

Randomized Controlled Trial of Individualized Dialysate Cooling for Cardiac Protection in Hemodialysis Patients

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Abstract

Background and objectives Cardiovascular disease is the most common cause of death in patients on hemodialysis (HD). HD-associated cardiomyopathy is appreciated to be driven by exposure to recurrent and cumulative ischemic insults resulting from hemodynamic instability of conventionally performed intermittent HD treatment itself. Cooled dialysate reduces HD-induced recurrent ischemic injury, but whether this confers long-term protection of the heart in terms of cardiac structure and function is not known.

Design, setting, participants, & measurements Between September 2009 and January 2013, 73 incident HD patients were randomly assigned to a dialysate temperature of 37°C (control) or individualized cooling at 0.5°C below body temperature (intervention) for 12 months. Cardiac structure, function, and aortic distensibility were assessed by cardiac magnetic resonance imaging. Mean between-group difference in delivered dialysate temperature was 1.2°C ± 0.3°C. Treatment effects were determined by the interaction of treatment group with time in linear mixed models.

Results There was no between-group difference in the primary outcome of left ventricular ejection fraction (1.5%; 95% confidence interval, -4.3% to 7.3%). However, left ventricular function assessed by peak systolic strain was preserved by the intervention (-3.3%; 95% confidence interval, -6.5% to -0.2%) as was diastolic function (measured as peak diastolic strain rate, 0.18 s⁻¹; 95% confidence interval, 0.02 to 0.34 s⁻¹). Reduction of left ventricular dilation was demonstrated by significant reduction in left ventricular end-diastolic volume (-23.8 ml; 95% confidence interval, -44.7 to -2.9 ml). The intervention was associated with reduced left ventricular mass (-15.6 g; 95% confidence interval, -29.4 to -1.9 g). Aortic distensibility was preserved in the intervention group (1.8 mmHg⁻¹ × 10⁻³; 95% confidence interval, 0.1 to 3.6 mmHg⁻¹ × 10⁻³). There were no intervention-related withdrawals or adverse events.

Conclusions In patients new to HD, individualized cooled dialysate did not alter the primary outcome but was well tolerated and slowed the progression of HD-associated cardiomyopathy. Because cooler dialysate is universally applicable at no cost, the intervention warrants wider adoption or confirmation of these findings in a larger trial.

Clin J Am Soc Nephrol 10: 1408–1417, 2015. doi: 10.2215/CJN.00200115

Introduction

Over 2 million people worldwide require on-going dialysis to sustain life. Most patients endure unpleasant dialysis-related symptoms and generally have a poor quality of life. Patients on dialysis continue to have a lower life expectancy than many patients with cancer, with cardiovascular disease being the leading cause of death. Several cardiovascular disease therapies effective in the general population have been entirely ineffective in patients on hemodialysis (HD). However, cardiovascular disease in patients on dialysis is not solely caused by traditional risk factors or the uremic milieu (1). HD itself causes recurrent and cumulative ischemic injury to the heart, brain, and other organs (2). Recurrent HD-induced myocardial stunning results in long-term contractile dysfunction,

abnormal ventricular morphology, and increased mortality (3–5).

The reduction in intradialytic hypotension by cooling the dialysate was first demonstrated by the original pioneering work of Maggiore *et al.* (6). However, this therapy remains greatly underused. In the first half of 2014, 24% of in-center HD treatments had dialysate temperature of <36.5°C in a sample of a large dialysis organization in the United States (Len Usvyat, Fresenius Medical Care, personal communication). We have demonstrated in several small short-term pilot studies that improvement in hemodynamic tolerability of HD is associated with marked reduction in myocardial stunning (7–9). The use of extremely low temperature dialysate (34°C–35°C) is effective but limited by cold symptomatic intolerance.

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The cardioprotective effect and cold symptom tolerability can be optimized by an individualized approach to dialysate temperature prescription (10).

We recently reported that an individualized dialysate cooling strategy is effective in reducing HD-associated progressive white matter brain injury (11). This trial aimed to test whether dialysate cooling could provide long-term cardiac protection and abrogate progressive morphologic and functional changes characteristic of HD-associated cardiomyopathy in patients new to conventional thrice-weekly HD.

Materials and Methods

Study Design and Treatment Regimen

The trial was conducted in accordance with the Declaration of Helsinki of 1975 and as revised in 1983. The trial design was a prospectively registered (ISRCTN00206012, October 15, 2009), multicenter, randomized, controlled, open-label, blinded end point study, and the protocol has been published (12). Nottingham Ethics Committee approved the protocol, and all patients gave written informed consent.

Participants

Participants were recruited from the HD centers of four university teaching hospitals in the United Kingdom. Inclusion criteria were ≥ 16 years of age, being within 180 days of commencing in-center HD treatment three times per week, and capacity to consent for the trial. Exclusion criteria were inability to tolerate cardiac magnetic resonance imaging (CMR) because of claustrophobia, contraindications for CMR, pregnancy or lactating, and New York Heart Association grade IV heart failure.

