Impact of cooled hemodialysis for preservation of residual kidney function among Egyptian patients
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Background/aim
Emerging evidence on lowering dialysate temperature suggests a cardiorenal protective effect of dialysate cooling (CD) against dialysis-induced ischemia in hemodialysis (HD) patients prone to intradialytic hypotension (IDH). Whether this benefit of CD could be extended to incident HD populations without baseline IDH to preserve residual kidney function (RKF) is unknown.

Patients and methods
One hundred incident HD patients were randomly assigned to receive either incremental CD less than or equal to 36°C (intervention, N=50 patients) or standard-temperature (ST) dialysate (control, N=50 patients) for 12 months. The primary endpoint was to test the safety and efficacy of CD to preserve RKF.

Results
By the end of 12 months, CD patients showed less decline in estimated glomerular filtration rate compared with standard-temperature patients (6.2 vs. 4.6 ml/min/1.73 m², P=0.025); in addition, Cox regression analysis showed that CD was an independent variable for the preservation of RKF (P=0.044, hazard ratio: 0.478, confidence interval: 0.23–0.89). CD was well tolerated, with less fatigue and IDH; however, coldness, shivering, and discomfort were significantly higher in the CD group.

Conclusion
In incident HD patients without baseline IDH, cooled dialysis might help preserve RKF with a reasonable safety profile. Further studies are warranted to explore these findings.

Keywords:
cooled dialysis, glomerular filtration rate, intradialytic hypotension, randomized-controlled trial, residual kidney function

Introduction
In hemodialysis (HD) patients, the survival and health benefits of residual kidney function (RKF) remain quite significant, far in excess of dialysis clearance [1]. Even at glomerular filtration rate (GFR) values as low as 1 ml/min/1.73 m², preserved RKF provides longer survival, higher quality-of-life and better health outcomes [2,3]. Yet, maintaining RKF remains a poorly managed target in the HD population.

In fact, HD, in and of itself, can be counterproductive to the RKF preservation in two ways: first, HD is a cardinal circulatory stressor, especially in patients prone to intradialytic hypotension (IDH) [4]. Repetitive episodes of IDH end in a widespread HD-mediated ischemic organ injury with a subsequent decrease in renal perfusion (DRP) [5–7]. Second, setting the dialysate temperature (td) at a ‘one-size-fits-all,’ ‘standard’ 37°C, unwittingly, exposes HD patients to further hemodynamic compromise [8]. The HD-induced heat gain in patients with low baseline core body temperature (CBT) can cause inappropriate vasodilatation and impairs appropriate vasoconstrictor reflexes, leading to more IDH [9].

Dialysate cooling (CD), in contrast, improves hemodynamic tolerability to ultrafiltration-induced hypovolemia [10]. Traditionally, CD has been used as a first-line option to offset (IDH) [11–13]. More recently, emerging data from randomized-controlled trials (RCTs) have shown a new potential for CD to delay the HD-induced ischemic organ injury. Evolving evidence supports a protective role of CD against myocardial stunning (MS), brain white matter ischemia and DRP [5–7]. The preservation of renal perfusion is a key determinant for maintenance of RKF.

To our knowledge, no previous study has investigated whether the benefit of CD can be extended to other...
HD patients without IDH to protect renal perfusion. Therefore, the aim of the present study was to investigate whether CD could offer a safe and effective means to preserve RKF in incident HD patients without baseline IDH.

**Patients and methods**

**Patients and study design**

From October 2018 to October 2020, we conducted an open-label, prospective, RCT to test whether CD would help preserve RKF in incident HD patients.

One hundred incident HD patients from Benha University hospital were enrolled in the study. A 1:1 computer-generated sequencing placed in sealed envelopes was used for randomization. Fifty patients were randomly assigned to each treatment arm. Blinding (of the intervention) was not technically feasible because of the need to serially adjust td prescription settings. The study was carried out as a parallel RCT; however, crossover was allowed between groups if clinically indicated as per the treating physician. Upon follow-up, seven patients assigned to each original arm crossed over to the opposite study arm. Data analysis was carried out eventually as per original treatment allocation with intention-to-treat analysis at the end of the trial period. The duration of the study for each patient was 12 months.

