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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Author contributions

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

Abstract

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, age 55±18 years) underwent 60 min of isolated ultrafiltration and 60 min of isovolemic dialysis in randomized order. Myocardial perfusion was assessed by ^{13}N-NH_3 PET 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/h) induced hypovolemia whereas isovolemic dialysis did not (blood volume change -6.4±2.2% versus +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 wall motion score index did not change significantly during either treatment. Regional LV systolic dysfunction developed in 1 patient during isolated ultrafiltration and in 3 patients during isovolemic dialysis. In conclusion, global and regional myocardial perfusion were 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.

Key words: haemodialysis; 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, 27, 33, 6, 26, 23, 10, 7). Using intradialytic Positron Emission Tomography (PET), we and others showed that conventional HD elicits acute reductions in myocardial blood flow (MBF) (23, 10). A proportion of patients in these studies developed regional left ventricular (LV) systolic dysfunction suggestive of myocardial ischemia (23, 10). Using intradialytic cardiac magnetic resonance imaging, Buchanan et al. 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 (7). Echocardiography studies in larger patient cohorts have shown that HD-induced regional LV systolic dysfunction has a prevalence ranging between 23% and 63% (8, 3, 12). These studies also showed that the occurrence of HD-induced LV systolic dysfunction is associated with a greater incidence of all-cause mortality (8, 3) 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 fall in blood pressure that may compromise myocardial perfusion. Burton et al. 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 (8). 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 minutes after the start of HD before significant UF (3). Buchanan et al. also observed regional LV systolic dysfunction as early as 70 minutes from the start of HD (7). 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 (31, 29, 16), changes in acid base balance (5, 2) or bioincompatibility reactions (15, 13, 34, 4, 22, 18, 24, 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 8 patients.

Materials and Methods

Patients

Eligible for this study were adult (age ≥18 years) patients from the Dialysis Center Groningen and University Medical Center Groningen (UMCG) that were treated with HD for >3 months, were on a thrice-weekly schedule, and had an arteriovenous fistula without recirculation at routine Transonic flow measurements. Exclusion criteria were: 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 months) cardiovascular event; use of long-acting nitrates; use of beta-blockers for angina pectoris; recent hemorrhage; (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 UMCG. 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 2 needles and an intravenous indwelling catheter was placed in in the non-dialysis 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 non-dialysis 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 approximately 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, 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 per 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 pre-treatment 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 polysulphone 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 RBV decrease per unit of ultra-filtered fluid (9). Excess weight was calculated as the difference between pre-treatment

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 cardio-vascular response (30, 20), 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 extra-corporeal 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, 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, USA). Data acquisition and data analysis are detailed in reference (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 per 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, polar maps were reconstructed 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/100 g. Gating data from the ^{13}N-NH_3 studies were re-orientated 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, USA), a commercially (Siemens Medical Systems, Hoffman Estates, IL, USA) available cardiac software package (14, 21). This program automatically detects the contours of the endocardium of the LV. Left ventricular end-diastolic (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-segments model by a single technician (Y.M.H.) who was blinded to treatment modality. The 18-segment was chosen to align per-segment WMS with per-segment longitudinal strain measurements (vide infra). 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 pre-treatment. HD-induced LV systolic dysfunction was defined as the development of new RWMA in two or more LV segments compared with pre-treatment. 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 mean ± standard deviation (SD) and skewed data as median (interquartile range). Changes in parameters during treatment within treatment groups and differences in pre-treatment parameters between UF-only and dialysis-only were compared with the paired student 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 versus 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 inc, IBM company, USA) and GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA), R version 3.4.0 (R Core Team (2017). Two-sided P-values <0.05 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 years and the mean time on dialysis was 17.9±12.0 months. Mean BMI was 25.9±3.9 kg/m^2. Average pre-dialysis 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 4 patients. These 4 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 beta-blocker.

Treatment data and laboratory parameters

In all but one patient the UF-rate during UF-only was 1 l/h; patient number 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 pre-treatment 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 1125±354 ml; the average UF-rate was 13.6±3.9 ml/kg/h. During dialysis-only, the total UF-volume was zero in compliance with the study protocol. The pre-treatment weight above target weight was non-significantly (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 non-significantly 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. Pre-treatment systolic and diastolic blood pressure were 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 nor between UF-only and dialysis-

only (Table 2). Baseline heart rate was similar for the 2 treatments and did not change significantly during UF-only and dialysis-only.

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 non-significantly 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 significantly 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 inter-individual 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 s' 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 6 patients. Mean longitudinal strain did not change significantly during UF-only and dialysis-only (Table 4 and Figure 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 3 patients during dialysis-only. The number of affected LV segments was 4 in the patient who developed LV systolic dysfunction during UF-only and 3, 2, and 3 LV segments in the 3 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 years versus 11.3 ± 8.5 years; 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 to those that did not. Myocardial perfusion decreased to a greater extent in affected regions compared with unaffected regions in patient 4 and 5 during dialysis-only but the difference between affected and unaffected regions was not significant (Table 5).