Randomization and Blinding

Patients were randomized 1:1 by a computer-generated sequence placed into sealed envelopes by an independent statistician. Because the HD monitor was iteratively programmed per treatment session with potentially visible settings, it was not pragmatic to reliably maintain blinding for 12 months. Per the prospectively registered, multicenter, randomized, controlled, open-label, blinded end point design, all cardiac imaging analyses were centrally conducted and blinded to patient details or treatment group allocations.

Dialysis Intervention

The control group used a dialysate temperature of 37°C for 12 months. The intervention group used an individualized cooled dialysate temperature for 12 months. The latter was set at 0.5°C less than the patient's, determined from the mean of six prior treatment sessions with a tympanic thermometer, between a minimum of 35°C and a maximum of 36°C. The allocated dialysate temperature remained unchanged for the study period. This ensured a minimum between-group temperature separation of 1°C in the event that a participant had a mean temperature $>36.5^\circ\text{C}$. Preliminary review of electronically recorded data indicated the mean allocated intervention group temperature was likely to be 1°C–1.5°C lower than the control group. Protocol adherence was regularly assessed and recorded by HD center staff.

Concurrent Treatments

Patients in both trial arms had standard management with dry weight prescribed by the clinical team according to local protocol, including thrice-weekly HD to achieve an equilibrated $\text{Kt/V}_{\text{urea}} > 1.1$, a standardized $\text{Kt/V}_{\text{urea}} > 2.0$, and a treatment time of between 3.5 and 4 hours. HD treatments used low-flux polysulfone dialyzers (1.8–2.0 m^2 ; LOPS 18/20; Braun Medical, Sheffield, UK). Dialysate composition was sodium 313–317 mg/dl, potassium 3.9 mg/dl, calcium 5.0 mg/dl, magnesium 1.2 mg/dl, bicarbonate 32–38 mEq/L and glucose 101 mg/dl. Dialysate flow rate was 500 ml/min, and blood pump speed was 250–450 ml/min using anticoagulation by unfractionated heparin.

Data Collection

Imaging studies by CMR occurred on a midweek post-dialysis day at baseline and 12 months to avoid the long interdialytic break after the weekend, when patients are most hypervolemic (13,14). Studies were conducted at two centers using a 1.5-T scanner (GE Signa HDxt; GE Healthcare, Milwaukee, WI) by validated methods (15). Acquisition parameters achieved a spatial resolution of < 2 mm and a temporal resolution of 20–40 ms. Radiofrequency tagging used a spatial modulation of magnetization sequence applied at basal, midventricular, and apical levels. An oblique sagittal orientation was acquired to image the aorta in long axis, and a 5-mm-thick axial cine was acquired at the level of the pulmonary artery bifurcation.

Body Composition

Volume status was assessed by segmental multiple frequency bioelectric impedance measurements at baseline and 12 months, using tetrapolar 8-point tactile electrodes (InBody S20; Biospace, Seoul, South Korea) (16). Hypervolemia was estimated by the ratio of extracellular water to total body water (17).

Data Analysis

Planimetry, as previously described, was used to determine left ventricular (LV) mass, volumes, and ejection fraction (EF) with cvi42 software version 4.0.2 (Circle Cardiovascular Imaging, Calgary, AB, Canada) (15). Values were indexed to body surface area using the method described by Mosteller (18).

LV Strain Analysis

Direct assessment of regional motion within myocardial tissue by LV strain has inherently greater sensitivity and specificity to detect LV dysfunction than the EF, which infers function from the bulk effect of LV boundaries. Greater LV strain denotes better LV function. Reduced LV strain precedes LV dilation, LV hypertrophy, and reduced EF in a range of cardiomyopathies (19). Tagged CMR is a highly reproducible, reference standard technique to quantify regional LV strain (19). This involves changing magnetization during CMR image acquisition to tag the left ventricle with a grid pattern. Software then tracks the motion of these tags to quantify the magnitude (strain) and velocity (strain rate) of tissue motion. Midwall circumferential strain was measured in tagged LV short-axis images using validated software (HARP 3.0;

Diagnosoft, Palo Alto, CA) as depicted in Figure 1, A–D (20). Values were mapped to the 16-segment model of the left ventricle recommended by the American Heart Association (21) then averaged to derive global peak systolic strain (%), peak systolic strain rate (s^{-1}), and peak diastolic strain rate (s^{-1}).

Aortic Distensibility

Aortic distensibility analysis is depicted in Figure 1, E and F as previously described (22). The ascending thoracic aortic area was manually traced using Jim version 6 (Xinapse software, UK) and graphically represented against time. Aortic distensibility was determined by the following validated formula:

$$\frac{(\text{maximum aortic area} - \text{minimum aortic area})}{(\text{minimum aortic area} \times \Delta P)},$$

where ΔP is the mean of three brachial pulse pressure readings performed during CMR (23).

