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**RESEARCH ARTICLE**

# Effect of isolated ultrafiltration and isovolemic dialysis on myocardial perfusion and left ventricular function assessed with $^{13}$N-$NH_3$ positron emission tomography and echocardiography

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**Assa S, Kuipers J, Ettema E, Gaillard CA, Krijnen WP, Hummel YM, Voors AA, van Melle JP, Westerhuis R, Willemsen A, Slart RH, Franssen CF.** Effect of isolated ultrafiltration and isovolemic dialysis on myocardial perfusion and left ventricular function assessed with $^{13}$N-$NH_3$ positron emission tomography and echocardiography. *Am J Physiol Renal Physiol* 314: F445–F452, 2018. First published November 8, 2017; doi:10.1152/ajprenal.00368.2017.—Hemodialysis is associated with a fall in myocardial perfusion and may induce regional left ventricular (LV) systolic dysfunction. The pathophysiology of this entity is incompletely understood, and the contribution of ultrafiltration and diffusive dialysis has not been studied. We investigated the effect of isolated ultrafiltration and isovolemic dialysis on myocardial perfusion and LV function. Eight patients (7 male, aged 55 ± 18 yr) underwent 60 min of isolated ultrafiltration and 60 min of isovolemic dialysis in randomized order. Myocardial perfusion was assessed by $^{13}$N-$NH_3$ positron emission tomography before and at the end of treatment. LV systolic function was assessed by echocardiography. Regional LV systolic dysfunction was defined as an increase in wall motion score in ≥2 segments. Isolated ultrafiltration (ultrafiltration rate 13.6 ± 3.9 ml·kg$^{-1}$·h$^{-1}$) induced hypovolemia, whereas isovolemic dialysis did not (blood volume change −6.4 ± 2.2 vs. +1.3 ± 3.6%). Courses of blood pressure, heart rate, and tympanic temperature were comparable for both treatments. Global and regional myocardial perfusion did not change significantly during either isolated ultrafiltration or isovolemic dialysis and did not differ between treatments. LV ejection fraction and the wall motion score index did not change significantly during either treatment. Regional LV systolic dysfunction developed in one patient during isolated ultrafiltration and in three patients during isovolemic dialysis. In conclusion, global and regional myocardial perfusion was not compromised by 60 min of isolated ultrafiltration or isovolemic dialysis. Regional LV systolic dysfunction developed during isolated ultrafiltration and isovolemic dialysis, suggesting that, besides hypovolemia, dialysis-associated factors may be involved in the pathogenesis of hemodialysis-induced regional LV dysfunction.

hemodialysis; ultrafiltration; cardiac stunning; myocardial perfusion

## INTRODUCTION

Although hemodialysis (HD) is life-saving by replacement of renal function, there is increasing evidence that the HD procedure itself contributes to the high cardiac risk of dialysis patients (1, 6, 7, 10, 23, 26, 27, 33). Using intradialytic positron emission tomography (PET), we and others showed that conventional HD elicits acute reductions in myocardial blood flow (MBF) (10, 23). A proportion of patients in these studies developed regional left ventricular (LV) systolic dysfunction, suggestive of myocardial ischemia (10, 23). Using intradialytic cardiac magnetic resonance imaging, Buchanan et al. (7) recently confirmed these findings by showing that global MBF decreased significantly during HD and that all 12 patients developed some degree of regional LV systolic dysfunction. Echocardiography studies in larger patient cohorts have shown that HD-induced regional LV systolic dysfunction has a prevalence ranging between 23% and 63% (3, 8, 12). These studies also showed that the occurrence of HD-induced LV systolic dysfunction is associated with a greater incidence of all-cause mortality (3, 8) and a faster decline in LV ejection fraction over time (8).

The pathogenesis of HD-induced LV systolic dysfunction is incompletely understood. Most attention has, thus far, been given to the role of ultrafiltration-induced hypovolemia and the fall in blood pressure that may compromise myocardial perfusion. Burton et al. (8) found that higher ultrafiltration (UF) volumes and greater intradialytic reductions in systolic blood pressure were risk factors for the development of HD-induced regional LV systolic dysfunction. In two other studies, however, the UF volume, UF rate, and the change in blood volume did not differ significantly between patients who did and those who did not develop HD-induced LV systolic dysfunction (3, 12). We previously found that regional LV systolic dysfunction developed already within 60 min after the start of HD before significant UF (3). Buchanan et al. (7) also observed regional

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LV systolic dysfunction as early as 70 min from the start of HD. These findings suggest that besides UF-induced hypovolemia, other factors may have a role in the pathophysiology of HD-induced regional LV systolic dysfunction. Such dialysis-related factors could include intradialytic changes in plasma electrolyte concentrations (16, 29, 31), changes in acid base balance (2, 5), or bioincompatibility reactions (4, 13, 15, 18, 22, 24, 34, 35) that may all affect the cardiac contractile function. To assess the contribution of UF and diffusive dialysis to the development of HD-induced regional LV systolic dysfunction, we investigated the effect of isolated ultrafiltration (UF-only) and isovolemic diffusive dialysis (dialysis-only) on myocardial perfusion and LV function in eight patients.

