Dialysis-Induced Regional Left Ventricular Dysfunction Is Ameliorated by Cooling the Dialysate

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Dialysis patients who develop cardiac failure have a poor prognosis. Recurrent subclinical myocardial ischemia is important in the genesis of heart failure in nondialysis patients. It has previously been demonstrated that subclinical ischemia occurs during hemodialysis; therefore, this study examined whether the improved stability of cool-temperature dialysis lessens this phenomenon. Ten patients who were prone to intradialytic hypotension entered a randomized, crossover study to compare the development of dialysis-induced left ventricular (LV) regional wall motion abnormalities (RWMA) at dialysate temperatures of 37 and 35°C. Serial echocardiography with quantitative analysis was used to assess ejection fraction and regional systolic LV function. BP and hemodynamic variables were measured using continuous pulse wave analysis. The severity of thermal symptoms was scored using a simple questionnaire. Forty-nine new RWMA developed in nine patients during hemodialysis with dialysate at 37°C (HD$_{37}$), compared with thirteen RWMA that developed in four patients during HD$_{35}$ (odds ratio 3.8; 95% confidence interval 2.1 to 6.9). The majority of RWMA displayed improved function by 30 min after dialysis. Overall, regional systolic LV function was significantly more impaired during HD$_{37}$ ($P < 0.001$). BP was higher during HD$_{35}$, with fewer episodes of hypotension as a result of a higher peripheral resistance and no difference in stroke volume. The development of thermal symptoms was heterogeneous, with most patients tolerating HD$_{35}$ well. This study confirms previous findings of reversible LV RWMA that develop during hemodialysis. It also shows that this phenomenon can be ameliorated by reducing dialysate temperature, a simple intervention with no cost implications.

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Cardiovascular mortality is hugely elevated in hemodialysis patients and is at least 30 times greater than that of age-matched control subjects (1). The development of cardiac failure, which occurs in up to 25 to 50% of patients, confers a particularly bleak outlook (2). This excess of cardiovascular death is only partly explained by an increase in the traditional risk factors, and several mechanisms of cardiac damage that are specific to the uremic state now have been identified. In nondialysis patients, transient subclinical myocardial ischemia can cause left ventricular (LV) dysfunction (myocardial stunning) (3). Repeated episodes of stunning are cumulative and contribute to the pathophysiology of heart failure (4). We and other investigators have previously shown evidence that subclinical ischemia occurs in response to the stress of hemodialysis (5–7). We also demonstrated that it was possible to reduce the frequency and the severity of this phenomenon by using biofeedback dialysis (Hemocontrol, Gambro-Hospal, Mirandora, Italy) to improve the hemodynamic tolerability of dialysis. However, Hemocontrol requires a relatively complicated prescription, is not widely available, and works by reacting to changes in relative blood volume that may not predict intradialytic hypotension (IDH) in all patients (8). Although many different strategies have been used in an attempt to reduce IDH, reducing the temperature of the dialysate is one of the most simple (9). Cooling the dialysate has been shown to be effective and is universally available at no additional cost. However, cooling of the dialysate is relatively underused because of concerns regarding unpleasant symptoms of cold, although it is difficult to ascertain from the published literature the extent to and the severity at which this occurs (10). Therefore, using the development of reversible abnormalities in regional LV function as a marker of subclinical myocardial ischemia, we performed a study to examine whether the improved hemodynamic tolerability of cool temperature dialysis leads to a reduction in the frequency of dialysis-induced ischemia, as compared with standard dialysis.

Materials and Methods

Patients

Ten patients who were on chronic hemodialysis and were prone to IDH were recruited for a randomized, crossover study. Four patients were male, and all had been on dialysis for longer than 6 mo. All patients received dialysis *via* native arteriovenous fistulas, and all were anuric. Remaining characteristics are shown in Table 1.

Patients were defined as being IDH prone when they had episodes of IDH in >30% of dialysis sessions in the month before recruitment to the study. IDH was defined as systolic BP (SBP) ≤100 mmHg, even in the

Table 1. Patient demographics[a]

Patient	Age (yr)	Months on Dialysis	Cause of ESRF	Atherosclerotic Vascular Disease	Diagnosed IHD	LVMI $(g/m^{2.7})$	Angiogram	Antianginal or BP-Lowering Drugs
1	83	11	Myeloma	Y	N	85.0	N	
2	71	60	Unknown	Y	Y (angina)	52.1	N	Felodipine 10 mg once daily, atenolol 50 mg once daily
3	72	33	Diabetes	N	N	55.3	N	Valsartan 150 mg once daily
4	71	19	Diabetes	Y	Y (MI)	96.7	Y[b]	Diltiazem 90 mg once daily
5	42	44	Sarcoid	N	N	25.7	N	
6	65	52	Diabetes	N	N	52.1	N[c]	
7	60	6	APKD	N	N	51.3	N	
8	66	6	Diabetes	Y	N	61.9	N	Diltiazem 300 mg, doxazosin 4 mg once daily, irbesartan 150 mg once daily
9	55	17	Unknown	N	N	55.8	N	Nifedipine 60 mg once daily, ramipril 10 mg once daily
10	68	40	Anti-GBM	N	N	46.3	N	
Mean ± SD or n (%)	65 ± 11	29 ± 19		4 (40)	2 (20)	58.2 ± 20	1 (10)	

[a]APKD, adult polycystic kidney disease; ESRF, end-stage renal failure; GBM, glomerular basement membrane; IHD, ischemic heart disease; LVMI, left ventricular mass index; MI, myocardial infarction.
[b]Angiogram result for patient 4: Diffuse three-vessel disease, not suitable for intervention.
[c]Patient 6 had had a dipyridamole stress test 12 mo before entering the study, which was negative.

absence of symptoms, or a fall in SBP >10% of the predialysis reading in association with any of the classical symptoms of hypotension (*e.g.*, headaches, cramps, light-headedness). Patients were excluded when they had significant symptomatic cardiac failure (New York Heart Association classification ≥3), had previously received a cardiac transplant, or when it was not possible to obtain echocardiographic images of sufficient quality to allow meaningful analysis.