Statistical Analyses

Descriptive statistics for continuous variables were tested for normality and summarized using mean $\pm$ SD or median (interquartile range; 75th percentile–25th percentile). Discrete variables were summarized by proportions. Treatment outcomes were estimated by the interaction of treatment group with time in linear mixed-effects models. Patients were specified as random intercepts adjusted for study center, age, sex, and diabetes status, and the covariance matrix was unstructured. Treatment effect estimates for the segmental strain also accounted for correlations of LV segments within patients. Because outcomes were assessed at a single follow-up time, these models produced essentially identical results to the analysis of covariance. All prespecified analyses used a two-sided significance at $P < 0.05$, with the per-comparison error rate controlled using the correction described by Šidák (24). To minimize bias in treatment outcome estimates, analyses were performed by the intention-to-treat principle with multiple imputation of missing follow-up CMR data, as detailed

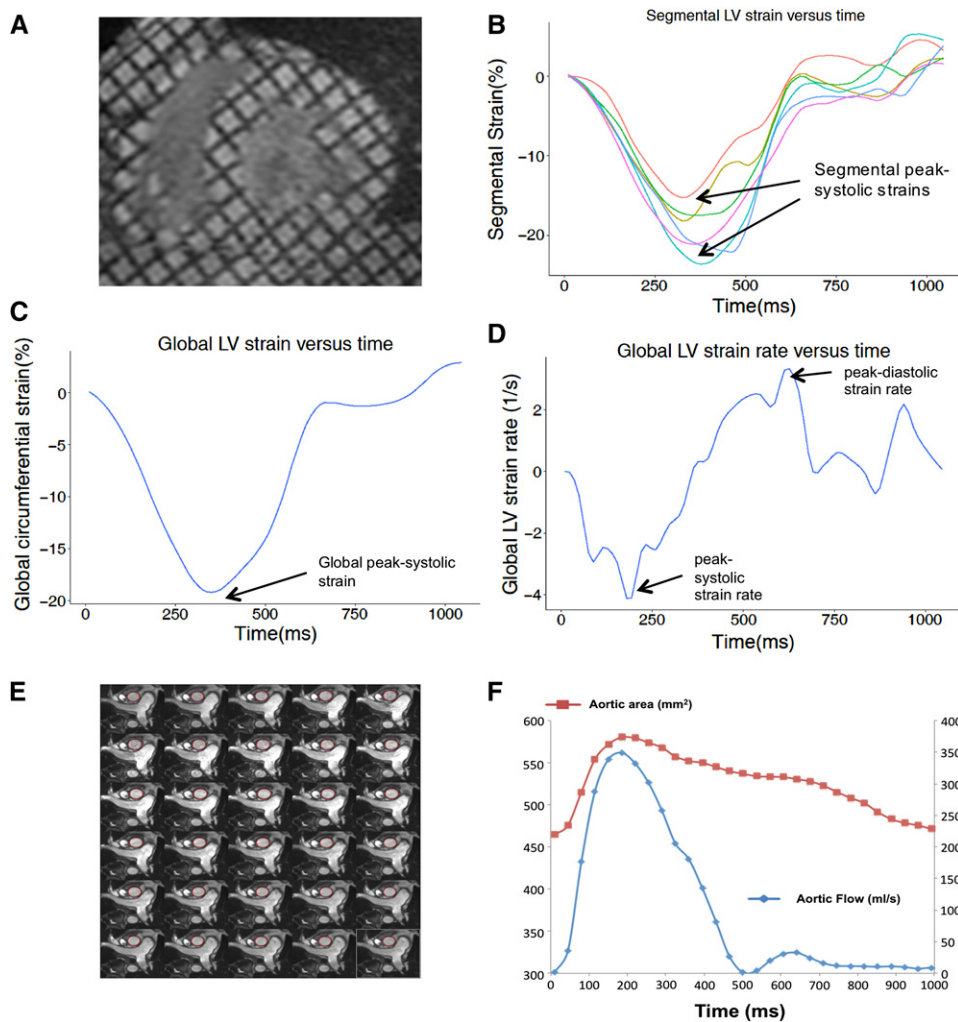


Figure 1. | Cardiac magnetic resonance imaging analysis in a typical study participant. Tagged LV short-axis images (A) and derived LV segmental strain curves (B). These were averaged to determine the global LV strain (C) and strain-rate (D) curves from which peak systolic and diastolic values were used as study outcomes (arrows). Aortic distensibility was determined by semiautomated tracing of the ascending aorta in 30 phases per cardiac cycle (E) to derive the aortic area (F, red line, left y axis) and aortic blood flow (F, blue line, right y axis). LV, left ventricular.

in the Supplemental Material (25). *Post hoc* explanatory analyses of interdialytic weight gain and predialysis BP were done without data imputation using a two-sided significance level of $P < 0.001$. SPSS version 21.0 was used for all analyses.

Primary Study Outcome

The prespecified primary outcome was the change in the resting EF by CMR at 12 months compared with baseline between the intervention and control groups.

Secondary Study Outcomes

The prespecified secondary outcomes were LV mass and LV volumes, global peak systolic strain, global peak systolic strain rate, global peak diastolic strain rate, and aortic distensibility.