## MATERIALS AND METHODS

*Patients.* Eligible for this study were adult (aged ≥18 yr) patients from the Dialysis Center Groningen and the University Medical Center Groningen (UMCG) who were treated with HD for >3 mo, were on a thrice weekly schedule, and had an arteriovenous fistula without recirculation at routine transonic flow measurements. Exclusion criteria were the inability to get echocardiographic windows of adequate quality, LV ejection fraction ≤30%, cardiac rhythm other than sinus rhythm, artificial heart valve, implantable cardioverter defibrillator, recent (<3 mo) cardiovascular event, use of long-acting nitrates, use of β-blockers for angina pectoris, recent hemorrhage, and (suspicion of) pregnancy.

*Study protocol.* The study was performed according to the Declaration of Helsinki and was approved by the Medical Ethical Committee of the University Medical Center Groningen. All patients gave written informed consent.

Each patient underwent two study sessions: UF-only and dialysis-only. The order was randomized using sealed envelopes. All studies took place after the longest interdialytic interval (Monday or Tuesday) and were carried out at the Department of Nuclear Medicine and Molecular Imaging. The ambient temperature of the PET scan room was kept constant at 20°C, excluding an effect of outside temperature on cardiovascular stability during study sessions. Patients were asked to refrain from smoking, alcoholic beverages, and caffeine starting from the evening before the study until completion of the study sessions.

At arrival at the PET center, the patient was placed in a supine position. Next, the arteriovenous access was punctured with two needles, and an intravenous indwelling catheter was placed in the nondialysis access arm. During treatment with UF-only or dialysis-only, patients were in a supine position and were not allowed to eat to avoid possible influences of posture and food intake on blood volume and hemodynamic stability (9).

At each study session, patients underwent two gated $^{13}$N-NH$_3$ PET scans: before and at the end of treatment. Each PET scan lasted 20 min. Data collection for the second PET scan was completed after 60 min of treatment. The second PET scan is referred to as the 60-min scan, although data collection started 20 min preceding this time point. $^{13}$N-NH$_3$ was administered intravenously at a constant rate through an indwelling catheter in the nondialysis access arm. At each study session, two echocardiography studies were performed: just before the first PET scan and immediately after completion of the second PET scan. Echocardiographic image acquisition took ~10 min. The images were digitally stored for offline analysis.

Blood sampling (from the arterial line) for hematocrit, electrolytes, acid-base parameters, cardiac troponin T and I, and inflammatory and endothelial function parameters was performed just before and at the end (60 min) of the study sessions. The volume of blood drawn was 35 ml/session. The relative blood volume change was calculated from the change in hematocrit (9). Blood pressure and heart rate were measured immediately before and after each PET scan using an automated oscillometric monitor and averaged for pretreatment and 60-min treatment values. UF rate was calculated by dividing the cumulative UF volume at 60 min by session length (60 min) and target body weight.

The primary study parameter was the change in global MBF as assessed by PET scan. Secondary study parameters were the change in global and regional LV function assessed by echocardiography.

*Settings for UF-only and dialysis-only.* Both study sessions were performed with an AK 200 (Gambro-Hospal, Lund, Sweden) using a low-flux polysulfone hollow-fiber dialyzer (F8, Fresenius Medical Care, Bad Homburg, Germany).

UF-only was performed at a rate of 1 l/h, 1.5 l/h, and 2 l/h in patients with an excess weight at the start of the study session of 1–3 kg, 3–4 kg, and >4 kg, respectively. The rationale behind using higher UF rates with increasing excess weight is that the more overhydrated the patient is, the less pronounced will be the relative blood volume decrease per unit of ultrafiltered fluid (9). Excess weight was calculated as the difference between pretreatment weight and target weight. Blood flow was 250 ml/min. During UF-only, there was no dialysate flow. Since UF-only is associated with a fall in body temperature that may affect the cardiovascular response (20, 30), bloodlines were isolated and warmed using a bloodline heater. We aimed at similar courses of body temperature during UF-only and dialysis-only. At the start of UF-only, the temperature of the bloodline heater was set at 37°C. In preliminary studies, this setting resulted in a stable course of body temperature during UF-only over a period of 60 min that was comparable to the temperature course during regular HD with a dialysate temperature of 36.0°C (data not shown). The temperature of the heating device was lowered to 36.5°C if tympanic temperature increased by >0.5°C at 30 min or increased to 37.5°C if tympanic temperature decreased by >0.5°C at 30 min of UF-only.

Dialysis-only was performed with a net zero fluid balance. To this end, the extracorporeal circuit was filled with NaCl 0.9% before connection to the patient, and UF rates were set at zero. Blood and dialysate flow rates were 250 and 500 ml/min, respectively. Dialysate composition was sodium (139 mmol/l), potassium (1 or 2 mmol/l) depending on the prevailing predialysis potassium concentration, calcium (1.5 mmol/l), magnesium (0.5 mmol/l), chloride (108 mmol/l), bicarbonate (32 mmol/l), acetate (3 mmol/l), and glucose (1.0 g/l). Dialysate temperature was 36.0°C.