Discussion

In this cross-over study in 8 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/kg/h 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 (23, 10, 7), 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.

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 non-volume dialysis-associated factors play a role, as we observed that 3 out of 8 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 (10, 4).

Several non-volume 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 (31, 29). 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 relation between the intradialytic change of 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 relation 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 (30, 20). 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 (15, 13, 34, 4) could affect cardiac function, e.g. through cardio-depressive action of pro-inflammatory cytokines or complement factors (22, 18, 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 (22, 18, 24) and results in an early granulocytopenia due to sequestration in (mainly) the pulmonary vasculature. This coincides with a transient drop in arterial blood PO_2 (15, 32) which may contribute to myocardial ischemia. In this study, PO_2 decreased slightly but non-significantly during both isolated ultrafiltration and isovolemic dialysis. The small number of patients precludes an analysis of the relation 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 non-volume 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 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 intra-treatment 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 dialysers and the treatment duration of 60 minutes 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 were not compromised by 60 minutes 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

None to declare.

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Figure captions

Figure 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).

Figure 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).

Table 1. Patient characteristics.

Patient NR	Sex M/F	Age (years)	Time on dialysis (months)	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
Mean ± SD		54.5 ± 16.7	15.5 ± 12.9	25.9 ± 3.9			

Abbreviations: 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: anti-neutrophil cytoplasmic autoantibodies.

Table 2. Treatment data and laboratory parameters.

	UF-only (n=8)		Dialysis only (n=8)		Difference in course between treatments [#]
	Pre-treatment	60 min	Pre-treatment	60 min	
Dialysis treatment data					
Pre-treatment weight (kg)	83.3±12.0	-	82.6 ± 11.9	-	
Pre-treatment weight above target weight (kg)	1.99 ± 1.64	-	1.20 ± 1.13	-	
UF volume (mL)	-	1125 ± 354	-	0	
UF rate (mL/kg/h)	-	13.6 ± 3.9	-	0	
Blood volume change (%)	-	-6.4 ± 2.2**	-	+1.3 ± 3.6	0.004
Tympanic temperature (ºC)	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/lL	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
Ionised 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
pO2 (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 mean ± SD. *Denotes P<0.05 and **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).

Abbreviations: UF: ultrafiltration volume; BP: blood pressure; cTnT: cardiac troponin T; cTnI:

cardiac troponin I; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro brain natriuretic peptide; vWF: von Willebrand factor.

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

	UF-only (n=8)		Dialysis-only (n=8)		Difference in course between treatments[#]
	Pre-treatment	60 min	Pre-treatment	60 min	
Myocardial perfusion (mL/min/100 g)					
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 represent mean ± SD. *Denotes P<0.05 compared with baseline within the treatment modality. [#]Significance of the difference in the course of the variable between UF-only and dialysis-only (linear mixed models).

Abbreviations: 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.

Table 4. LV systolic function parameters assessed by echocardiography.

	UF-only (n=8)		Dialysis-only (n=8)		Difference in course between treatments[#]
	Pre-treatment	60 min	Pre-treatment	60 min	
LVEF (%)	56.1 ± 5.7	55.4 ± 4.7	52.8 ± 7.9	54.0 ± 6.5	NS
Mean s' (cm/sec)	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
Nr of patients with an increase in WMS in ≥2	-	1	-	3	

Data represent mean ± SD. *Denotes $p<0.05$ compared with baseline. [#]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 6 patients.

Abbreviations: UF: ultrafiltration; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; WMS: wall motion score.

Table 5. Details on involved LV segments and it relation 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				3 segments: Basal infero-septal; basal anteroseptal; mid antero-septal	Affected segments: from -17,3 to -18.0%; Unaffected segments: from -17.1 to -19.7%	Affected segments: from 97 to 79 ml/min/100 g; Unaffected segments: from 93 to 84 ml/min/100 g
5	4 segments: Basal infero-septal; basal anterior; basal antero-septal; mid antero-septal	Affected segments: from -18.5 to -15.8% Unaffected segments: from -19.4 to -16.2%	Affected segments: from 120 to 105 ml/min/100 g; Unaffected segments: from 113 to 96 ml/min/100 g	2 segments: Basal infero-septal, mid inferoseptal	Affected segments: from -13.0 to -18.5%; Unaffected segments: from -15.4 to -18.9%	Affected segments: from 94 to 86 ml/min/100 g; Unaffected segments: from 89 to 89 ml/min/100 g
7				3 segments: Basal inferior, basal anteroseptal, mid antero-septal	Strain could not be reliably measured	Affected segments: from 81 to 81 ml/min/100 g; Unaffected segments: from 80 to 82 ml/min/100 g

Abbreviations: UF: ultrafiltration; WMS: wall motion score.

Figure 1.

