Vascular instability and severe episodes of intradialytic hypotension (IDH) represent the most frequent (up to 20%) (1) and challenging complications of conventional dialysis regimens (2), resulting in underdialysis and volume expansion (3). In addition, repeated episodes of IDH are uncomfortable for the patient and may cause multisystem morbidity and increased risk of mortality (3). These adverse health outcomes are thought to result from recurrent and cumulative ischemic insults to multiple organs, such as the brain (4), heart, skin vessels, and native kidneys. Catecholamine impairment, plasma sodium or osmolality changes, endothelial nitric oxide synthesis (5), and dialysate temperature may contribute to this instability (2).

Various hemodynamically friendly hemodialysis (HD) prescriptions to address IDH have previously been tested with variable success (3). In previous work, lowering the dialysate temperature (cool dialysis) has been advocated as a simple, useful, universally applicable, and economic procedure, especially for highly symptomatic patients (6–8). Most of the HD patients (76%–80%) report feeling more energetic after HD and request to be always dialyzed with cool dialysate (7,9).

Finally, in the study by Ayoub and Finlayson (9) the groups who appeared to benefit most from cool dialysate were women, patients >55 years old, patients with low body surface area, and patients with cardiovascular disease.

In this issue of CJASN, Odudu et al. (10) aimed to test whether dialysate cooling could provide long-term cardiac protection and attenuate progressive morphologic and functional changes characteristic of HD-associated cardiomyopathy in patients new to thrice-weekly HD. The study design was an open-label, multicenter, randomized controlled trial with blinded end point assessment. Participants were recruited from HD centers of four university hospitals in the United Kingdom. All cardiac imaging analyses were centrally blinded to patient details or treatment group allocations. Dialysis treatments used low-flux polysulfone dialyzers.

In this study, 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, cardiac function, and aortic distensibility were assessed by cardiac magnetic resonance imaging (MRI).

At the end of the study period, 44 patients completed cardiac MRI at 12 months and 54 patients were analyzed using multiple imputation approaches (28 controls, 26 interventions). There was no between-group difference in the primary outcome of left ventricular (LV) ejection fraction. However, LV function assessed by peak-systolic strain was preserved by the intervention, as was diastolic function (measured as the peak diastolic strain rate). A reduction of LV dilation was demonstrated by a significant reduction in LV end-diastolic volume. The intervention was associated with reduced LV mass while aortic distensibility was preserved. There were no intervention-related withdrawals or adverse events reported.

When considering whether this work should change patient care, it is important to note that this was a small study using surrogate outcomes. As noted by the investigators, the trial was not designed to reliably estimate clinical outcomes such as hospitalization or mortality. Furthermore, this was a relatively short-term study of incident patients, which may not be generalizable to the majority of patients currently undergoing HD. Importantly, there was a substantial difference in baseline LV mass between the control and intervention groups, which was likely related to the small number of patients randomized in the study with the intervention group having a larger LV mass. It is possible that the changes observed between the groups were related to the differences in LV mass at baseline, because a person with a relatively normal LV mass is unlikely to have a dramatic reduction. Other important questions were not directly addressed by this study design: What happens to the cardiac structure and function during dialysis with cooler dialysate? Are there other effects of lower temperature dialysate, such as improving sleep or reducing inflammation, which may influence outcomes?

When trying to understand the results presented by Odudu et al. (11), it is helpful to consider the hemodynamic challenges faced by patients undergoing HD. Pathophysiological mechanisms specifically related to IDH are patient related or treatment related. Pathogenic factors leading to symptomatic IDH include the following: (1) the decline in blood volume, resulting from the imbalance between ultrafiltration (UF) and refilling from the interstitial compartment; (2) cardiac factors; and (3) inadequate/impaired vascular response of both arterial and venous circulation during a related to thermal...
factors decline in blood volume (12). Potential treatment factors contributing to IDH include cytokine release as a result of blood-membrane interaction, a potential transfer of heat from dialysate to blood, and reduced skin heat losses owing to peripheral vasoconstriction in response to UF (1). Although an increase in metabolic rate/heat production during HD has not been proven (13), this positive thermal balance can contribute to a loss of the vascular tone and hypotension (1,11).