Study Protocol

Upon entry to the study, patients had their dry weight confirmed with reference to clinical examination. After this, dry weight and antihypertensive medications remained unchanged for the duration of the study. Patients then were randomly assigned to two groups. Group A patients were commenced on standard thrice-weekly bicarbonate-based hemodialysis with a dialysate temperature of 37°C (HD$_{37}$); group B patients started thrice-weekly dialysis with a dialysate temperature of 35°C (HD$_{35}$). Patients but not dialysis unit staff were blinded to the intervention. Both groups underwent one week of the dialysis therapy before undergoing a monitored session during one of the dialysis sessions during the second week. At the end of the second week, patients then crossed over to the other dialysis modality, thereby acting as their own controls. After an additional week on the alternate modality, patients underwent a second monitored session on the same day of the week as the first study session.

For each monitored dialysis treatment, serial echocardiography was performed and noninvasive hemodynamic monitoring was undertaken using a Finometer. The finger cuff was left in place for the entire session, and the nonfistula arm was used. For obtaining baseline values, monitoring was commenced 30 min before the start of dialysis. Also before dialysis, patients had segmental multifrequency bioimpedance performed (InBody BS20, Seoul, Korea) to assess intracellular, extracellular, and total body water. Body temperature was recorded before and after each session using a digital tympanic thermometer (First Temp; Sherwood Davis & Geck, St. Louis, MO), and ambient room temperature of the dialysis unit also was noted. Blood samples were collected before and after each session in lithium heparin and

EDTA tubes, and biochemical analysis was performed on a multichannel autoanalyzer. Cardiac troponin-T (cTnT) analysis was performed using a third-generation electrochemiluminescence assay (Roche Diagnostics, Lewes, UK). Postdialysis cTnT values were corrected individually for hemoconcentration with reference to percentage change in hematocrit and blood volume using the following formula:

$$\text{Adjusted cTnT} = \text{cTnT}_{post} \times \frac{BV_{post}\,(1 - Hct_{post})}{BV_{pre}\,(1 - Hct_{pre})}$$

where cTnT$_{post}$ is postdialysis cTnT, Hct$_{post}$ is postdialysis hematocrit, Hct$_{pre}$ is predialysis hematocrit, BV$_{post}$ is end dialysis blood volume, and BV$_{pre}$ is start dialysis blood volume. Single-pool Kt/V$_{urea}$ values were calculated from pre- and postdialysis urea levels (11). Predialysis blood tests were drawn immediately after insertion of access needles, and postdialysis levels were taken from the arterial line 10 s after reduction of blood pump speed to 50 ml/min. An investigator was present for the entirety of every dialysis session to record intradialytic symptoms. We also performed quality-of-life scoring for both types of dialysis using the validated Short Form (SF-36) questionnaire (12) and developed a simple questionnaire to evaluate systematically symptoms of cold (see Appendix). This questionnaire was formulated according to similar scoring tools (13), and the questions that assessed severe symptoms of cold were weighted to score more heavily. The lowest score, signifying no thermal symptoms, was 6, and the highest score, indicating severe symptoms of cold, was 24. The primary end point was the frequency of new LV regional wall motion abnormalities (RWMA) during HD$_{37}$ and HD$_{35}$ in relation to their effects on BP and systemic hemodynamics. All patients gave informed consent before commencement, and ethical approval for the project was granted by Derbyshire Local Research Ethics Committee.

Echocardiography

Two-dimensional echocardiography was performed serially throughout dialysis sessions using commercially available equipment (1.5- to 3.6-MHz 3S probe, Vivid 3; GE Medical Systems, Sonigen,

Germany). A single experienced operator (blinded to dialysis modality) carried out all measurements with the patients in the left lateral position. Images were recorded before commencing dialysis (baseline), at 120 and 240 min during dialysis, and 30 min after dialysis was finished (recovery). Standard apical two- and four-chamber views (to visualize the LV endocardial border in two planes at 90 degrees to each other) were recorded onto super-VHS videotape for off-line analysis.

Videotaped images subsequently were analyzed using a personal computer–based digitizing program (Echo-CMS; MEDIS, Leiden, The Netherlands) as described previously (14). Three consecutive heartbeats were analyzed for each time point (extrasystolic beats were excluded). Endocardial borders (excluding papillary muscles) were traced semiautomatically for each video frame of the three-beat sequence, and any anomalies were corrected manually. Maximal displacement of the endocardial border from a center point then was measured over each of 100 chords around the LV wall, corrected for LV circumference, and expressed as percentage shortening fraction (SF). Each apical view was divided into five segments, and SF for the chords in each segment was averaged so that 10 regions of the left ventricle were assessed at each time point. New RWMA were defined as segments that demonstrated a decline in SF of >20% from baseline. We calculated mean SF for all 10 segments (SF_{mean}) and for those segments that developed new RWMA (SF_{WMA}). Peak stress was defined for each patient as the point during the first monitored dialysis session when most RWMA were present (either 120 or 240 min). When dialysis modalities were compared, the same time point was used in the second dialysis session.

Ejection fraction (EF) was calculated using LV volumes at end systole and end diastole, measured by the biplane disk method. LV mass index was calculated from each patient's original baseline images using the Devereux formula corrected for height$^{2.7}$.