*$^{13}$N-NH$_3$ study, data acquisition, and data analysis.* PET imaging was performed on an ECAT EXACT HR+ PET scanner (Siemens/CTI, Knoxville, TN). Data acquisition and data analysis are detailed in Ref. 10. First, a transmission scan (using $^{68}$Ge/$^{68}$Ga rod sources) was performed, followed by an injection of 400 MBq of $^{13}$N-NH$_3$ intravenously. Dynamic data of $^{13}$N-NH$_3$ were acquired over 20 min, with the last 10 min acquired in gated mode with 16 frames/cardiac cycle. The length of each gate was based on the current RR-interval, which was allowed to vary 10%. Data were corrected for attenuation using the transmission scan and reconstructed using filtered back-projection (Hann filter: 0.5 pixels/cycle). A fit-procedure using the three-compartment model, described by Hutchins et al. (19), was performed, and absolute MBF was calculated. MATLAB was used for reorientation of the data into 12 short-axis slices of the $^{13}$N-NH$_3$ studies. Using a parametric polar map program, we reconstructed polar maps for baseline and T60 $^{13}$N-NH$_3$ MBF. Polar maps were divided into 17 segments (17). Segmental values of $^{13}$N-NH$_3$ MBF were expressed in ml·min$^{-1}$·100 g$^{-1}$. Gating data from the $^{13}$N-NH$_3$ studies were reorientated to short-axis, horizontal, and vertical long-axis sections. Gating data of $^{13}$N-NH$_3$ were analyzed quantitatively using the automatic quantitative gated SPECT (QGS) program (version 3; Cedars-Sinai Medical Center, Los Angeles, CA), a commercially (Siemens Medical Systems, Hoffman Estates, IL) available cardiac software package (14, 21). This program automatically detects the contours of the endocardium of the LV. Left ventricular end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and

LV ejection fraction (LVEF) are calculated with QGS. Results for global MBF are presented as the mean of the 17 LV segments. Perfusion of the 17 segments was further analyzed with the corresponding coronary regions LAD, RCA, and Cx, as described previously (25).

*Echocardiography.* Two experienced technicians performed two-dimensional echocardiography using a General Electric VIVID 7 system with a 2.5-mHz probe. Global and regional systolic function was evaluated by LV ejection fraction (LVEF) and wall motion score index (WMSI), respectively. LVEF was calculated using the biplane Simpson's method. WMSI was evaluated according to the 18-segment model by a single technician (Y. M. Hummel), who was blinded to treatment modality. The 18-segment model was chosen to align per segment wall motion score (WMS) with per-segment longitudinal strain measurements (see above). The number of LV regions that developed new (not present before treatment) regional wall motion abnormalities (RWMA) during HD was calculated. RWMA was defined as an increase in WMS in that specific LV segment at 60 min compared with pretreatment. HD-induced LV systolic dysfunction was defined as the development of new RWMA in two or more LV segments compared with pretreatment. LV mass index was calculated as described previously (11).

LV strain analysis was performed using 2d Speckle tracking (2d STE) and commercially available software (GE, EchoPac, Horten, Norway). Regions of interest (endocardial borders excluding papillary muscles) were traced for each image at the end-systolic frame. Segmental values of LV longitudinal myocardial strain were reported. Speckle patterns on a frame-by-frame basis were tracked using the EchoPAC tracking algorithm. Three consecutive heartbeats were analyzed for each image, and peak longitudinal systolic strain was measured for each of 18 LV segments: basal-inferior, basal-lateral, basal-septal, basal-anterior, basal posterior, basal-anteroseptal, mid-inferior, mid-lateral, mid-septal, mid-anterior, mid-posterior, mid-anteroseptal, apical-inferior, apical-lateral, apical-septal, apical-anterior, apical-posterior, and apical-anteroseptal.

*Statistical analysis.* Normal distributed data are presented as means ± SD, and skewed data are presented as median (interquartile range). Changes in parameters during treatment within treatment groups and differences in pretreatment parameters between UF-only and dialysis-only were compared with the paired Student's *t*-test. Linear mixed models were used to analyze differences in the course of parameters between UF-only and dialysis-only. For each of the response (dependent) variables, fixed effects were estimated for UF-only and dialysis-only, and for time and random intercepts for patients. For the comparison of the effect of UF-only vs. dialysis-only on the change in regional perfusion during treatment, the 17 perfusion segments were treated as within-patient effects.

All data were analyzed using SPSS version 20 (SPSS, IBM, Chicago, IL) and GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA), R version 3.4.0 (R Core Team (2017). Two-sided $P < 0.05$ values were considered statistically significant.

## RESULTS

*Patients.* Eight HD patients participated in the study. The patient characteristics are shown in Table 1. Seven patients were male. The mean age was 54.5 ± 16.7 yr, and the mean time on dialysis was 17.9 ± 12.0 mo. Mean BMI was 25.9 ± 3.9 kg/m$^2$. Average predialysis hemoglobin and albumin levels were 7.4 ± 0.8 mmol/l and 41.9 ± 2.1 g/l, respectively. None of the patients had diabetes. The cardiovascular history was unremarkable, except for hypertension in four patients. These four patients used cardiovascular medication: angiotensin-receptor blockers and/or calcium antagonist taken after HD for the indication hypertension (Table 1). None of the patients used a β-blocker.