In addition to cool dialysate attenuating a thermal load during dialysis, previous work examining cool dialysis demonstrated an improved cardiovascular response by avoiding vasodilation and increasing myocardial contractility (11). Cool HD is linked to improved LV contractility, independent of before and after load (9). In a randomized crossover study, Selby et al. (14) examined whether the improved stability of cool-temperature lessens the subclinical ischemia that occurs during HD in 10 IDH-prone patients. The authors compared the development of HD-induced LV regional wall motion abnormalities (RWMAs) at dialysate temperatures of 37°C (HD37) and 35°C (HD35). Overall, regional systolic LV function was significantly more impaired during dialysis treatments at 37°C. Ejection fraction increased during HD35 but remained unchanged during HD37, resulting in a significant difference between the dialysis modalities at peak stress. BP was higher using cooler dialysate, with fewer hypotensive episodes as a result of a higher peripheral resistance and no difference in stroke volume. This study confirmed previous findings of reversible LV RWMAs that develop during standard HD. The echocardiographic findings of HD-induced LV RWMAs in this study were strongly suggestive of subclinical ischemia. These investigators posited that these subclinical ischemic events may be a potential causative factor in the development of cardiac dysfunction in HD patients.

There are some potential side effects and hazards related to extended use of dialysate cooling in HD, including shivering, cramps, and a risk of impaired urea clearance as a result of compartmental disequilibrium by producing a thermally induced decrease in regional blood flow (3). However, the efficacy of “cool” HD with respect to low molecular weight molecules such as urea is not thought to be compromised (15). Furthermore, in 2006, Selby et al. (8) published a systematic review of 22 prospective randomized studies that compared any technique of reducing dialysate temperature with standard bicarbonate dialysis. No studies reported that cool dialysis led to a reduction in dialysis adequacy as assessed by urea clearance. But is urea an adequate representative of toxin removal? Urea is a small molecule with a negligible intercompartmental resistance. The same does not apply for large-sized or even other small-sized uremic toxins. In a recently published study protocol, Maheshwari et al. (16) aim to compare the toxin removal outcome associated with cool versus warm dialysate among stable HD patients. The results of this work will potentially answer whether prolonged usage of cool dialysis leads to poor patient outcomes by impaired toxin removal.

The goal of the dialysate temperature selection should be to maintain temperature homeostasis without engaging the physiologic defense mechanisms. The selection of 37°C as a neutral dialysate temperature assumes that this is the average normal body temperature for most patients. This assumption is not supported by the literature. HD patients exhibit, on average, a body temperature lower than that of the healthy population, with normal temperature usually lower than 37°C. Dialysis patients further exhibit significant sex, race, and measurable circadian changes in body temperature. Therefore, a one-size-fits-all approach to prescribing a dialysate temperature of 37°C most likely results in a positive thermal balance during HD and increases the body temperature. Thermoregulatory reflex skin vasodilation threatens hypotension because of decreased peripheral vascular resistance. This can be prevented by optimally adjusting the dialysate temperature (17).

The study by Odudu et al. prescribed a dialysate temperature of 0.5°C less than baseline body temperature in the intervention arm. There are otherwise very little data regarding the optimal dialysate temperature to maximize potential benefits while avoiding excessive hypothermia and shivering. An empirical approach is to reduce dialysate temperature stepwise by 0.5°C and stop in case of excessive symptoms or when 35°C is achieved. Isothermal dialysis is an alternative approach. In this method, the patient’s body temperature is kept constant through a biofeedback device that constantly adjusts dialysate temperature. Isothermal HD also reduces IDH effectively but has not been evaluated in terms of its effects on regional LV function. Furthermore, isothermic HD is less widely available because it requires a dedicated body temperature monitor (8).

The study by Odudu et al. 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. This study adds to previous work by the same group demonstrating significant recurrent and cumulative white matter brain injury caused by HD can be prevented or ameliorated by cool HD (4). On the basis of the study findings of Odudu et al. and previous work by other groups, nephrologists should consider offering cool dialysis prescription as an HD approach to patients with frequent intradialytic hypotensive episodes. Patient-specific dialysate temperature profiling should be considered in order to prevent IDH and maximize dialysis adequacy (16). The findings of this report further underscore the need for a large-scale study of dialysate temperature among patients undergoing thrice-weekly HD. Although this may be carried out as a large simple trial, it would be important to individualize prescription and to test whether certain groups have a differential benefit from cool dialysate.

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References


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