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Original Investigation

Acute Hemodynamic Response and Uremic Toxin Removal in Conventional and Extended Hemodialysis and Hemodiafiltration: A Randomized Crossover Study

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Background: Intensive hemodialysis (HD) may have significant benefits. Recently, the role of extended hemodiafiltration (HDF) has gained interest. The aim of this study was to evaluate the acute effects of extended HD and HDF on hemodynamic response and solute removal.

Study Design: Randomized crossover trial.

Settings & Participants: Stable patients with end-stage renal disease undergoing conventional HD.

Intervention: 13 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 study sessions. Between study sessions, patients received routine conventional HD treatments.

Outcomes: Acute hemodynamic effects and uremic toxin clearance.

Measurements: Blood pressure and heart rate, pulse wave analysis, cardiac output, and microvascular density by sublingual capillaroscopy, as well as relative blood volume and thermal variables, were measured. Clearance and removal of uremic toxins also were studied.

Results: Long treatments showed more stability of peripheral systolic blood pressure (change during HD4, -21.7 ± 15.6 mm Hg; during HDF4, -23.3 ± 20.8 mm Hg; during HD8, -6.7 ± 15.2 mm Hg [$P = 0.04$ vs HD4; $P = 0.08$ vs HDF4]; and during HDF8, -0.5 ± 14.4 mm Hg [$P = 0.004$ vs HD4; $P = 0.008$ vs HDF4]). A similar observation was found for peripheral diastolic and central blood pressures. Cardiac output remained more stable in extended sessions (change during HD4, -1.4 ± 1.5 L/min; during HDF4, -1.6 ± 1.0 L/min; during HD8, -0.4 ± 0.9 L/min [$P = 0.02$ vs HDF4]; and during HDF8, -0.5 ± 0.8 L/min [$P = 0.06$ vs HD4; $P = 0.03$ vs HDF4), in line with the decreased relative blood volume slope in long dialysis. No differences in microvascular density were found. Energy transfer rates were comparable (HD4, 13.3 ± 4.7 W; HDF4, 16.2 ± 5.6 W; HD8, 14.2 ± 6.0 W; and HDF8, 14.5 ± 4.3 W). Small-molecule and phosphate removal were superior during long treatments. β_2-Microglobulin and fibroblast growth factor 23 (FGF-23) reduction ratios were highest in HDF8.

Limitations: Small sample size, only acute effects were studied.

Conclusions: 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.

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INDEX WORDS: Hemodialysis (HD); hemodiafiltration (HDF); intensive; extended; hemodynamic analysis; hemodynamic stability; HD/HDF session duration; uremic toxin; end stage-renal disease (ESRD).

Intensive hemodialysis (HD; comprising short-daily HD, in-center nocturnal HD, and nocturnal home HD) is associated with significant improvements in several clinical, biochemical, and biological parameters.[1] A potential explanation for these observed results is the increased removal of uremic toxins due to the increased duration and/or frequency of HD.[2-7]

Long HD also results in better hemodynamic stability, likely due to more physiologic fluid removal.[8,9] It may reduce myocardial stunning, which is associated with cardiovascular morbidity and mortality.[10-13] Furthermore, beneficial effects of long HD on the autonomic nervous system might be involved.[14]

There is evidence that hemodiafiltration (HDF) has advantageous effects on hemodynamic stability.[15,16] This may be due to autonomous nervous system protection by HDF.[17] Online HDF also may provide an additional extracorporeal cooling effect by thermal

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energy loss.[18,19] However, it still is not proved that HDF provides hemodynamic benefits if extracorporeal energy balance is comparable.[19,20] Also, the effects of modality versus time have not been compared directly using detailed hemodynamic measurements.

The removal of uremic toxins also can be influenced by modality, also depending on molecular size and compartmental kinetics.[2] Studies have shown optimized β_2-microglobulin (B2M) and fibroblast growth factor 23 (FGF-23) clearance with HDF.[21-23] However, to our knowledge, only one study to date has assessed the effect of extended HDF on uremic toxin removal,[22] and none has compared this modality with extended HD.

The aims of the present study were first, to perform a detailed hemodynamic analysis comparing conventional and extended high-flux HD and HDF, and second, to compare the effects of these modalities on the removal of selected uremic toxins.

METHODS

Study Design

Prevalent conventional HD patients underwent, in random order (consecutive blind selection of 1 of the 24 closed envelopes, each enclosing 1 of the 24 possible study orders), a midweek 4-hour HD (HD4) session, a midweek 4-hour online HDF (HDF4) session, a midweek 8-hour HD (HD8) session, and a midweek 8-hour online HDF (HDF8) session with a 2-week interval between study sessions. Between study sessions, these patients received routine conventional HD treatments.

Patients were recruited from the prevalent conventional HD population of the Maastricht University Medical Centre. Inclusion criteria were as follows: prevalent conventional HD patients without significant residual urine production, arteriovenous fistula enabling double-needle vascular access with blood flow rate of 300 mL/min, written informed consent, and age 18 years or older. Exclusion criteria were withdrawal of consent and any acute illness such as infection or cardiovascular event.