*Treatment data and laboratory parameters.* In all but one patient, the UF rate during UF-only was 1 l/h; *patient 5* had an excess weight of 5.3 kg at the UF-only session, and the UF rate was set a 2 l/h, according to the study protocol. In this patient, the pretreatment weight above target weight at the dialysis-only session was 2.8 kg. The average cumulative UF volume at 60 min of UF-only was 1,125 ± 354 ml; the average UF rate was 13.6 ± 3.9 ml·kg$^{-1}$·h$^{-1}$. During dialysis-only, the total UF volume was zero in compliance with the study protocol. The pretreatment weight above target weight was nonsignificantly ($P = 0.07$) higher in the UF-only group compared with the dialysis-only group. Relative blood volume fell significantly during UF-only to −6.4 ± 2.2% at 60 min ($P < 0.001$), whereas it increased slightly but nonsignificantly during dialysis-only to +1.3 ± 3.6% at the end of treatment (Table 2). Courses of tympanic temperature were similar for UF-only and dialysis-only; at 60 min, the average tympanic temperature was almost identical (UF only: 36.11°C; dialysis-only: 36.06°C).

All 16 sessions were uneventful; none of the patients had angina or other complaints. Pretreatment systolic and diastolic blood pressure was higher at dialysis-only compared with UF-only ($P = 0.046$ and $P = 0.045$, respectively). Systolic and diastolic blood pressure did not change significantly during treatment in either group or between UF-only and dialysis-only (Table 2). Baseline heart rate was similar for the two treatments and did not change significantly during UF-only and dialysis-only.

Table 1. *Patient characteristics*

| Patient NR | Sex M/F | Age, yr | Time on Dialysis, mo | BMI, kg/m$^2$ | Cause of Renal Failure | Cardiovascular History | Cardioactive Medication (Daily Dose Taken After Hemodialysis) |
|---|---|---|---|---|---|---|---|
| *1* | M | 66 | 3.7 | 25.7 | Hypertensive nephropathy | Hypertension | Enalapril: 10 mg; Amlodipine: 10 mg |
| *2* | M | 73 | 9.5 | 27.9 | Unknown | None | None |
| *3* | M | 27 | 3.2 | 34.7 | C3-glomerulopathy | None | None |
| *4* | M | 52 | 30.4 | 23.4 | Membranous glomerulonephritis | Hypertension | Amlodipine: 5 mg |
| *5* | M | 35 | 36.3 | 25.2 | Urological | None | None |
| *6* | M | 61 | 18.3 | 22.8 | ADPKD | Hypertension | Nifedipine: 30 mg |
| *7* | F | 71 | 19.7 | 24.6 | IgA nephropathy | None | None |
| *8* | M | 51 | 21.8 | 23.0 | ANCA-associated glomerulonephritis | Hypertension | Enalapril: 5 mg |
| Means ± SD | | 54.5 ± 16.7 | 15.5 ± 12.9 | 25.9 ± 3.9 | | | |

NR, number; M, male; F, female; BMI, body mass index; C3, complement factor 3; LVH, left ventricular hypertrophy; ADPKD, autosomal dominant polycystic kidney disease; IgA, immunoglobulin A; ANCA, antineutrophil cytoplasmic autoantibodies.

