration X [Vd+Vuf+Vs]
*_Dialytic Clearance_ (CI)= TSR / log [mean pre- and post-dialysis concentration]
*Correction for hemoconcentration for B2M and FGF23
-**Statistical analysis**: data in mean±SD, repeated measurements ANOVA and paired t-tests, changes in hemodynamic parameters are expressed as slope of regression line multiplied by treatment time

RESULTS

Pretreatment Hemodynamic Indices - Serum Levels

	HD4	HDF4	HD8	HDF8
Peripheral SBP (mm Hg)	142.8 ± 19.5	138.6 ± 26.2	145.4 ± 28.7	137.9 ± 26.0
Peripheral DBP (mm Hg)	77.5 ± 16.0	81.5 ± 17.0	75.8 ± 18.2	73.4 ± 19.6
Central SBP (mm Hg)	129.3 ± 18.5	127.1 ± 21.4	128.8 ± 27.9	124.5 ± 28.0
Central DBP (mm Hg)	80.2 ± 16.2	83.9 ± 18.2	77.9 ± 18.6	74.8 ± 21.0
Heart rate (beats/min)	73.5 ± 8.6	73.2 ± 10.2	75.1 ± 4.8	71.5 ± 9.3
Cardiac output (L/min)	6.35 ± 1.92	6.50 ± 1.53	6.35 ± 1.25	6.28 ± 2.07
$Weight_{pre-post}$ (kg)	1.17 ± 0.66	1.53 ± 1.29	1.31 ± 0.78	1.10 ± 0.55
$(OH_{pre} + OH_{post})/2$ (L)	0.90 ± 1.18	0.68 ± 1.41	0.48 ± 1.41	0.04 ± 1.20
Serum urea (mg/dL)	112.8 ± 24.6	115.2 ± 19.8	114.6 ± 24.0	114.0 ± 22.8
Serum creatinine (mg/dL)	10.2 ± 3.3	10.4 ± 2.8	10.2 ± 3.1	10.4 ± 2.9
Uric acid (mg/dL)	6.0 ± 1.0	6.2 ± 0.8	5.9 ± 0.7	6.2 ± 0.5
Phosphorus (mg/dL)	4.5 ± 1.6	4.9 ± 1.9	5.0 ± 1.8	4.9 ± 1.6
B2M (mg/L)	21.0 ± 4.9	23.7 ± 4	22.4 ± 6.4	24.4 ± 6.1[a,b]
FGF-23 (RU/mL)	779 [404-4,203]	914 [488-3,958]	908 [436-4,307]	1,019 [545-6,606]

Note: Values are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: creatinine in mg/dL to µmol/L, X88.4; uric acid in mg/dL to µmol/L, X59.48; serum urea in mg/dL to mmol/L, X0.357; serum phosphorus in mg/dL to mmol/L, X0.3229.

Abbreviations and definitions: B2M, β_2-microglobulin; DBP, diastolic blood pressure; FGF-23, fibroblast growth factor 23; HD4, 4-hour hemodialysis; HD8, 8-hour hemodialysis; HDF4, 4-hour hemodiafiltration; HDF8, 8-hour hemodiafiltration; OH_{pre} and OH_{post}, overhydration pre- and postdialysis as assessed by bioimpedance; SBP, systolic blood pressure; $Weight_{pre-post}$, difference of the pre- and postdialysis weight.

[a]$P < 0.05$ versus HD4.
[b]$P < 0.05$ versus HD8.

Treatment Characteristics

Parameter	HD4	HDF4	HD8	HDF8
Effective dialysis time (min)	246 ± 4	245 ± 3	486 ± 2[a,b]	487 ± 6[a,b]
Blood volume (L)	67.9 ± 1.6	68.5 ± 1.1	134.9 ± 2.0[a,b]	135.3 ± 1.5[a,b]
Blood flow (mL/min)	283 ± 7	286 ± 5	287 ± 4	288 ± 3
Dialysate flow (mL/min)	569 ± 24	578 ± 7	576 ± 8	572 ± 11
Total ultrafiltration (L)	1.98 ± 0.76	1.77 ± 0.63	2.31 ± 0.82	2.21 ± 0.81
Ultrafiltration rate (mL/h)	500 ± 193	449 ± 160	295 ± 111[a,b]	265 ± 83[a,b]
Substitution volume (L)	—	14.6 ± 1.1	—	29.7 ± 0.4[b]
Dialysate sodium (mmol/L)	137.2 ± 1.4	137.2 ± 1.4	136.9 ± 1.6	137.2 ± 1.1
Dialysate temperature (°C)	35.9 ± 0.4	35.9 ± 0.4	35.8 ± 0.4	36.0 ± 0.4
Single-pool Kt/V	1.49 ± 0.21	1.60 ± 0.30	3.30 ± 0.54[a,b]	3.34 ± 1.05[a,b]
Equilibrated Kt/V	1.36 ± 0.26	1.41 ± 0.26	3.09 ± 0.51[a,b]	3.14 ± 0.99[a,b]

Note: Values are given as mean ± standard deviation.
Abbreviations: HD4, 4-hour hemodialysis; HD8, 8-hour hemodialysis; HDF4, 4-hour hemodiafiltration; HDF8, 8-hour hemodiafiltration.
[a]$P < 0.05$ versus HD4.
[b]$P < 0.05$ versus HDF4.