Finometer

The use of the Finometer (Finapres Medical Systems, Arnhem, The Netherlands) in dialysis patients has been described in detail elsewhere (5). Previously, we showed good concordance between echocardiographic and Finometer-derived measurements of stroke volume (SV) in dialysis patients (15). The Finometer is accurate in tracking relative change (as opposed to absolute values), so data are presented as percentage change from baseline except for BP, which is calibrated against brachial readings using a return-to-flow method, and for this, absolute values are shown.

Hemodialysis Details

Dialysis was performed using Hospal Integra monitors (Gambro-Hospal, Mirandola, Italy). For each session, net fluid removal was set on an individual basis according to ideal dry weight. However, when there was >20% difference in programmed ultrafiltration (UF) volume from the first session, the second monitored session was rescheduled. Low-flux polysulphone dialyzers were used, either 1.8 or 2.0 m^2 as per individual patients' usual prescription (LOPS 18/20; Braun Medical Ltd., Sheffield, UK). For all treatments, dialysate contained 138 mmol/L sodium, 1 mmol/L potassium, 1.5 mmol/L calcium, 0.5 mmol/L magnesium, 32 mmol/L bicarbonate, 1 g/L glucose, and 3 mmol/L acetate. All treatments were of 4 h duration, and anticoagulation was achieved with unfractionated heparin. Dialysate flow was 500 ml/min and conductivity was set at 13.6 mS/cm. Blood pump speed varied between 250 and 450 ml/min, depending on patients' vascular access, but each individual patient had the same blood flow for the two monitored sessions.

Statistical Analyses

Results are expressed as mean ± SD when parametric or as median (interquartile range [IQR]) when nonparametric unless otherwise stated. Echocardiographic, BP, and hemodynamic data were analyzed using one-way ANOVA with a design for repeated measures and Bonferroni test to correct for multiple comparisons. The frequencies of IDH and of new RWMA that occurred during each dialysis modality were compared using Poisson regression. For other data, either the paired t test or Wilcoxon rank sum test was used, depending on normality of the distribution. An α error at $P < 0.05$ was judged to be significant.

Results

BP

During HD$_{37}$, mean SBP was 141.6 ± 17 mmHg, mean diastolic BP was 69.4 ± 5 mmHg, and mean of the mean arterial pressure (MAP) was 92.6 ± 10 mmHg. During HD$_{35}$, BP was significantly higher: Mean SBP of 158.8 ± 14 mmHg, mean diastolic BP of 78.6 ± 4 mmHg, and mean MAP of 110.9 ± 7 mmHg ($P < 0.001$ for all comparisons). The lower mean BP with HD$_{37}$ was the result of a fall in BP after the first hour of dialysis, whereas with HD$_{35}$ BP was maintained until the last third of the treatment. These data are summarized in Figure 1.

There were two episodes of symptomatic hypotension during HD$_{37}$ as compared with one with HD$_{35}$ (NS), all of which required administration of normal saline plus temporary cessation of UF. However, there was a significant difference in the number of asymptomatic IDH between the treatments, which occurred with a frequency of 0.4 episodes per session with HD$_{35}$ as compared with a rate of 6.2 episodes per session with HD$_{37}$ (odds ratio [OR] 15.5; 95% confidence interval [CI] 5.6 to 14.2).

Echocardiographic Data

Throughout the study, all patients were in sinus rhythm, and none had significant valvular disease or pulmonary hypertension. SF at baseline in all regions was compared on an individual basis for each type of dialysis; there were no significant differences in baseline SF in any of the patients.

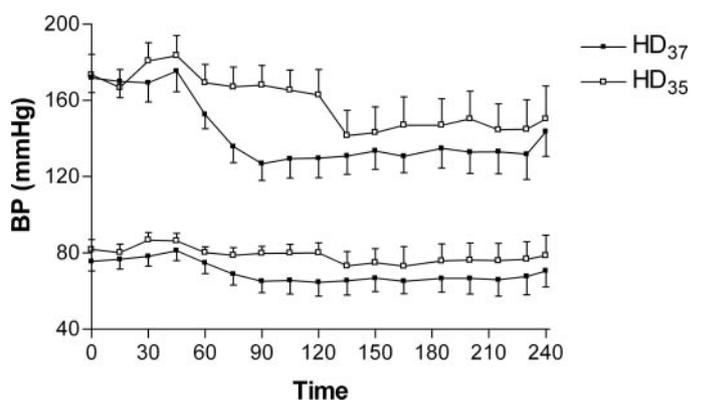A total of 49 new RWMA occurred in nine patients during

Figure 1. Overall mean BP for hemodialysis with a dialysate temperature of 37°C (HD$_{37}$) and HD$_{35}$. BP was significantly higher during HD$_{35}$ ($P < 0.001$ for all comparisons).

HD_{37}. In contrast, only 13 new RWMA occurred in four patients during HD_{35} (OR 3.8; 95% CI 2.1 to 6.9). By 30 min after dialysis, 24 (49%) of the affected areas with HD_{37} had recovered normal motion, whereas with HD_{35}, 8 (62%) RWMA had improved (OR 4.9; 95% CI 1.9 to 12.1). Therefore, with both types of dialysis but to a greater extent with HD_{37}, a significant proportion of affected regions still had SF >20% less than baseline at 30 min after dialysis. These data are summarized in Figure 2.