Rationale for Study Outcomes

No applicable strain-based data on patients on HD were available before this study. We used data from a previous natural history study of patients well established on HD, using the observed 13% reduction in the EF by echocardiography over 12 months seen in patients experiencing HD-induced LV wall motion abnormalities versus those who did not (3). Prior data supported the EF as a predictor of cardiovascular mortality, with a change of 5% approaching the minimum clinically important difference (26). CMR is the reference technique to determine the EF (27). Because some clinical therapy trials for heart failure reported mortality reductions with an unaltered EF, we augmented assessment of the EF with LV mass, LV strain, and aortic distensibility, characterizing potentially subclinical cardiomyopathy. Several studies in patients on HD showed an independent association of changes in LV mass with cardiovascular mortality (28,29). Recent studies determined that systolic strain and diastolic dysfunction predicted all-cause mortality or cardiovascular events in patients on HD with a normal EF (30,31). Both HD and non-HD population studies show that aortic distensibility independently predicts future cardiovascular events (22,32).

Sample Size Estimation

Assuming a mean $\pm$ SD EF of $67\% \pm 6\%$ in the control arm, a study of 64 participants would resolve a 5% difference in the EF between groups with 90% power at 5%, two-sided significance level (15). The trial would require 52 participants to retain 80% power for a 5% difference in the EF under the same assumptions. Allowing for study attrition of 10%, target recruitment was set at 72 participants.

Monitoring for Adverse Events

Treatment-related adverse events were summarized for each treatment group.

Results

Patient Characteristics

Seventy-three patients were enrolled into the trial and randomized; 54 patients were analyzed (28 control, 26

intervention; age, 60 ± 24 years). The Consolidated Standards of Reporting Trials flowchart is provided in Figure 2. Baseline characteristics were similar between the two randomized groups (Table 1).

Adverse Events and Protocol Adherence to Treatment Allocation

There were no intervention-related withdrawals in the intervention group. Two patients in the control group did not tolerate a dialysate temperature of 37°C and had dialysate temperature lowered to 36°C by the clinical team independent of the investigators. They were included in all analyses by their original treatment allocation. The mean delivered dialysate temperature in the intervention group was $35.8^\circ\text{C} \pm 0.3^\circ\text{C}$ achieving a $1.2^\circ\text{C} \pm 0.3^\circ\text{C}$ between-group separation.

The prespecified treatment outcomes are summarized in Table 2 and additionally represented as standardized effect sizes in Figure 3.

Primary Outcome

There was no statistically significant change in EF between control and intervention groups (1.5%; 95% confidence interval [95% CI], -4.3% to 7.3%).

Secondary Outcomes

The intervention was associated with significant reductions in LV mass (-15.6 g; 95% CI, -29.4 to -1.9 g) (Table 2). The intervention was also associated with a significant reduction in LV end-diastolic volumes compared with no change in the control group (-23.8 ml; 95% CI, -44.7 to -2.9 ml) (Table 2). Global LV systolic function by peak systolic strain was preserved in the intervention group and significantly reduced in the control group (within-group change $0\% \pm 7.6\%$ in intervention group versus $3.3\% \pm 6.9\%$ decrease in control group; difference, -3.3% ; 95% CI, -6.5% to -0.2%). Similarly, the intervention preserved the peak systolic strain rate (-0.2 s $^{-1}$; 95% CI, -0.3 to -0.08 s $^{-1}$). There was also preservation of diastolic function in the intervention group relative to the control group (0.18 s $^{-1}$; 95% CI, 0.02 to 0.34 s $^{-1}$). Regional LV analysis showed significant segmental strain reduction in 10 of 16 LV segments in the control group compared with no significant change in the intervention group (Figure 4). Aortic distensibility was preserved in the intervention group and significantly decreased in the control group (-0.3 ± 2.6 mmHg $^{-1} \times 10^{-3}$ intervention group versus -2.3 ± 0.6 mmHg $^{-1} \times 10^{-3}$ control group; difference, 1.8 ; 95% CI, 0.1 to 3.6 mmHg $^{-1} \times 10^{-3}$).

Post Hoc Explanatory Analyses

Analyses of volume status by bioimpedance, interdialytic weight gain, and predialysis mean arterial BP showed no significant differences between groups over 12 months and no differential effects of baseline LV mass on treatment effects (as detailed in the Supplemental Material).

Discussion

This randomized controlled trial demonstrates that the use of individualized cooler dialysate results in preservation, or