All treatments were performed with the Fresenius 5008 Therapy System (Fresenius Medical Care). FX80 dialyzers (Fresenius) were used for HD, and FX800 dialyzers (Fresenius) were used for HDF. Blood flow was 300 mL/min and dialysate flow was 600 mL/min in all study sessions. Substitution flow was 83.3 mL/min to achieve a total substitution volume of 15 L for HDF4 and 30 L for HDF8. Online HDF was performed in postdilution mode. Dialysate composition was as follows: calcium, 1.5 mmol/L; potassium, 2 mmol/L; sodium, 136-138 mmol/L; and bicarbonate, 35-38 mmol/L. Dialysate temperature varied among patients from 35.5°C-36.5°C. Dialysate composition and temperature were unchanged during the study period. Potassium supplementation was provided if necessary. Total ultrafiltration volume was calculated based on target weight and intake during dialysis. Target weight was set on the basis of clinical assessment of volume status in combination with bioimpedance results.

This study was approved by the local ethics committee at the Maastricht University Medical Centre under number NL34908.068.10/MEC10-2-098.

Hemodynamic Measurements

All measurements were performed before the start of the study session and subsequently at 30, 60, 120, and 240 minutes. In the 8-hour sessions, a measurement also was done at 360 and 480 minutes. Intermittent blood pressure (BP) and heart rate were measured with the Task Force Monitor (CNSystems).[24] Relative blood volume (RBV) was monitored continuously with the Fresenius Blood Volume Monitor system (Fresenius Medical Care).[25] Sublingual microcirculation assessing microvascular density and red blood cell filling percentage was measured with the Sidestream Dark Field camera (MicroVision Medical Inc) and GlycoCheck software (GlycoCheck BV)[26]; further detail is available in Item S1 (provided as online supplementary material). Pulse wave analysis, including central systolic and diastolic BP, augmentation index, subendocardial viability ratio, and ejection duration, was measured with the SphygmoCor system (AtCor Medical).[27,28] Cardiac output was measured with the Transonic system (Transonic Systems).[24,29] Bioimpedance was performed with the Body Composition Monitor (Fresenius Medical Care) to assess pre- and postdialysis overhydration.[30,31] Detailed methods regarding use of the SphygmoCor, Body Composition Monitor, and Transonic system are available in Item S1.

Thermal Balance and Energy Expenditure

Venous and arterial blood temperatures were measured continuously with the Blood Temperature Monitor system (Fresenius Medical Care).[32] The blood temperature monitor calculates extracorporeal arteriovenous temperature gradients (ΔT_{av}) and energy transfer rates. Energy transfer (in kilojoules per hour) is calculated using the following formula: $c \times p \times Q_b \times (T_{art} - T_{ven})$, where c is the specific thermal capacity (3.64 kJ/kg), p is density of the blood (1,052 kg/m^3), Q_b is extracorporeal blood flow, T_{art} is arterial temperature, and T_{ven} is venous temperature. Further information is available in Item S1.

Blood and Dialysate Sampling and Measurements

Serum samples were obtained from the inlet blood lines immediately before the onset of dialysis and at 15, 30, 60, 120, and 240 minutes during the 4- and 8-hour sessions. Additional samples were taken at 360 and 480 minutes during the long sessions. Samples were always obtained after decreasing the blood flow to 50 mL/min for at least 1 minute. A mixture of dialysate and ultrafiltrate was collected continuously in a fractionated fashion in a bag. At the end of the treatment and after thorough mixing, a 10-mL sample was drawn from the collection bag in order to quantify solute concentration. All samples were stored at −80°C until analysis.

Urea, creatinine, uric acid, and phosphorus were measured using routine assays on a cobas 6000 analyzer (Roche Diagnostics). B2M was detected in serum and dialysate using a 2-site chemoluminescent immunometric assay (Immulite 2000 System; Diagnostic Products Corp). Carboxy-terminal FGF-23 was measured in stored serum samples using a 2-site second-generation enzyme-linked immunosorbent assay kit (Immutopics), with antibodies directed against 2 epitopes within the carboxy-terminal region of the FGF-23 molecule (further information available in Item S1).

Calculations

Total solute removal was calculated by multiplying the dialysate concentration of the solute by the sum of dialysate volume, ultrafiltration volume, and (in the HDF sessions) substitution volume. Dialytic clearances were calculated as total solute removal divided by dialysis duration and by the log mean of the pre- and postdialysis blood concentrations of the solute. Reduction ratio (RR) of solutes was defined as a function of predialysis (C_{pre}) and postdialysis (C_{post}) concentration ($RR = [1 - (C_{post}/C_{pre})] \times 100$). For B2M and FGF-23, concentration at the dialysis end (C_{post}) was corrected for hemoconcentration based on total protein concentration at start versus end of the dialysis session.