SF_{WMA} declined with both types of dialysis at peak stress before improving in recovery. There were no differences in SF_{WMA} between HD_{37} and HD_{35} at any of the time points, showing that the areas that did develop new RWMA were affected to a similar magnitude. However, because of the difference in the overall number of new RWMA, SF_{mean} at peak stress was significantly lower with HD_{37} (2.5 ± 1.6%) as compared with HD_{35} (3.9 ± 1.9%; $P < 0.001$). This pattern of lower SF_{mean} with HD_{37} also was seen in recovery ($P < 0.001$). Complete SF_{WMA} and SF_{mean} data are shown in Table 2 and Figures 2 and 3.

With HD_{35}, EF rose during dialysis and was higher than baseline at peak stress and in recovery. However, EF did not

Table 2. Global (EF) and regional (SF) LV function during HD_{37} and HD_{35}[a]

Parameter	EF (%)	SF_{mean} (%)	SF_{WMA} (%)
HD_{37}			
baseline	61 ± 14	3.0 ± 1.8	3.7 ± 2
peak	61 ± 10[b]	2.5 ± 1.6[c]	1.7 ± 1.2
recovery	60 ± 12	2.7 ± 1.5[c]	2.8 ± 1.6
HD_{35}			
baseline	57 ± 10	2.5 ± 1.2	3.2 ± 1.3
peak	72 ± 9[b]	3.9 ± 1.9[c]	1.8 ± 0.9
recovery	69 ± 11	3.7 ± 1.9[c]	3.1 ± 1.7

[a]Baseline is before start of dialysis, peak stress is the point at which most regional wall motion abnormalities (RWMA) were present during dialysis, and recovery is 30 min after dialysis. EF, ejection fraction; HD_{35}, hemodialysis with a dialysate temperature of 35°C; HD_{37}, hemodialysis with a dialysate temperature of 37°C; SF, shortening fraction.
[b]$P < 0.05$ by ANOVA, HD_{37} *versus* HD_{35}.
[c]$P < 0.001$ by ANOVA, HD_{37} *versus* HD_{35}.
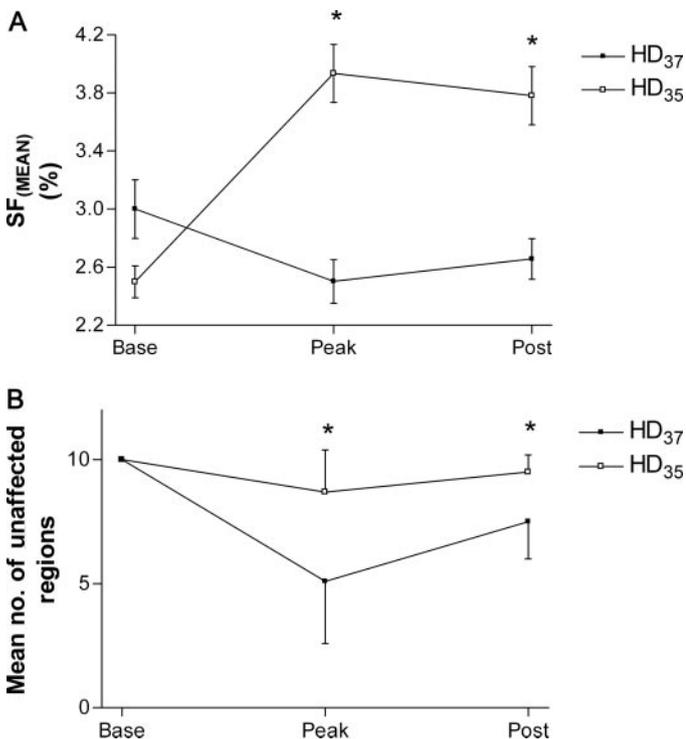

Figure 2. (A) Mean number of *un*affected left ventricular (LV) regions during HD_{37} and HD_{35}. Only new regional wall motion abnormalities (RWMA) were counted; therefore, all regions are scored as "unaffected" at baseline. Baseline is before start of dialysis, peak stress is the point at which most RWMA were present during dialysis, and recovery is 30 min after dialysis. Data are expressed as means ± SEM. Comparison at peak stress (odds ratio 3.8; 95% confidence interval 2.1 to 6.9) and in recovery (odds ratio 4.9; 95% confidence interval 1.9 to 12.1). (B) Overall mean regional LV function (shortening fraction [SF]) during HD_{37} and HD_{35}. Data are expressed as means ± SEM. *$P < 0.001$ by ANOVA.
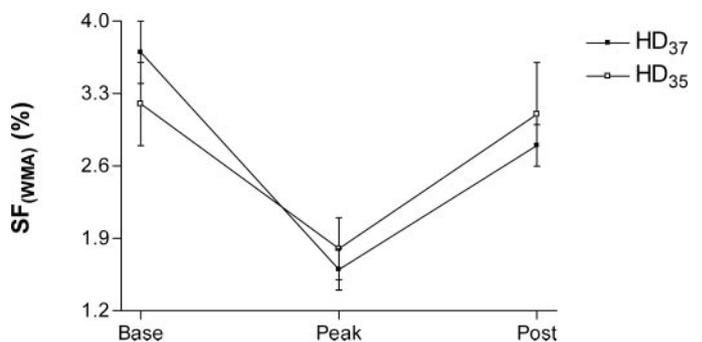

Figure 3. Mean regional LV function (SF) in regions that developed new RWMA during HD_{37} and HD_{35}. Data are expressed as means ± SEM.

change during HD_{37}; therefore, there was a significant difference in EF at peak stress when dialysis modalities were compared ($P < 0.05$). Data for EF are shown in Table 2 and Figure 4. We observed no differences in LV dimensions when comparing the two types of dialysis; these data are displayed in Table 3.