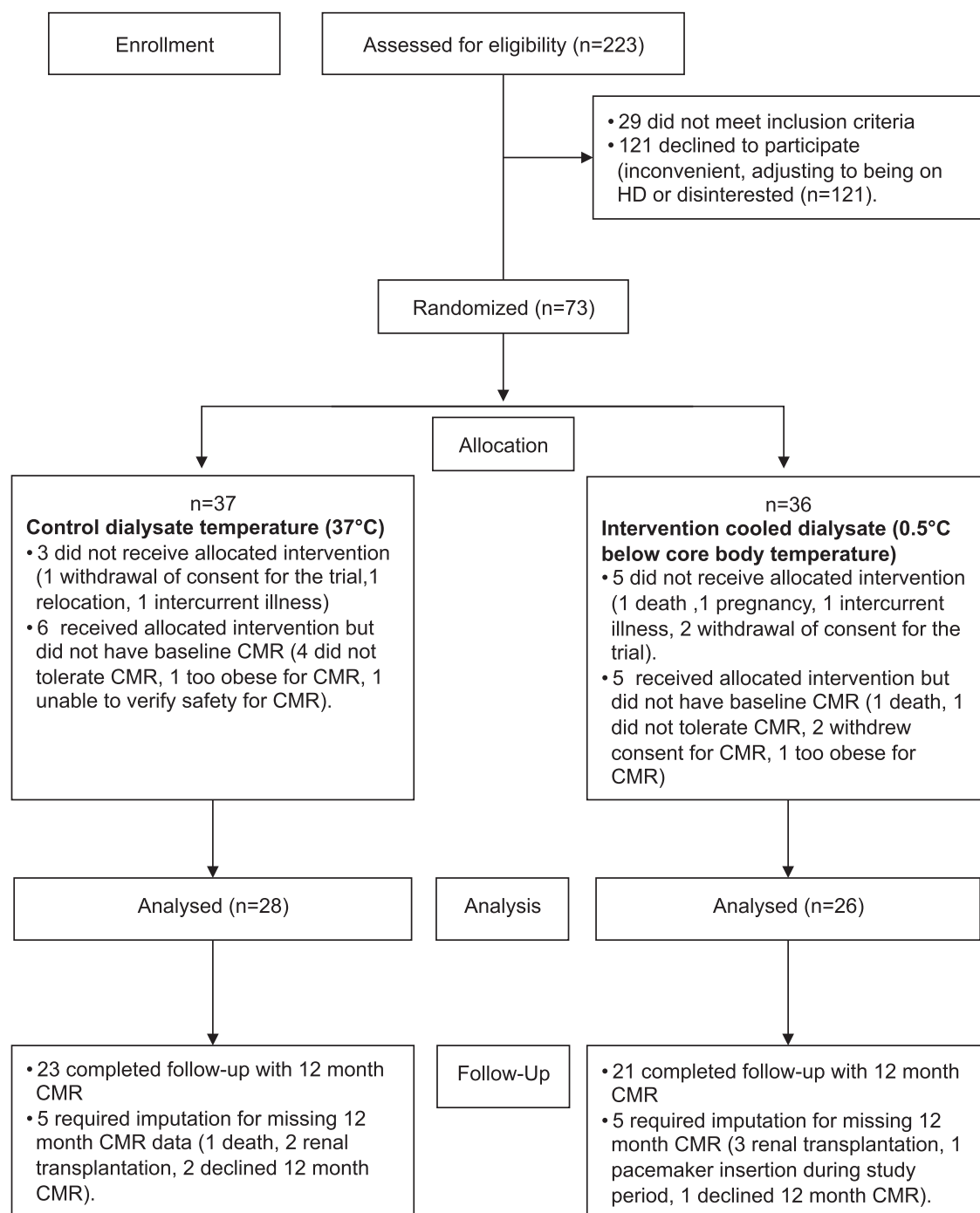


Figure 2. | Consolidated Standards of Reporting Trials flowchart. CMR, cardiac magnetic resonance imaging; HD, hemodialysis.

improvements, in important structural and functional cardiovascular abnormalities in patients on HD. The intervention was operationally simple to deliver, fitting well within an existing model of care for patients on HD and providing a substantial differential in delivered temperature. The existence of this differential reinforces the considerable variation in core temperature encountered within patients on dialysis. Although a significant difference in the primary outcome of EF was not evident, it should be emphasized that the intervention was associated with preservation or improve-

ment in an otherwise complete range of prespecified and clinically relevant secondary outcomes. This comprehensive assessment was made possible by the application of advanced CMR, to directly quantify included measures of LV systolic and diastolic function, aortic distensibility, and LV mass. The observed effect sizes are of a magnitude previously associated with changes in cardiovascular mortality in patients on HD (28,33).

The more recent application of strain analysis has confirmed the prognostic value when the EF is preserved,

Table 1. Baseline patient characteristics

Characteristic	Control Dialysate Temperature 37°C (n=28)	Individualized Cooled Dialysate Temperature (n=26)
Age (y)	60 (25)	60 (26)
Female (%)	8 (36)	7 (33)
BMI (kg/m ²)	28±6	28±6
BSA (m ²)	1.9±0.2	1.9±0.2
Systolic BP (mmHg)	142 (28)	140 (28)
Diastolic BP (mmHg)	76±13	75±11
Pulse pressure (mmHg)	62 (29)	59 (30)
Medical history		
HD vintage (d)	135±69	122±69
Tunneled catheter (%)	8 (29)	5 (19)
Arteriovenous fistula (%)	20 (71)	21 (81)
Ischemic heart disease (%)	4 (14)	3 (12)
Current/ex-smoker (%)	8 (36)	13 (59)
Peripheral vascular disease (%)	2 (9)	5 (24)
Primary renal disease		
Diabetes mellitus (%)	8 (29)	6 (21)
GN (%)	4 (14)	3 (11)
Interstitial nephritis (%)	2 (7)	4 (14)
Vasculitis (%)	3 (11)	1 (4)
Polycystic kidney disease (%)	2 (7)	1 (4)
Renovascular disease/malignant hypertension (%)	2 (7)	4 (14)
Plasma cell dyscrasias (%)	1 (4)	3 (11)
Unknown/others (%)	6 (21)	4 (14)
Medication		
Treated hypertension (%)	21 (75)	21 (81)
RAAS antagonist (%)	8 (29)	6 (23)
β-Blocker (%)	9 (32)	10 (39)
Statin use (%)	12 (43)	11 (42)
Phosphate binder		
Calcium containing (%)	11 (39)	4 (15)
Noncalcium (%)	9 (32)	5 (19)
Erythropoiesis-stimulating agent (%)	21 (75)	26 (69)
Vitamin D analog (%)	16 (57)	15 (58)
Laboratory values		
Hemoglobin (g/dl)	10.9±1.4	11.1±1.6
Calcium (mg/dl)	9.2±0.8	9.2±0.4
Phosphate (mg/dl)	5.0 (1.2)	4.7 (2.8)
Albumin (g/dl)	3.6±0.4	3.6±0.3
Total cholesterol (mg/dl)	127.6 (23.2)	139.2 (30.9)
Ultrafiltration per session (L)	2.0±0.9	2.0±0.8