Table 2. *Treatment data and laboratory parameters*

| | UF-Only ($n$ = 8) | | Dialysis Only ($n$ = 8) | | Difference in Course Between Treatments# |
|---|---|---|---|---|---|
| | Pretreatment | 60 min | Pretreatment | 60 min | |
| Dialysis treatment data | | | | | |
| Pretreatment weight, kg | 83.3 ± 12.0 | | 82.6 ± 11.9 | | |
| Pretreatment weight above target weight, kg | 1.99 ± 1.64 | | 1.20 ± 1.13 | | |
| UF volume, ml | | 1125 ± 354 | | 0 | |
| UF rate, ml·kg$^{-1}$·h$^{-1}$ | | 13.6 ± 3.9 | | 0 | |
| Blood volume change, % | | −6.4 ± 2.2** | | +1.3 ± 3.6 | 0.004 |
| Tympanic temperature, °C | 36.29 ± 0.29 | 36.11 ± 0.16 | 36.48 ± 0.36 | 36.06 ± 0.36 | NS |
| Systolic BP, mmHg | 143 ± 7 | 149 ± 7 | 154 ± 10 | 163 ± 19 | NS |
| Diastolic BP, mmHg | 73 ± 14 | 75 ± 15 | 81 ± 10 | 81 ± 10 | NS |
| Heart rate, bpm | 66 ± 10 | 64 ± 12 | 66 ± 10 | 69 ± 16 | NS |
| Blood sample data | | | | | |
| Hematocrit | 0.362 ± 0.039 | 0.387 ± 0.046** | 0.367 ± 0.045 | 0.362 ± 0.046 | <0.001 |
| Sodium, mmol/l | 140.4 ± 2.7 | 140.4 ± 2.1 | 140.0 ± 2.0 | 140.6 ± 1.3 | NS |
| Potassium, mmol/l | 5.4 ± 0.9 | 5.3 ± 0.9 | 5.2 ± 1.1 | 3.9 ± 0.5** | 0.001 |
| Total calcium, mmol/l | 2.25 ± 0.18 | 2.32 ± 0.16 | 2.27 ± 0.17 | 2.32 ± 0.14 | NS |
| Ionized calcium, mmol/l | 1.21 ± 0.11 | 1.17 ± 0.07 | 1.15 ± 0.07 | 1.20 ± 0.06** | NS |
| Phosphate, mmol/l | 1.53 ± 0.47 | 1.42 ± 0.48** | 1.49 ± 0.37 | 0.96 ± 0.24** | 0.0014 |
| Magnesium, mmol/l | 0.90 ± 0.06 | 0.91 ± 0.06 | 0.89 ± 0.06 | 0.82 ± 0.03* | 0.0023 |
| pH | 7.42 ± 0.04 | 7.41 ± 0.04 | 7.41 ± 0.04 | 7.46 ± 0.04* | 0.0014 |
| Bicarbonate, mmol/l | 23.9 ± 1.8 | 23.6 ± 1.6 | 23.7 ± 1.9 | 26.1 ± 1.1** | <0.001 |
| $Po_2$, kPa | 14.0 ± 4.8 | 13.0 ± 2.5 | 13.7 ± 2.4 | 12.9 ± 2.1 | NS |
| cTnT, ng/l | 50.6 ± 18.8 | 52.9 ± 19.6 | 53.3 ± 19.8 | 52.8 ± 20.1 | NS |
| cTnI, pg/ml | 13.3 ± 8.7 | 14.4 ± 8.6 | 15.1 ± 13.1 | 15.5 ± 14.3 | NS |
| BNP, pg/ml | 150 ± 161 | 178 ± 182 | 139 ± 189 | 150 ± 196 | NS |
| NT-proBNP, ng/l | 3337 ± 2118 | 3953 ± 2576 | 3517 ± 2732 | 3518 ± 2631 | NS |
| hsCRP, mg/l | 3.6 ± 4.6 | 3.9 ± 5.0 | 4.2 ± 3.5 | 4.1 ± 3.5 | NS |
| Pentraxin 3, ng/ml | 1.5 ± 0.7 | 2.6 ± 1.5** | 1.5 ± 0.9 | 2.0 ± 0.6** | 0.09 |
| Myeloperoxidase, ng/ml | 0.9 ± 0.15 | 1.8 ± 0.35** | 1.0 ± 0.11 | 1.7 ± 0.5** | NS |
| Endothelin, ng/ml | 1.4 ± 0.3 | 1.8 ± 0.6** | 1.3 ± 0.2 | 1.8 ± 0.4** | NS |
| vWF, % | 180 ± 49 | 200 ± 43 | 186 ± 35 | 190 ± 34 | NS |

Data are presented as means ± SD. UF, ultrafiltration volume; BP, blood pressure; cTnT, cardiac troponin T; cTnI, cardiac troponin I; BNP, brain natriuretic peptide; NT-proBNP, $NH_2$-terminal probrain natriuretic peptide; vWF, von Willebrand factor. *Denotes $P < 0.05$ compared with baseline within the treatment modality. **$P < 0.01$ compared with baseline within the treatment modality. #$P$ value indicates the significance of the difference in the course of the variable between UF-only and dialysis-only (linear mixed models).

Electrolytes and acid-base parameters did not change significantly during UF-only except for phosphate, which decreased slightly but significantly ($P = 0.004$). During dialysis-only, plasma concentrations of potassium, phosphate, and magnesium decreased ($P = 0.0021$, $P < 0.001$, and $P = 0.012$, respectively), whereas ionized calcium increased significantly ($P = 0.0026$). Blood pH and bicarbonate increased during dialysis-only ($P = 0.020$ and $P = 0.002$, respectively). $Po_2$ decreased slightly, but nonsignificantly, during both treatments without a difference between treatments. Cardiac troponin T, cardiac troponin I, BNP, NT-proBNP, CRP, and von Willebrand factor did not change significantly during either treatment. Pentraxin 3, myeloperoxidase, and endothelin increased significantly during both UF-only and dialysis-only (all $P < 0.01$); the courses of these parameters did not differ between treatments.

*Myocardial perfusion and cardiac dimensions by $^{13}N$-$NH_3$ PET.* Baseline global MBF was comparable for UF-only and dialysis-only (Table 3). Global MBF did not change signifi-

Table 3. *Myocardial perfusion and cardiac dimensions assessed by $^{13}N$-$NH_3$ PET*