Hemodynamic Data

Hemodynamic data are summarized in Figure 5. SV declined throughout both dialysis modalities to a similar degree, with means of −19 ± 5% during HD_{37} and −23 ± 13% with HD_{35} (NS). Total peripheral resistance (TPR) rose to a significantly greater extent with HD_{35}. Overall, mean TPR for the entire HD_{35} dialysis session was 42 ± 18% above baseline as compared with a mean of 10 ± 8% during HD_{37} ($P < 0.001$). Heart rate (HR) was lower with HD_{35} with a mean of 69 ± 2 bpm, representing a −4 ± 3% change from baseline. Mean HR with HD_{37} was 78 ± 2 bpm, a change of 5 ± 3% from baseline ($P < 0.05$). As a product of HR and SV, cardiac output therefore was

Table 3. Echocardiographic measurements of cardiac dimensions before, during, and after dialysis[a]

Parameter	HD_{37}	HD_{35}
Before dialysis		
LVDd (cm)	4.7 (4.3, 5.4)	5.0 (4.3, 5.5)
LVDs (cm)	3.2 (3.0, 3.8)	3.6 (3.0, 4.2)
120 min		
LVDd (cm)	4.7 (4.1, 5.3)	4.5 (4.0, 5.6)
LVDs (cm)	3.1 (2.6, 3.9)	3.2 (2.7, 3.8)
240 min		
LVDd (cm)	4.4 (3.9, 5.5)	4.8 (4.0, 5.5)
LVDs (cm)	2.8 (2.2, 4.0)	3.2 (2.8, 4.2)
30 min after dialysis		
LVDd (cm)	4.9 (4.2, 5.5)	4.6 (4.4, 5.7)
LVDs (cm)	3.3 (2.9, 3.9)	3.4 (2.9, 4.0)

[a]There were no significant differences in any of the dimensions when the two dialysis modalities were compared. LVDd, left ventricular diameter in diastole; LVDs, left ventricular diameter in systole. Data are expressed as medians (interquartile range [IQR]).
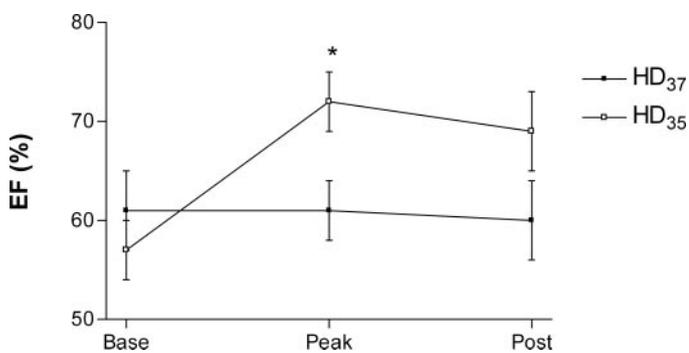

Figure 4. Global systolic function (ejection fraction [EF]) during HD_{37} and HD_{35}. Data are expressed as means ± SEM. *$P < 0.05$ by ANOVA.

lower during HD_{35} with an overall mean of $-26 \pm 14\%$ as compared with a mean of $-15 \pm 5\%$ with HD_{37} ($P < 0.01$).

Thermal Symptoms and Quality-of-Life Assessments

Temperature score was higher (representing a greater sensation of cold) with HD_{35}, with a median of 12 (IQR 7 to 14) as compared with a median of 8 (IQR 6 to 12) with HD_{37} ($P = 0.01$). Of the 10 patients, three experienced cold symptoms to a degree that made them uncomfortable during dialysis, two were able to detect the difference between modalities but did not feel uncomfortable or felt better with HD_{35}, and five were unable to differentiate between the treatments. During HD_{35}, the median temperature score for the patients who experienced unpleasant symptoms of cold was 14 (range 12 to 16) as compared with 10 (IQR 6 to 12) for those who tolerated the intervention ($P = 0.066$). There were no obvious differences that distinguished the patients who did not tolerate HD_{35}; in particular, there were no correlations between temperature score

and either predialysis body temperature or change in body temperature. In addition, there was no difference between the two types of dialysis in quality-of-life score as rated by the SF-36 questionnaire, with median values of 61 (IQR 39 to 78) with HD_{37} and 62 (IQR 50 to 73) with HD_{35} (NS).

There were no differences in body temperature before dialysis, but body temperature after dialysis was lower, and change in body temperature was negative with HD_{35}. Ambient room temperature also was similar between the two types of dialysis and varied by $<1°C$ from the median for all study sessions. Complete temperature data are displayed in Table 4.

Fluid Status and Bioimpedance

Volume status of the patients was similar when the two dialysis modalities were compared. Equally, there were no differences in body weight before and after dialysis or in programmed UF volume (Table 5).

Laboratory Data

There were no differences in any of the biochemical parameters when the two types of dialysis were compared. In particular, Kt/V_{urea} was almost identical between HD_{37} and HD_{35}. In addition, cTnT levels were similar between the two modalities and did not change significantly after dialysis after correction for hemoconcentration. Laboratory data are shown in Table 6.

Discussion

We have shown that a significant number of new, reversible LV RWMA occur during standard dialysis, confirming our previous findings (5). We have also demonstrated that cooling the dialysate, a simple maneuver that is widely available at no additional cost, results in a significant reduction in the development of RWMA.