**Ethical approval**

The study was carried out in accordance with the principles and regulations of the Helsinki declaration. The study protocol was approved by the Ethical Committee of Benha University on 30/9/2018, with approval number 3515/275. All the participants provided an informed written consent in the Arabic language after a full explanation of the study and the potential hazards and benefits was provided.

**Intervention**

The present study used two different prescription protocols for dialysate temperature (td):

1. The intervention arm (50 patients) received CD to less than or equal to 36°C, and with a stepwise decrease in td by 0.5°C as long as cooling was tolerated down to 35°C.
2. The control arm (50 patients) received standard-temperature (ST) dialysate individualized to the same degree of the patient’s CBT measured before the HD session.

Conventional HD was delivered to all patients using Fresenius HD4008 B machines, low-flux poly-sulfone dialyzers and bicarbonate-based dialysate. Dialysate composition was almost similar between groups.

**CBT** was monitored using a Tympatic membrane Thermometer taken at the beginning of HD and then serially every hour.

**End points**

The primary endpoint of our study was to test; first, efficacy: to determine the difference in the decrease of RKF (both the rate of decline and the proportion of patients with lost RKF) between groups over a 12-month period. In addition, we carried out multiple regression analysis to assess the interaction between RKF and other independent variables (age, sex, comorbidities, and td). Second, safety: adverse events in the two groups were recorded and analyzed.

**Endpoint definitions**

RKF: we adopted the European Best Practice Guidelines (EBPG) and used the averaged urea and creatinine clearances; in addition, we assessed the patient-reported urine output volume as an additional measure of the RKF. Preserved RKF was defined as greater than or equal to 3 ml/kg/1.73 m² and/or urine volume (UV) greater than or equal to 200 ml/day. IDH was defined as per EBPG [11]. Post-HD fatigue was measured using the fatigue severity scale [14].

**Inclusion criteria**

Incident HD patients with UV greater than or equal to 200 ml/day and estimated GFR greater than or equal to 3 ml/min/1.73 m² were included in the study.

**Exclusion criteria**

Patients ≤18 years, patients with UV less than or equal to 200 ml/day, patients with baseline hypotension and uncontrolled hypertension, pregnant patients and patients with failed kidney allografts were excluded from the study.

**Statistical analysis**

The collected data were coded and entered into a PC using the Statistical package for Social Science (released 2017, IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, New York, USA). Parametric data were presented as mean±SD, nonparametric data as median and range and categorical variables as counts (frequency and percentage). As to the Analytical statistics, the Student t-test was used to assess the statistical
significance of the mean values. The Mann–Whitney Test was used to assess the statistical significance of variable medians, Wilcoxon’s signed tests were used to compare between the baseline characteristics and \( \chi^2 \) tests were used for qualitative variables. Repeated measures analysis of variance (for parametric) or Freidman’s test (for nonparametric) variables were used for comparison of repeated measures across all time points, with post-hoc Bonferroni test used to perform many t-tests at once. Correlation analysis was carried out to assess the strength of association between two quantitative variables expressed as the correlation coefficient. Linear Regression analysis was carried out for prediction of risk factors. The Kaplan–Meier estimate was used to compare the 1-year cumulative survival of RKF between the two study groups. All P values were two-sided; P values less than 0.05 were considered significant.

**Results**

**Study population**

As shown in Fig. 1, we evaluated 178 incident HD patients for enrollment in the study; 78 patients were ruled out (46 were ineligible and 32 were not interested in the study).

The majority of the study population in both groups were males; otherwise, the baseline characteristics of both randomized groups were balanced, with no significant differences as summarized in Table 1.

With respect to HD prescription, as summarized in Table 2, the average temperature achieved in the CD group was 35.3±0.45 versus 36.5±0.55 in the ST group. The time frequency of sessions, Ultrafiltration (UF)
rates, and achieved URR targets were, overall, similar between groups.