| | UF-Only ($n$ = 8) | | Dialysis-Only ($n$ = 8) | | |
|---|---|---|---|---|---|
| | Pretreatment | 60 min | Pretreatment | 60 min | Difference in Course Between Treatments# |
| Myocardial perfusion, ml·min$^{-1}$·100 g$^{-1}$ | | | | | |
| Global | 90.4 ± 22.5 | 94.1 ± 18.0 | 91.2 ± 23.4 | 91.1 ± 25.6 | NS |
| LAD region | 82.0 ± 24.5 | 85.4 ± 18.8 | 81.0 ± 16.9 | 81.8 ± 17.7 | NS |
| RCA region | 99.8 ± 34.8 | 96.8 ± 16.3 | 94.4 ± 25.5 | 91.9 ± 26.6 | NS |
| Cx region | 91.6 ± 22.4 | 93.9 ± 18.6 | 90.7 ± 17.8 | 91.2 ± 25.8 | NS |
| LV volumes and LVEF | | | | | |
| LVEDV, ml | 145.1 ± 55.4 | 140.4 ± 9.2 | 147.8 ± 63.3 | 139.6 ± 58.8 | NS |
| LVESV, ml | 56.9 ± 37.1 | 48.8 ± 33.9* | 49.1 ± 28.8 | 46.3 ± 26.9 | NS |
| Stroke volume, ml | 88.3 ± 22.9 | 91.6 ± 27.9 | 98.6 ± 37.1 | 93.4 ± 34.8 | NS |
| LVEF, % | 63.1 ± 11.0 | 67.9 ± 8.7 | 68.0 ± 5.5 | 68.0 ± 6.3 | NS |

Data are expressed as means ± SD. UF, ultrafiltration; MBF, myocardial blood flow; LAD, left anterior descending artery; RCA, right coronary artery; Cx, circumflex coronary artery; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction. *Denotes $P < 0.05$, compared with baseline within the treatment modality. #Significant difference in the course of the variable between UF-only and dialysis-only (linear mixed models).

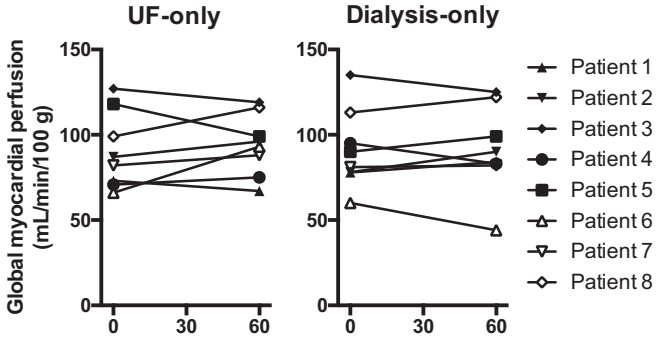


Fig. 1. Individual change in global myocardial perfusion. Each line represents one patient. The course does not differ significantly UF-only and dialysis-only (linear mixed models $P = 0.63$).

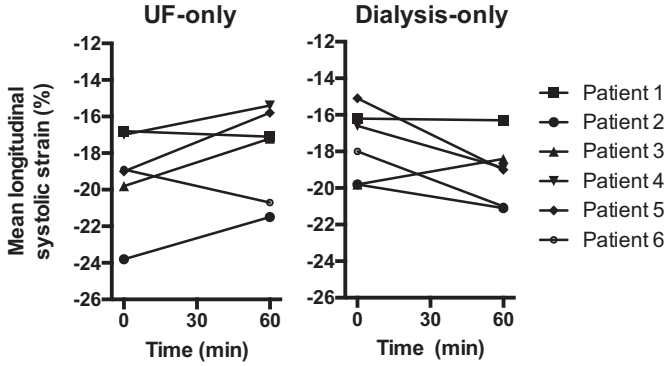


Fig. 2. Individual change of the mean longitudinal systolic strain. Each line represents one patient. The course differs significantly between UF-only and dialysis-only (linear mixed models, $P = 0.028$).

cantly during UF-only and dialysis-only, and courses did not differ between treatments. Figure 1 shows the individual data of the global MBF, showing that there was considerable interindividual variation during both UF-only and dialysis-only. Myocardial perfusion of the coronary regions LAD, RCA, and Cx did also not change during either UF-only or dialysis-only, and courses did not differ between treatments (Table 3). Courses of the regional perfusion of the 17 segments from baseline to 60 min of treatment did not differ between UF-only and dialysis-only (linear mixed models, *F*-test: $P = 0.13$).

LVEDV, LVESV, stroke volume, and LV ejection fraction did not change significantly during UF-only and dialysis-only, and courses did not differ between treatments (Table 3).

*Systolic LV function by echocardiography.* LV ejection fraction, mean strain, and WMSI did not change significantly during UF-only and dialysis-only, and courses did not differ between treatments. Longitudinal strain could be reliably measured in only six patients. Mean longitudinal strain did not change significantly during UF-only and dialysis-only (Table 4 and Fig. 2). However, the course during treatment differed significantly between the two treatments (linear mixed models, $P = 0.028$) with more negative values of mean longitudinal strain during dialysis-only compared with UF-only, indicating an increase in myocardial contractility during dialysis-only compared with UF-only.

HD-induced LV systolic dysfunction occurred in one patient during UF-only and in three patients during dialysis-only. The number of affected LV segments was four in the patient who developed LV systolic dysfunction during UF-only and 3, 2, and 3 LV segments in the three patients who developed LV systolic dysfunction during dialysis-only (Table 5). The three patients that developed LV dysfunction during either UF-only or dialysis-only had a longer dialysis vintage compared with the patients that did not develop LV dysfunction (dialysis vintage 28.8 ± 8.4 yr vs. 11.3 ± 8.5 yr; unpaired *t*-test with Welch correction $P = 0.042$).