An increasing body of evidence suggests that subclinical myocardial ischemia develops during hemodialysis. Using similar methods to this study, we previously demonstrated that new RWMA occur during standard dialysis. We also showed that this phenomenon was ameliorated by biofeedback dialysis, during which mean BP was higher and IDH occurred less frequently (5). The echocardiographic findings of dialysis-induced LV RWMA that were seen in both our previous study and in these results are strongly suggestive of subclinical ischemia, analogous to dobutamine stress echocardiography (16). In addition to the work from our center, one study demonstrated dialysis-induced perfusion defects using single photon emission computed tomography (7), and there are 10 reports of silent intradialytic ST depression detected by Holter monitoring (6,17–25). Although initially there was concern that some electrocardiographic changes that were observed during dialysis were related to changes in electrolyte concentrations as opposed to myocardial hypoperfusion, the demonstration of dialysis-induced ischemia by electrocardiographic, echocardiographic, and isotopic techniques certainly suggests that such findings are attributable to ischemia.

Transient myocardial ischemia may lead to LV dysfunction that can persist despite the return of normal perfusion. This is known as myocardial stunning (3). Repeated episodes of isch-
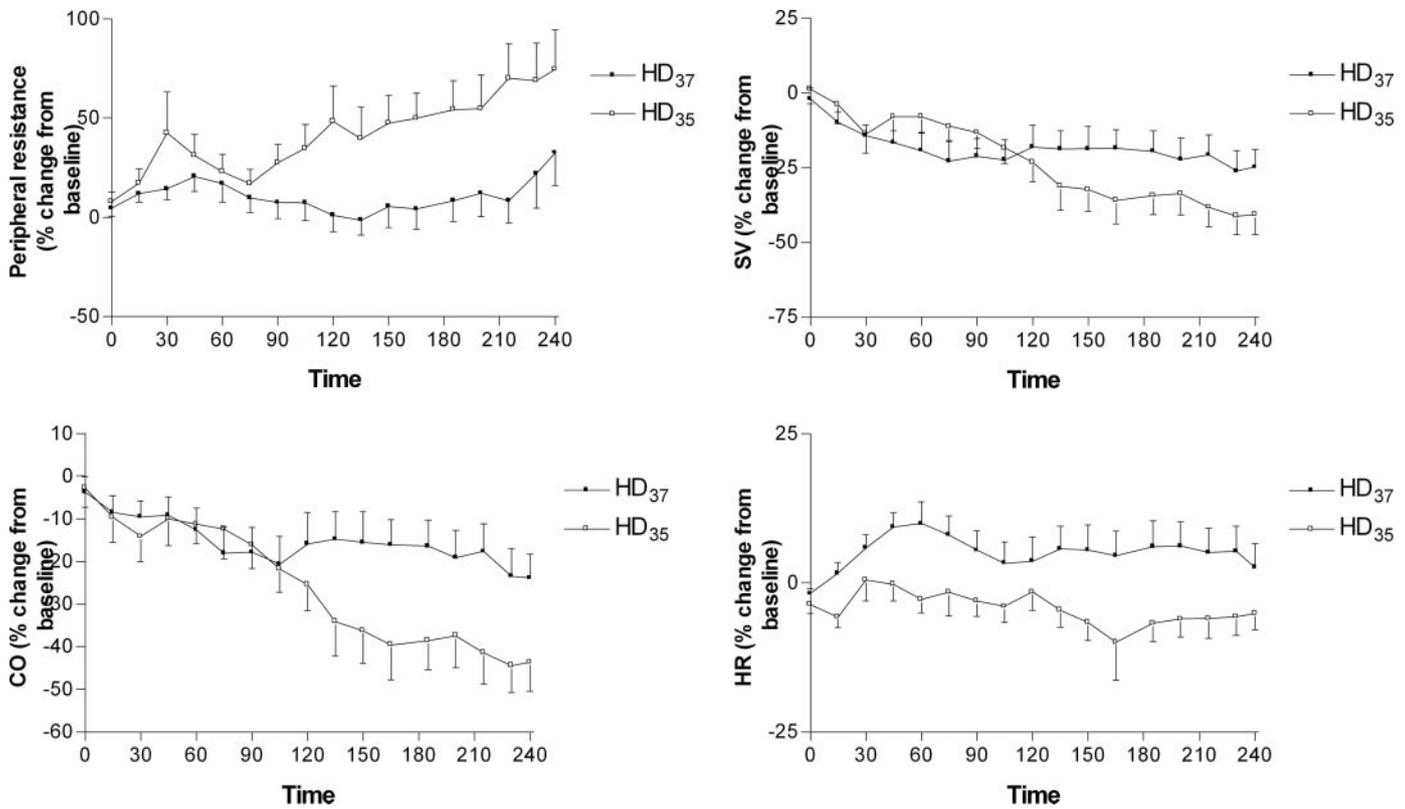
Figure 5. Systemic hemodynamics during HD_{37} and HD_{35}. There was no difference in mean stroke volume (SV) between the two dialysis modalities, but peripheral resistance was significantly higher during HD_{35}. Heart rate (HR) was also lower with HD_{35} as was cardiac output (CO). Data are expressed as means ± SEM.

Table 4. Temperature data[a]

Parameter	HD_{37}	HD_{35}
Temperature score	8 (6 to 12)[b]	12 (7 to 14)[b]
Body temperature before dialysis (°C)	35.3 (34.9 to 36.3)	35.6 (35.1 to 36.6)
Body temperature after dialysis (°C)	36.5 (35.3 to 36.3)[c]	35.5 (35.0 to 35.9)[c]
Change in body temperature (°C)	0.7 (0.05 to 1.3)[d]	−0.6 (−1.35 to 0.05)[d]
Ambient room temperature (°C)	25.1 (24.3 to 25.5)	24.7 (24.5 to 25.4)

[a]Data are medians (IQR). Temperature score rates how cold a patient is feeling during the dialysis treatment, with the lowest score of 6 signifying no thermal symptoms and the highest score of 24 indicating severe symptoms of cold.
[b]$P = 0.01$, [c]$P = 0.02$, [d]$P < 0.001$ by Wilcoxon rank sum.

emia and stunning may be cumulative and lead to the phenomenon of myocardial hibernation that in turn contributes to chronic heart failure in patients with ischemic heart disease (4). In our patients, a significant number of RWMA persisted at 30 min after dialysis, when the conditions that favor the development of ischemia during dialysis had been removed. This could be interpreted as preliminary evidence of dialysis-induced myocardial stunning, backed up by similar results from our previous study (5). Therefore, the occurrence of subclinical ischemia in response to dialysis with sustained but reversible abnormalities in regional function potentially could contribute to the genesis of uremic cardiac failure. However, our short-term study does not assess the long-term sequelae of the pres-

ence of new RWMA on systolic function, which at present remain speculative.