Total Solute Removal and Dialytic Clearance

	Urea (60 Da)	Cr (113 Da)	Uric Acid (168 Da)	P (95 Da)	B2M (11.8 kDa)
Total solute removal					
HD4	31.8 ± 10.8	2.2 ± 0.9	1.0 ± 0.2	875 ± 262	99.5 ± 39.3
HDF4	31.8 ± 8.3	2.3 ± 0.8	1.1 ± 0.2	932 ± 264	135.0 ± 49.4[a]
HD8	42.5 ± 12.6[a,b]	3.1 ± 1.1[a,b]	1.4 ± 0.4[a,b]	1,408 ± 295[a,b]	143.3 ± 49.6[a]
HDF8	42.0 ± 13.9[a,b]	3.4 ± 1.3[a,b]	1.3 ± 0.4	1,490 ± 283[a,b]	188.6 ± 60.2[a,b,c]
Dialytic clearance					
HD4	214.0 ± 24.3	147.0 ± 19.8	145.9 ± 22.3	108.0 ± 18.1	31.4 ± 11.9
HDF4	222.8 ± 28.9	153.9 ± 22.0	156.7 ± 38.0	110.1 ± 10.3	48.9 ± 11.7[a]
HD8	242.6 ± 36.8	146.2 ± 2.5	147.9 ± 40.7	99.5 ± 17.8	28.5 ± 8.2[b]
HDF8	229.5 ± 28.0	144.1 ± 17.9	131.7 ± 26.6	102.9 ± 13.2	40.9 ± 7.8[a,c]

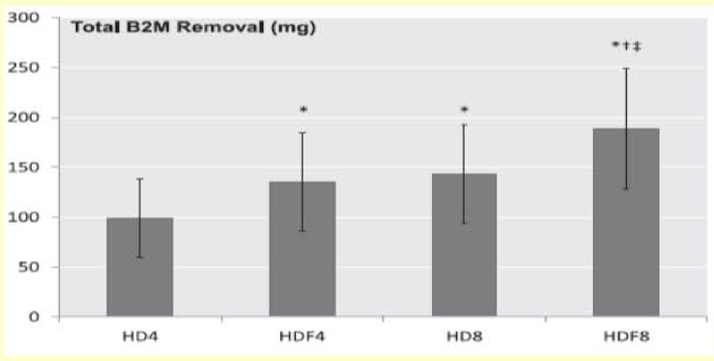
Note: Values are given as mean ± standard deviation. Total solute removal for urea, Cr, and uric acid expressed in grams, and for P and B2M, expressed in milligrams; dialytic clearance expressed in milliliters per minute.
Abbreviations: B2M, β_2-microglobulin; Cr, creatinine; HD4, 4-hour hemodialysis; HD8, 8-hour hemodialysis; HDF4, 4-hour hemodiafiltration; HDF8, 8-hour hemodiafiltration; P, phosphorus.
[a]$P < 0.05$ versus HD4.
[b]$P < 0.05$ versus HDF4.
[c]$P < 0.05$ versus HD8.