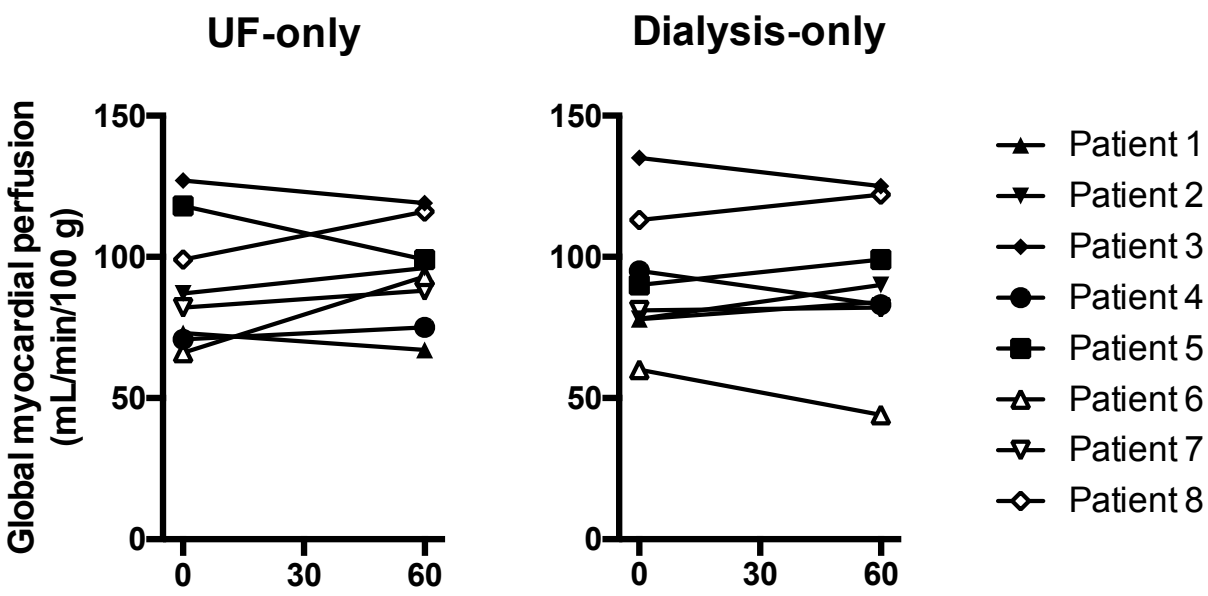
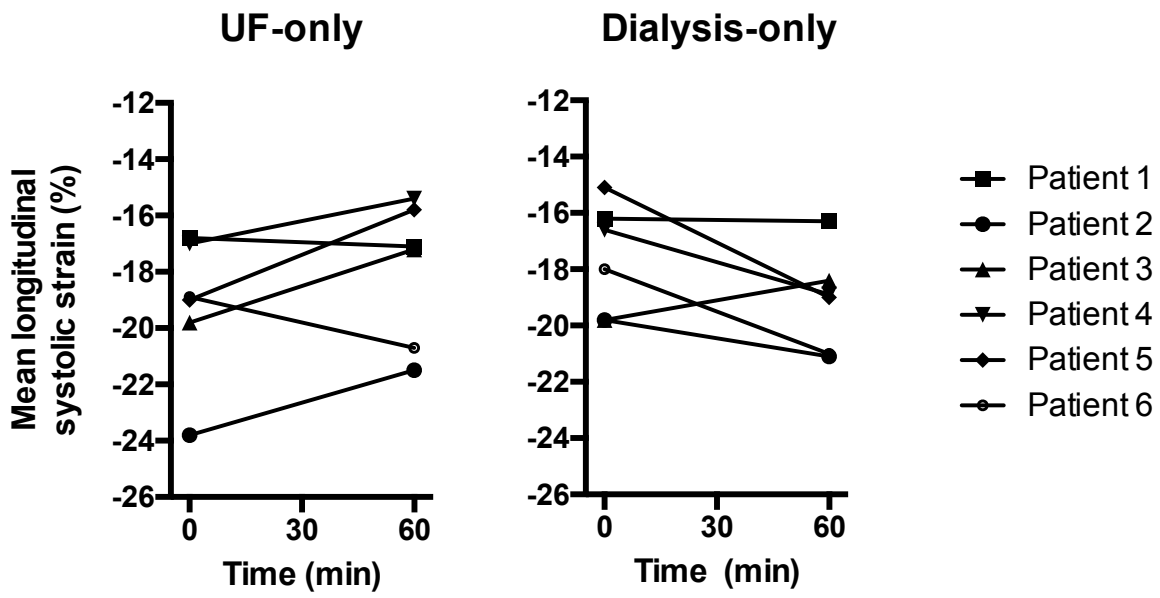

UF-only
Dialysis-only
Global myocardial perfusion (mL/min/100 g)
150
100
50
0
0
30
60
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8

Figure 2.


UF-only
Dialysis-only
Mean longitudinal systolic strain (%)
-12
-14
-16
-18
-20
-22
-24
-26
0
30
60
Time (min)
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6