RWMA developed to a much lesser degree during HD_{35}, suggesting less dialysis-induced ischemia. In addition, a greater proportion of affected regions had recovered by 30 min after dialysis with HD_{35}. This finding also may suggest less of an ischemic burden, because more severe episodes of myocardial hypoperfusion cause more prolonged reductions in regional LV function (26). Clear separation was seen in terms of BP and hemodynamic response between HD_{37} and HD_{35}. BP was maintained at a higher overall level with less change throughout the HD_{35} dialysis session. In addition, there were fewer episodes of IDH. With no difference in SV, these differences

Table 5. Bioimpedance data and pre- and postdialysis body weights[a]

Parameter	HD$_{37}$	HD$_{35}$
Body weight before dialysis (kg)	71.8 (60 to 86.4)	71.6 (60 to 87.3)
Body weight after dialysis (kg)	69.7 (59 to 84.4)	69.8 (59.3 to 84.7)
UF volume (ml)	2.0 (1.4 to 2.3)	2.1 (1.6 to 2.4)
Relative blood volume (%)	−4.1 (−8 to −2)	−6.3 (−10 to −4)
ECW (L)	14.5 (12.4 to 16.7)	14.4 (12.7 to 16.6)
ICW (L)	22 (17.9 to 24.3)	21.5 (18.4 to 24)
ECW/TBW	0.41 (0.4 to 0.41)	0.41 (0.4 to 0.42)

[a]Data are median (IQR). There were no significant differences between HD$_{37}$ and HD$_{35}$ for any of the parameters. ECW, extracellular water; ICW, intracellular water; TBW, total body water; UF, ultrafiltration volume.

Table 6. Biochemical data[a]

Parameter	HD$_{37}$		HD$_{35}$	
	Before Dialysis	After Dialysis	Before Dialysis	After Dialysis
Hemoglobin (g/dl)	10.6 (9.6 to 12.0)	10.9 (9.7 to 12.1)	11.2 (10.0 to 12.6)	11.3 (10.1 to 12.9)
Bicarbonate (mmol/L)	23.5 (22.0 to 26.0)	28.0 (28.0 to 29.5)	24.5 (19.5 to 25.5)	28.0 (27.0 to 29.0)
Na$^+$ (mmol/L)	138.0 (135.0 to 140.0)	137.0 (136.0 to 138.0)	138.0 (136.5 to 140.5)	138.0 (137.0 to 138.0)
Corrected Ca^{2+} (mmol/L)	2.42 (2.19 to 2.53)	2.39 (2.25 to 2.45)	2.44 (2.12 to 2.55)	2.38 (2.22 to 2.52
Phosphate (mmol/L)	1.65 (1.24 to 1.92)	0.79 (0.6 to 0.92)	1.52 (1.26 to 2.03)	0.79 (0.67 to 0.91)
Albumin (g/L)	34.5 (32.5 to 37.0)	33.5 (32.0 to 40.0)	34.0 (33.0 to 38.5)	36.5 (33.0 to 39.5)
CRP (mg/L)	5.0 (4.0 to 16.5)	5.0 (5.0 to 16.5)	8.5 (4.0 to 16.0)	8.0 (4.0 to 17.0)
cTnT (μg/L)	0.05 (0.02 to 1.0)	0.05 (0.05 to 0.076)	0.05 (0.02 to 0.12)	0.06 (0.02 to 0.13)
PTH (ng/L)	290.0 (120.0 to 532.0)		302.0 (140.0 to 589.0)	
Kt/V$_{urea}$	1.49 (1.2 to 1.73)		1.48 (1.1 to 1.73)	

[a]Data are median (IQR). There were no significant differences between HD$_{37}$ and HD$_{35}$ for any of the parameters. CRP, C-reactive protein; cTnT, cardiac troponin-T; PTH, parathyroid hormone.

were explained by a greater rise in TPR with HD$_{35}$, signifying vasoconstriction in response to the cooler temperature. These changes, including the lower HR with HD$_{35}$, are consistent with the published studies (10,27), but this favorable hemodynamic and BP response to HD$_{35}$ may result in improved coronary artery perfusion during diastole and therefore explain why fewer RWMA developed. It is possible that either the higher mean BP or the reduction in IDH may be responsible for the reduction in the incidence of RWMA, although it also is conceivable that the effects of both of these factors are synergistic, with IDH that occurs at a lower mean BP potentially having a greater detrimental affect on myocardial perfusion. In summary, the results from this study and our previous study have shown that two different dialysis techniques that both improve the intradialytic BP profile reduce the incidence of new RWMA in two different patient groups.