Δ Hemodynamic Parameters and Thermal Balance

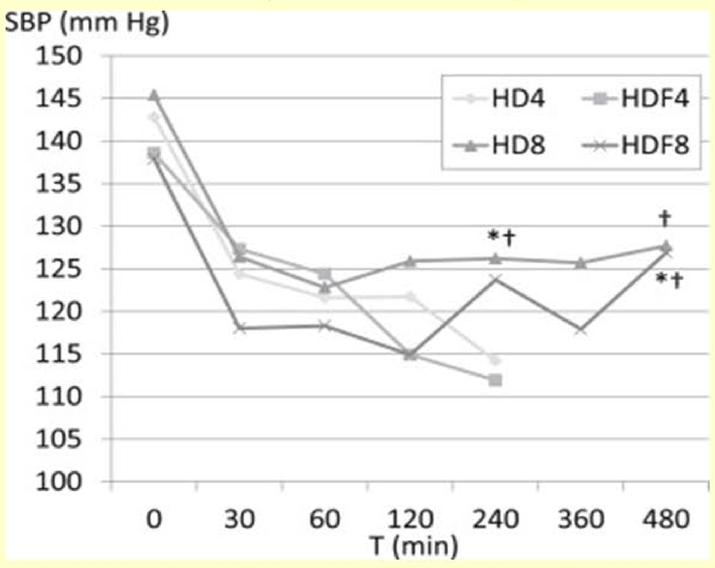
Parameter	HD4	HDF4	HD8	HDF8
Peripheral SBP (mm Hg)	21.7 ± 15.6	23.3 ± 20.8	6.7 ± 15.2[a]	0.5 ± 14.4[a,b]
Peripheral DBP (mm Hg)	5.0 ± 10.2	11.5 ± 12.9	1.1 ± 7.2[b]	1.2 ± 10.1[b]
Central SBP (mm Hg)	19.2 ± 19.8	24.2 ± 14.8	7.1 ± 11.3	3.8 ± 14.4[b]
Central DBP (mm Hg)	5.0 ± 11.6	12.1 ± 13.1[a]	2.6 ± 5.3	+3.5 ± 8.6[b]
Heart rate (beats/min)	1.0 ± 7.9	0.9 ± 10.6	0.7 ± 11.9	+0.9 ± 8.3
Cardiac output (L/min)	1.4 ± 1.5	1.6 ± 1.0	0.4 ± 0.9[b]	0.5 ± 0.8[b]
RBV (%)	8.1 ± 5.4	9.1 ± 5.4	4.4 ± 6.5[b]	3.3 ± 4.7[a,b]
Total ET (kJ)	191.2 ± 68.5	230.3 ± 79.8[a]	410.0 ± 170.4[a,b]	413.3 ± 122.9[a,b]
ET rate (W)	13.3 ± 4.7	16.2 ± 5.6	14.2 ± 6.0	14.5 ± 4.3

Note: Values are given as mean ± standard deviation.
Abbreviations: DBP, diastolic blood pressure; ET, energy transfer; HD4, 4-hour hemodialysis; HD8, 8-hour hemodialysis; HDF4, 4-hour hemodiafiltration; HDF8, 8-hour hemodiafiltration; RBV, relative blood volume; SBP, systolic blood pressure.
[a]$P < 0.05$ versus HD4.
[b]$P < 0.05$ versus HDF4.

Total B2M Removal

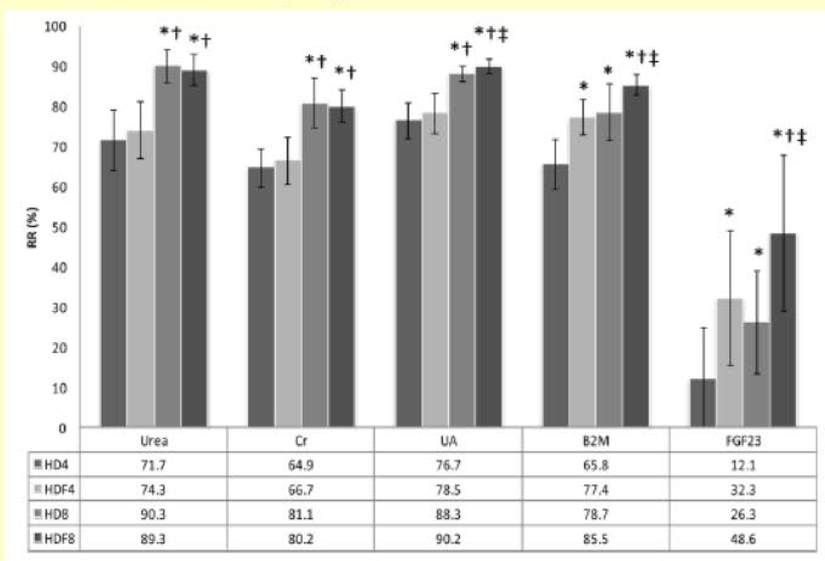


Mean Peripheral Systolic BP at Resp. Time Points



* P <0.05 versus HD4; † P <0.05 versus HDF4; ‡ P <0.05 versus HD8

Reduction Ratios (RR)



	Urea	Cr	UA	B2M	FGF23
HD4	71.7	64.9	76.7	65.8	12.1
HDF4	74.3	66.7	78.5	77.4	32.3
HD8	90.3	81.1	88.3	78.7	26.3
HDF8	89.3	80.2	90.2	85.5	48.6

CONCLUSIONS

-Treatment time, and not modality, was the determinant for the hemodynamic response (under circumstances of comparable thermal control)
-HDF significantly improved removal of middle molecules, with superior results in extended HDF
-More studies are required to assess the potential long-term benefits of nocturnal HDF

-Limitations: small sample size, only acute effects were studied, low ultrafiltration and substitution volumes
-Strengths: randomized crossover study, hemodynamic effects were assessed under controlled conditions with multiple measurements, direct dialysate quantification

51ERA-EDTA
427-SP
M) Dialysis. M1) Extracorporeal dialysis: techniques and adequacy.
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