As to adverse events as shown in Table 3, the rate of coldness, shivering and discomfort was significantly higher in the cool HD group ($P>0.005$); nevertheless, most of the patients (96%) were able to tolerate most of the prescribed sessions (96.4%). Furthermore, the CD group reported less fatigue after HD.

Blood pressure values were higher in the DC group compared with the ST group as shown in Table 3; in addition, patients in the DC group needed more blood pressure medications compared with the standard group (average 0.25 more tablets), whereas IDH rates were higher in the ST (14%) versus CD group (6%) for the same UF rate and liters removed/session. As per the treating physician, seven patients were switched from CD to standard HD (four due to cold dialysate
intolerance and three for high blood pressure). In contrast, seven patients were transferred from the standard group to the CD group due to IDH. There was no significant difference in the deaths in the CD group versus the ST group (seven vs. eight, respectively). Death was due to sepsis (3,2), arrhythmia (2,2), Heart Failure (HF) (1,2), and liver disease (1,2), respectively.

End points
As shown in Table 4, cool HD was more effective in preserving the RKF as evidenced by the slower rate of eGFR decline that was statistically significant in the cool HD group (using the Friedman test for comparison of repeated measures across time; \( P=0.025 \)). In addition, as shown in Table 5, the percentage of patients who had a preserved eGFR was also higher in the cool HD group.

Using the Kaplan–Meier survival analysis, 64.2% of the patients survived without loss of RKF, mean time 10.2 months, while in the standard HD group, only 43.7% survived without loss of renal function, mean time 8.4 months.

As shown in Table 6, Cox regression analysis carried out to adjust for covariates revealed that cool HD was an independent variable for the preservation of RKF after adjustment of the other variables (\( P=0.044 \), hazard ratio: 0.478, confidence interval: 0.23–0.89).

Discussion
Among (100) incident HD patients randomized to either cooled dialysis (CD) or standard (ST) td, we
found that by the end of 12 months, the CD group showed less decline in eGFR. In addition, more patients in the CD group had preserved RKF compared with the ST group. The mean time of 1-year cumulative survival without loss of RKF on Kaplan–Meier analysis was 10.8 months in the CD group versus 8.4 months in the ST group. Cox regression analysis carried out to adjust for age, sex, and comorbidities revealed that cool HD was an independent variable for the preservation of RKF after adjustment of the other variables.

The marginal difference in RKF noted between the CD and ST groups at the end of the study is likely to be clinically significant; previous studies have shown that minimal amounts of preserved eGFR as low as 1 ml/min/1.73 m² lead to survival and health benefits [1–3].

The present study is the first to use CD for preservation of RKF in incident HD patients. The rationale for performing this RCT derives from previous studies showing a cardiorenal risk reduction in patients individualized to CD, by delaying the ultrastructural ischemic organ injury accruing during repetitive episodes of the hypoperfusion caused by IDH [5–7]. McIntyre and coworkers have shown HD to inversely cause a contemporary DRP and MS, even without significant hypotension, and have demonstrated that CD minimized DRP and MS, albeit not statistically significant [5]. Conversely, in the present study, patients individualized to CD achieved a statistically significant higher preserved RKF. It should be noted that McIntyre’s cohort of patients included vintage HD patients (5.3 years on HD) with low RKF and received CD for 1 session only, whereas in our study, incident HD patients with higher RKF received CD for 1 year. The underlying mechanisms accounting for this protective role of CD are still elusive and at best speculative [10].