EF increased during HD$_{35}$ but remained unchanged during HD$_{37}$, resulting in a significant difference between the dialysis modalities at peak stress. The effect of hemodialysis on EF remains controversial, with different studies reporting increases, no change, and also decreases (28–31). The effect of dialysis on EF is related in part to changes in volume status as are the changes in SV, so EF may increase while there is a concurrent decrease in SV. However, there is some evidence

that the degree of cardiac disease also may influence the change in EF (30), possibly determining the degree to which myocardial contractility can be increased. In our study, in the absence of any differences in UF volume, fluid status, or LV dimensions between the two types of dialysis, the greater number of RWMA with HD$_{37}$ potentially could explain why EF did not rise in the same way as during HD$_{35}$. This is consistent with the work of Levy *et al.* (32), who also found an improvement in LV contractility with cool dialysis, which is the only other study of which we are aware that examines LV function in response to cool dialysis.

Reducing the temperature of the dialysate improves IDH, and our results show for the first time that it has a beneficial effect on intradialytic regional LV function. Furthermore, cooling the dialysate is possible on all dialysis monitors and is extremely simple to perform. However, concerns regarding unpleasant symptoms of cold and negative effects on small-solute clearance as a result of increased peripheral sequestration have persisted. Although it is clear from the published literature and from this study that there is no adverse affect on Kt/V$_{urea}$ (10), the effects on patients' symptoms are less clear. In this study, we found that the patient response to HD$_{35}$ was heterogeneous, with three patients finding a dialysate temperature of 35°C too cold (although no patients found it intolerable

in the short term). The majority of patients were unable to detect a difference between the two types of dialysis, and some patients who normally experience hot flushes with a dialysate temperature of 37°C preferred HD$_{35}$. Our study design may have magnified any symptoms of cold by switching directly from 37 to 35°C as opposed to a gradual reduction in temperature. However, there were no obvious features that predicted which patients did and did not tolerate the cooler dialysate; in particular, tolerability was not predicted by predialysis body temperature. Therefore, a practical approach would be to reduce dialysate temperature gradually in steps of 0.5°C, stopping if the patient experiences excessive symptoms or when 35°C is achieved (33). This approach is necessary because there are no data concerning the optimal dialysate temperature to maximize potential benefits while avoiding excessive thermal symptoms. An alternative strategy is isothermic dialysis, in which a biofeedback device constantly adjusts dialysate temperature to keep patient body temperature constant. Isothermic dialysis also has been shown to reduce IDH effectively and causes thermal symptoms in only 5% of treatments (34). However, isothermic dialysis has not been evaluated in terms of its effects on regional LV function and has the disadvantage that it is less widely available because it requires specific dialysis monitors with a dedicated BTM module (Fresenius, Bad Homburg, Germany).

cTnT often is elevated in dialysis patients and predicts mortality (35). Furthermore, cTnT levels are higher in patients who are prone to IDH as compared with stable patients (36). However, there is continuing debate as to whether cTnT rises acutely after dialysis (36–38). In this study, we found no difference in cTnT levels between HD$_{37}$ and HD$_{35}$ and also no acute rise in cTnT after correction for hemoconcentration. In addition, there were no correlations between cTnT levels and the frequency of RWMA. However, all of the studies that examined pre- and postdialysis cTnT levels collected the postdialysis sample at the end of the session, but it is widely recognized that plasma cTnT levels may become elevated only after 6 to 12 h after an episode of ischemia. Therefore, although our findings in respect to cTnT do not refute that myocardial ischemia develops in response to dialysis, they do mean that the development of RWMA cannot be determined by measurement of plasma cTnT levels in this way. It remains to be seen whether cTnT levels before the subsequent dialysis session correlate with the frequency of RWMA; one study found a significant increase in troponin I levels 44 h after dialysis sessions that were complicated by IDH as compared with sessions in which patients were stable (39).

Our study does have some potential weaknesses. Patient numbers are relatively small, and measurements were taken from only one dialysis session, but the results do replicate those of our previous study. We used endocardial borders as the sole marker of abnormal contraction and therefore did not take account of wall thickening or transmyocardial heterogeneity. However, our method is repeatable and quantitative. There is some debate as to whether tympanic temperature accurately reflects body temperature, and although several studies support its accuracy, we did not have the facility to measure blood

line temperature (40,41). Finally, we did not perform coronary angiography on these patients, so we cannot tell to what extent the degree of large-vessel epicardial disease underlay our results.

Conclusion

We have confirmed our previous findings that reversible reductions in regional LV function occur in response to standard hemodialysis. We suggest that these are most likely to represent subclinical myocardial ischemia and may be a potential causative factor in the development of cardiac dysfunction in this patient group. Reducing the temperature of the dialysate is an effective intervention to lessen the development of RWMA and also is associated with improved hemodynamics and less IDH. Further work is now needed to measure myocardial blood flow in conjunction with LV function, to study the long-term development of heart failure in response to repeated dialysis-induced myocardial stunning, and also to determine the optimal dialysate temperature to maximize the benefits of cool dialysis while minimizing thermal symptoms.

Acknowledgments

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Temperature Questionnaire

1. Have you felt cold during dialysis in the past 2 wk?
   - every session ☐
   - sometimes ☐
   - once ☐
   - never ☐

2. In the past 2 wk, have you had to use blankets or extra clothes during dialysis to keep warm?
   - every session ☐
   - sometimes ☐
   - once ☐
   - never ☐

3. Have you felt uncomfortable because of symptoms of cold during dialysis in the past 2 wk?
   - every session ☐
   - sometimes ☐
   - once ☐
   - never ☐

4. In the past 2 wk, have you shivered during dialysis?
   - every session ☐
   - sometimes ☐
   - once ☐
   - never ☐

5. Overall, in the past 2 wk, while on dialysis, have you felt
   - much better than usual ☐
   - slightly better than usual ☐
   - no different than usual ☐
   - slightly worse than usual ☐
   - much worse than usual ☐

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