The change in longitudinal strain during treatment did not differ significantly between regions that developed RWMA compared with those that did not. Myocardial perfusion decreased to a greater extent in affected regions compared with unaffected regions in *patients 4* and *5* during dialysis-only, but the difference between affected and unaffected regions was not significant (Table 5).

## DISCUSSION

In this crossover study, in eight patients, global and regional myocardial perfusion did not change significantly during 60 min of isolated ultrafiltration at an average UF rate of 13.6 $ml \cdot kg^{-1} \cdot h^{-1}$ nor during 60 min of isovolemic dialysis. Treatment-induced regional LV systolic dysfunction developed during both isolated ultrafiltration and isovolemic dialysis, with a higher prevalence during isovolemic dialysis.

In contrast with previous studies that showed that myocardial perfusion falls significantly during combined diffusive dialysis and ultrafiltration (7, 10, 23), myocardial perfusion did not change significantly during either isolated ultrafiltration or isovolemic dialysis. Although speculative, the combined treatment of ultrafiltration and dialysis may have a greater negative effect on cardiac perfusion than isolated ultrafiltration or isovolemic dialysis alone. Alternatively, the treatment duration of 60 min may have been too short for changes in myocardial perfusion to develop.

Table 4. *LV systolic function parameters assessed by echocardiography*

| | UF-Only ($n = 8$) | | Dialysis-Only ($n = 8$) | | Difference in Course Between Treatments# |
|---|---|---|---|---|---|
| | Pretreatment | 60 min | Pretreatment | 60 min | |
| LVEF, % | 56.1 ± 5.7 | 55.4 ± 4.7 | 52.8 ± 7.9 | 54.0 ± 6.5 | NS |
| Mean s′, cm/s | 8.3 ± 0.9 | 7.4 ± 1.2 | 8.0 ± 1.0 | 7.5 ± 1.3 | NS |
| Wall motion score index | 1.11 ± 0.12 | 1.12 ± 0.10 | 1.12 ± 0.12 | 1.18 ± 0.18 | NS |
| Mean longitudinal systolic strain, %[a] | −19.2 ± 2.5 | −18.0 ± 2.6 | −17.6 ± 2.0 | −19.1 ± 1.8 | 0.028 |
| Number of patients with an increase in WMS in ≥2 segments | | 1 | | 3 | |

Data represent means ± SD. UF, ultrafiltration; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; WMS, wall motion score. #*P* value indicates the significance of the difference in the course of the variable between UF-only and dialysis-only (linear mixed models). [a]Mean longitudinal strain was measured in only six patients.

Table 5. *Details on involved LV segments and their relationship with changes in longitudinal strain and regional perfusion in the patients that developed treatment-induced regional LV systolic dysfunction*

| | UF-Only | | | Dialysis-Only | | |
|---|---|---|---|---|---|---|
| Patient NR | Segments with Increase in WMS | Δ Strain in Affected Segments vs. Other Segments | Δ Perfusion in Affected Segments vs. Other Segments | Segments with Increase in WMS | Δ Strain in Affected Segments vs. Other Segments | Δ Perfusion in Affected Segments vs. Other Segments |
| *4* | | | | Three segments: Basal inferoseptal; basal anteroseptal; midanteroseptal | Affected segments: from −17.3 to −18.0%;<br>Unaffected segments: from −17.1 to −19.7% | Affected segments: from 97 to 79 ml·min$^{-1}$·100 g$^{-1}$;<br>Unaffected segments: from 93 to 84 ml·min$^{-1}$·100 g$^{-1}$ |
| *5* | Four segments: basal inferoseptal; basal anterior; basal anteroseptal; mid-anteroseptal | Affected segments: from −18.5 to −15.8%<br>Unaffected segments: from −19.4 to −16.2% | Affected segments: from 120 to 105 ml·min$^{-1}$·100 g$^{-1}$;<br>Unaffected segments: from 113 to 96 ml·min$^{-1}$·100 g$^{-1}$ | Two segments: basal inferoseptal; mid-inferoseptal | Affected segments: from −13.0 to −18.5%;<br>Unaffected segments: from −15.4 to −18.9% | Affected segments: from 94 to 86 ml·min$^{-1}$·100 g$^{-1}$;<br>Unaffected segments: from 89 to 89 ml·min$^{-1}$·100 g$^{-1}$ |
| *7* | | | | Three segments: basal inferior; basal anteroseptal; midanteroseptal | Strain could not be reliably measured | Affected segments: from 81 to 81 ml·min$^{-1}$·100 g$^{-1}$;<br>Unaffected segments: from 80 to 82 ml·min$^{-1}$·100 g$^{-1}$ |

UF, ultrafiltration; WMS, wall motion score.

The current study shows that LV ejection fraction and WMSI, as indices of global systolic LV function, did not change significantly during either isolated ultrafiltration or isovolemic dialysis. However, myocardial contractility measured by longitudinal strain was better preserved during isovolemic dialysis compared with isolated ultrafiltration. The difference in the course of longitudinal strain between both treatments may, at least in part, be explained by the reduction in preload during isolated ultrafiltration as a result of fluid removal followed by a reduction in myocardial contractility through the Frank Starling mechanism.