Continuous data were tested for normality and summarized using mean±SD or median (interquartile range). Categorical data were expressed as counts (percentages). BMI, body mass Index; BSA, body surface area; HD, hemodialysis; RAAS, renin-angiotensin aldosterone system.

supporting that the EF may not have been the optimal primary cardiac imaging-based outcome (30,31). In this trial there was a clear and consistent signal of both preservation of function directly measured by LV strain and inferred from reductions in LV mass and LV dilation that the cooling intervention was effective at protecting the heart.

LV hypertrophy is an established predictor of cardiovascular mortality in patients on HD, and reducing LV mass is recognized as an important therapeutic goal (28). Conventional approaches to achieve this have largely relied on the control of pressure and volume overload. Daily dialysis is an effective approach in this respect, and the

Frequent Hemodialysis Network trials reported that HD six times weekly led to an adjusted mean reduction in LV mass (−13.8 g; 95% CI, −21.8 to −5.8g) and LV end-diastolic volume (−11.0%; 95% CI, −16% to −6%), with no change in EF over 12 months compared with conventional thrice-weekly HD (34,35). This trial reports a similar reduction in LV mass (−15.6 g; 95% CI, −29.4 to −1.9 g) and LV end-diastolic volume (−23.8 ml; 95% CI, −44.7 to −2.9 ml), with no change in EF over 12 months. In keeping with the Frequent Hemodialysis Network trials, the magnitude of the LV mass reduction was partially dependent on baseline LV mass (36). It is of particular interest in our trial that the observed reductions of LV mass cannot be

Table 2. Trial outcomes

End Point ^a	Treatment	Baseline	12 mo	Treatment Difference Between Groups ^f
EF (%)	Control	58.7±8.5	57.6±8.5	1.5 (−4.3 to 7.3)
	Intervention	57.4±15.3	61.0±18.4	
LV mass (g)	Control	140.3±48.7	141.3±48.7	−15.6 (−29.4 to −1.9)
	Intervention	157.9±50.5	145.6±50.5	
LV mass indexed to BSA (g/m ²)	Control	72.4±21.7	73.5±31.7	−8.1 (−15.5 to −0.8)
	Intervention	80.7±17.8	75.0±26.5	
Global peak systolic strain (%) ^b	Control	−16.3±3.7	−13.0±6.9	−3.3 (−6.5 to −0.2)
	Intervention	−15.9±4.6	−15.9±7.6	
Global peak systolic strain rate (s ^{−1}) ^c	Control	−0.97±0.2	−0.87±0.21	−0.2 (−0.3 to −0.08)
	Intervention	−1.02±0.3	−1.03±0.25	
Global peak diastolic strain rate (s ^{−1}) ^d	Control	1.05±0.3	0.90±0.42	0.18 (0.02 to 0.34)
	Intervention	1.12±0.4	1.00±0.41	
LV end-diastolic volume (ml)	Control	150.3±37	156.1±37	−23.8 (−44.7 to −2.9)
	Intervention	162.9±39.8	144.5±39.8	
LV end-diastolic volume indexed to BSA (ml/m ²)	Control	78.8±21.2	75.6±31.2	−12.4 (−23.2 to −1.5)
	Intervention	83.5±27	73.3±29.1	
Aortic distensibility (mmHg ^{−1} ×10 ^{−3}) ^e	Control	4.4±2.6	2.1±2.6	1.8 (0.1 to 3.6)
	Intervention	3.4±2.5	3.1±2.5	

EF, left ventricular ejection fraction; LV, left ventricle; BSA, body surface area.

^aMean±SD of observed values were adjusted using a linear mixed-effects model for study center, age, sex, and diabetes status.

^bSystolic strain values are conventionally expressed on a negative scale as a percentage change in LV length from baseline, with more negative changes denoting better systolic function.

^cSystolic strain rate values are expressed on a negative scale, with more negative changes denoting better systolic function.

^dDiastolic strain rate values are a measure of diastolic function, with greater values denoting better function.

^eAortic distensibility data were skewed and therefore logarithmically transformed values were used, with coefficients back-transformed for presentation.

^fTreatment effects are expressed as mean (95% CI) and were determined by the interaction of treatment group with time.

explained by differences in predialysis BP, fluid status, or interdialytic weight gain. However, the myocardium is capable of responding to a wide variety of other remodeling signals (37,38). Repetitive cardiac ischemia leads to cardiac hypertrophy and fibrosis; reduced HD induced ischemia by cooler dialysate may exert a potent influence (39,40). Directly protective benefits of lower temperatures on cardiac myocytes have also been described (41). Furthermore, there are important interactions between the left ventricle and aortic function (so-called ventriculovascular coupling). Prior data showed reduced aortic distensibility or LV hypertrophy increased myocardial oxygen demand or reduced diastolic coronary artery perfusion (42). Therefore, patients with lesser aortic distensibility or increasing LV mass are more vulnerable to repetitive HD-induced cardiac ischemia (43,44). The preserved aortic distensibility over 12 months in the intervention group compared with significant reductions in the control group may have contributed to the observed cardiac effects (22,32). The interactions between intradialytic events and fluid/volume status are complex, and additional investigations are warranted to understand the mechanisms by which dialysate cooling might attenuate the progression of cardiomyopathy in patients on HD. Future trials might be predicated on clinical outcomes and run as registry-based, cluster randomized controlled trials. On the basis of current event rates, 3-year follow-up, and average facility size of 121 patients, we estimate a study would require 14 clusters per arm to detect a 20% reduction in a primary composite end point of all-cause mortality or

hospitalizations with a major cardiovascular event. However, because dialysate cooling is universally applicable without cost and well tolerated, with no apparent harm and probable benefits to both the heart and brain (11), dialysis clinicians and patients may alternatively consider that these data approach proof beyond a reasonable doubt and adopt wider use without further trials.

Limitations

This first randomized trial of dialysate cooling has important limitations. The trial was not designed to reliably estimate hard clinical outcomes such as hospitalization rates or mortality. Data on nursing interventions and intradialytic hypotensive events were beyond the scope and resources of the trial but may have better explained the mechanisms of the reported benefits. Data to reliably inform the likely effect size were unavailable. With multiple imputation, the sample size retained 80% power to determine differences in the primary outcome of EF compared with the original target of 90%. The sample size also retained 90% power to resolve a 10% difference in LV peak systolic strain (45); however, data to inform estimations for this more sensitive outcome were unavailable when the trial was designed. There was greater than anticipated attrition before the first CMR assessment that was not treatment related. Similar attrition from CMR assessment has been reported in recent clinical trials in patients on HD using CMR (35). Such attrition might in part be caused by recruiting from an incident population, who