In previous studies, higher UF volumes and greater intradialytic reductions in blood pressure during HD were independent risk factors for the development of HD-induced regional LV systolic dysfunction (7, 8). The novelty of the present study is that it suggests that also nonvolume dialysis-associated factors play a role, as we observed that three out of eight patients developed regional LV systolic dysfunction during isovolemic dialysis. This observation is in line with previous studies showing that regional LV dysfunction may occur early during HD before significant ultrafiltration (4, 10).

Several nonvolume dialysis-related factors could affect cardiac function. First, intradialytic changes in electrolytes and acid-base balance may affect cardiac contractility and hemodynamic stability. An intradialytic decrease in plasma calcium concentration is best known for its adverse cardiac and hemodynamic effects (29, 31). In the present study, however, plasma calcium concentrations increased during isovolemic dialysis. At the same time, magnesium, potassium, and phosphate levels decreased during isovolemic dialysis, but the relationship between the intradialytic change in these electrolytes and the development of LV systolic dysfunction is unclear. Isovolemic dialysis was associated with a significant increase in plasma pH and bicarbonate. A rise in bicarbonate has been shown to have adverse cardiac effects in patients with heart disease (5). A rise in pH is also known to lower cerebral perfusion by vasoconstriction (28), but whether intradialytic changes in plasma pH and bicarbonate affect myocardial contractility is unknown as far as we know. Unfortunately, the small number of patients in this study precludes an analysis of the relationship between intradialytic changes in electrolytes and acid-base parameters and the development of regional LV systolic dysfunction. In a previous study, however, plasma levels of potassium, magnesium, calcium, pH, and bicarbonate followed a similar course in patients with and without HD-induced regional systolic LV dysfunction (3). Second, treatment-related changes in body temperature may affect hemodynamic stability and, thus, cardiac function (20, 30). However, it is unlikely that dialysis-induced temperature effects were involved in the development of regional systolic LV dysfunction in this study since we used a low dialysate temperature of 36.0°C during isovolemic dialysis, and tympanic temperature fell slightly during both treatments. Notably, tympanic temperature followed a similar course during isovolemic dialysis and isolated ultrafiltration. Third, bioincompatibility reactions resulting from the contact between blood and the extracorporeal system (4, 13, 15, 34) could affect cardiac function, e.g., through cardiodepressive action of proinflammatory cytokines or complement factors (18, 22, 24, 35). Bioincompatibility reactions are expected to occur during both isolated ultrafiltration and isovolemic dialysis. In this study, indeed, isolated ultrafiltration and isovolemic dialysis induced a similar acute inflammatory response with significant rises of pentraxin 3 and of myeloperoxidase due to neutrophil degranulation. Leukocyte activation may have cardiodepressive effects (18, 22, 24) and result in an early granulocytopenia due to sequestration in (mainly) the pulmonary vasculature. This coincides with a transient drop in arterial blood $P_{O_2}$ (15, 32), which may contribute to myocardial

ischemia. In this study, $Po_2$ decreased slightly but nonsignificantly during both isolated ultrafiltration and isovolemic dialysis. The small number of patients precludes an analysis of the relationship between intradialytic changes in inflammatory markers and the development of regional systolic LV dysfunction.

This study has limitations. First, the number of patients was small and, therefore, this research should be viewed as an explorative study of the concept that nonvolume factors could play a role in the pathophysiology of HD-induced regional LV systolic dysfunction rather than a quantitative comparison between ultrafiltration and isovolemic dialysis. Although the PET scan is considered the gold standard to study myocardial perfusion, the logistical challenges and patient inconvenience of intradialytic PET scanning limit the number of patients that can be studied. Future studies using other imaging modalities, such as intratreatment MRI (8), could further explore possible divergent effects of isolated ultrafiltration and isovolemic dialysis on myocardial perfusion and function in larger patient cohorts. Second, we studied a selected group of relatively young and predominantly male HD patients without significant cardiovascular comorbidity. Therefore, our results may not be representative of elderly and female dialysis patients and patients with significant cardiac comorbidity. Finally, the use of low-flux dialyzers and the treatment duration of 60 min are not representative of real-world dialysis treatment. We cannot exclude that changes in myocardial perfusion and LV function could have occurred with longer treatment duration.

*Conclusion.* Global and regional myocardial perfusion was not compromised by 60 min of isolated ultrafiltration or isovolemic dialysis. Regional LV systolic dysfunction developed during both isolated ultrafiltration and isovolemic dialysis with a higher prevalence during isovolemic dialysis. This latter observation suggests that, besides hypovolemia, dialysis-associated factors may also be involved in the pathogenesis of hemodialysis-induced regional LV dysfunction.

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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

S.A. and C.F.F. conceived and designed research; S.A., H.K., E.E., Y.M.H., and A.W. performed experiments; S.A., W.P.K., Y.M.H., and C.F.F. analyzed data; S.A., C.A.G., A.A.V., J.P.v.M., R.W., and C.F.F. interpreted results of experiments; S.A. and C.F.F. drafted manuscript; S.A., H.K., E.E., W.P.K., Y.M.H., J.P.v.M., R.H.S., and C.F.F. edited and revised manuscript; S.A. and C.F.F. approved final version of manuscript.

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