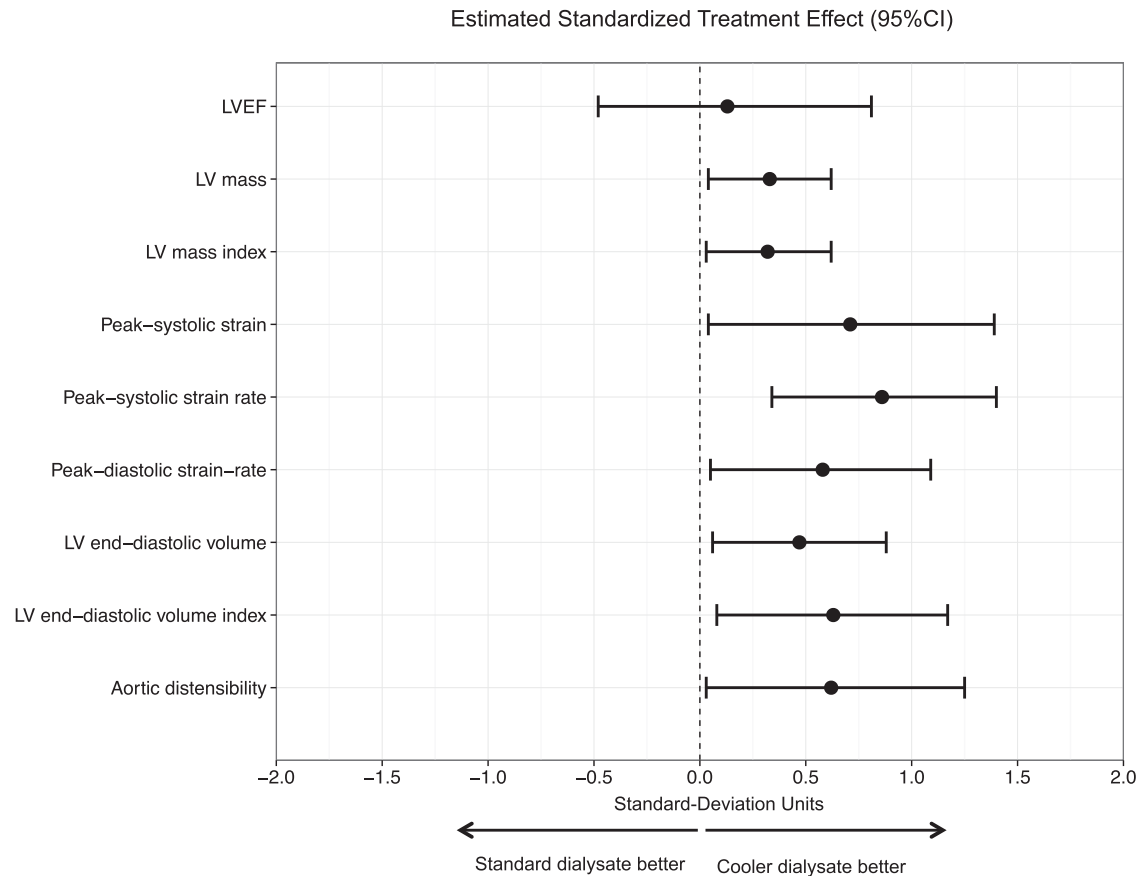


Figure 3. | Trial outcomes expressed as standardized effect sizes with 95% confidence intervals. The mean changes from Table 2 are divided by the pooled SD of the variable at baseline. LV, left ventricular; LVEF, left ventricular ejection fraction.

were adjusting to starting on HD, and wide inclusion criteria allowing enrollment of patients with significant comorbidities who were less likely to undergo CMR.

Although the primary outcome of EF was unchanged, this study is the first to demonstrate that an intervention delivered within the context of conventional thrice-weekly HD attenuates the progression of cardiomyopathy by reducing LV mass and dilation and preserving LV strain and aortic distensibility without adverse events. Dialysate cooling was operationally simple to deliver, well tolerated, universally applicable, and cost free. This strongly suggests that attention to the hemodynamic tolerability of dialysis is

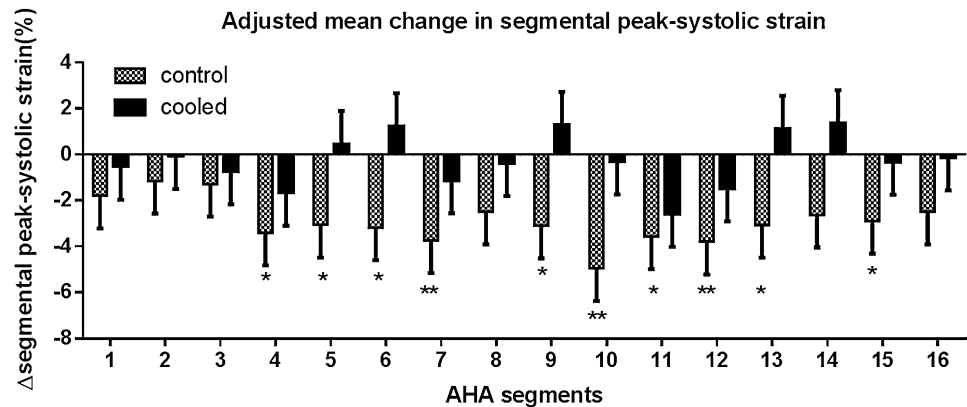


Figure 4. | Within-group comparisons of adjusted mean ± SEM of absolute change in peak systolic strain (%) from baseline to 12 months using the American Heart Association 16-segment model of the left ventricle. Strain values are conventionally expressed on a negative scale as a percentage change in length from baseline, with larger changes denoting better function. *P* values are for the interaction of treatment group with time in a linear mixed-effects model. **P*<0.05; ***P*<0.01. AHA, American Heart Association.

important to improve long-term outcomes for patients on HD and warrants further definitive study or wider adoption.

Acknowledgments

We acknowledge the statistical support of Mr. Apostolos Fakis. We acknowledge the use of software and analytic assistance of Dr. Mark Horsfield. We thank Prof. Simon Davies, Dr. Veena Reddy, Dr. Indranil Dasgupta, study participants, and nursing and allied health care professionals for their time. We thank the magnetic resonance radiographers led by Mrs. Kathryn Appleyard at the Nuffield Derby Hospital and Mr. David Capener at the University of Sheffield. We acknowledge useful discussions with Dr. Robert Foley and the assistance of Dr. James Fotheringham with data parsing. We acknowledge the helpful comments of the anonymous peer reviewers.

This study was funded by a National Institute for Health Research Research for Patient Benefit Grant (PB-PG-0408-16195). Dr. Odudu acknowledges the support of a British Heart Foundation Clinical Research Training Fellowship Grant (FS/11/10/28564) and a National Institute for Health Research Clinical Lectureship. Dr. McCann is supported by a National Institute for Health Research Post-Doctoral Research Fellowship (PDF-2011-04-51). The study was sponsored by Derby Hospitals National Health Service Foundation Trust.

Parts of the study outcomes were presented in preliminary form at the American Society of Nephrology conference in November 2013.

The funder had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Disclosures

None.

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Received: January 7, 2015 **Accepted:** March 30, 2015

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, “Lower Dialysate Temperature in Hemodialysis: Is It a Cool Idea?,” on pages 1318–1320.

This article contains supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.00200115/-/DCSupplemental>.