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CD group</th>
<th>ST group</th>
<th>P, value</th>
</tr>
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<tr>
<td>Preserved RKF%</td>
<td>66%</td>
<td>40%</td>
<td>0.018</td>
</tr>
<tr>
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<td>2</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Died</td>
<td>3</td>
<td>2</td>
<td>–</td>
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<tr>
<td>Total (censored)</td>
<td>9 (2 Tx)</td>
<td>9 (2 Tx)</td>
<td>–</td>
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<tr>
<td>Total (died)</td>
<td>7</td>
<td>8</td>
<td>–</td>
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<tr>
<td>P&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Post-hoc test</td>
<td>P&lt;0.016</td>
<td>P&lt;0.001</td>
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One-way repeated measures analysis of variance: the % of patients with preserved RKF was statistically higher in the CD group. The F-ratio value is 8.15686. The P-value is 0.046. CD, dialysate cooling; P₁, comparison between CD and ST groups during each 4-month duration using the Mann–Whitney U-test (0.5, 0.018, 0.18); P₂, comparison of repeated measures across all time points using Friedman’s test; P₃, comparison between the initial and the fourth month; P₄, comparison between the fourth, eighth, and 12th month; RKF, residual kidney function; ST, standard-temperature.
hypothesized that CD by its cardiorenal protective effect would help preserve RKF by maintaining renal perfusion and minimizing myocardial injury and circulatory stress (as depicted in Fig. 2).

Different cooling modalities have been used [15]; yet, in all previous studies, the td was set to 37°C in the control arm [13]. Abundant evidence [16,17] suggests that the so-called ‘standard’ td arbitrarily set to 37°C is unphysiological, in the sense that it inadvertently exposes patients to supraphysiological heating during HD with net energy transfer to the patients. The impact of this increase in CBT during HD can be quite detrimental because it offsets the thermal autoregulatory mechanisms set to combat IDH [16]. Thus, a cardinal difference that sets our present study apart from previous work is that our control group was prescribed a (td) adjusted to the same degree of baseline (CBT) before each HD session. This individualized iso-thermic (td) is a cooling prescription compared with the ‘standard’ td in other studies that prescribed 37°C for their control groups. The average prescribed temperature in the ST (control) group was 36.5±0.55. Thus, by individualizing (td) for the control group, the present study can be viewed as more of a comparison between two cooling strategies rather than a classic standard versus cooled HD in previous studies [13].

The cohort population in our study has a male predominance; Apart from sex, the rest of the cohort demographics were similar. Nevertheless, it should be noted that our population is different from previous studies on CD in two fundamental aspects: first, they are incident HD patients with short HD vintage (<1 month) and higher baseline RKF (9.7 and 9.6 min/ml/1.72 m², respectively). Previous studies enrolled patients with long HD vintage [5,13]; however, an earlier study [18] suggested that early IDH during the first 3 months negatively affects RKF, and hence, individualizing incident HD patients to CD early on is more beneficial. Second, in the present study, baseline IDH was an exclusion criterion. Previous studies have addressed the benefits of CD to ameliorate IDH [10]; while those studies were quite justified and plausible, it should be noted that IDH itself might be a confounder for a higher comorbidity index (an epiphenomenon) [19]. In addition, patients with frequent IDH require other interventions such as sequential ultrafiltration, sodium profiling, volume expanders and vasopressors. Such interventions are likely to confound the impact of CD on RKF.

With respect to safety, coldness-related symptoms were, as expected, significantly higher (P>0.005) in the CD group; nevertheless, most of the sessions were tolerated in most of the patients in the CD group. It is noteworthy that IDH and fatigue were significantly less in the CD group. Still, in our cohort, IDH occurred in 6 versus 14%, respectively, despite (td) individualization. The occurrence of IDH speaks to the complexity of IDH and the multitude of factors driving it.
The observed higher BP values in the CD are likely directly related, at least in part, to CD itself. Given the fact that for the same degree of UFR, patients on CD had higher BP values and needed higher doses of BP medications, it is noteworthy that data on high BP effect on RKF are not consistent [20,21] and are mostly derived from patients on peritoneal dialysis.

It is fair to acknowledge that our study has some salient limitations including the following:

1. Small number of patients; however, incident HD patients are difficult to recruit in large numbers from a single center.
2. No imaging of the renal perfusion was performed; using a contrast material in our cohort would have negatively affected the RKF.
3. In the present study, we used averaged urea and creatinine clearance and urine volume as surrogate markers for RKF. Notwithstanding their imperfections and limitations of performance [22], there is no universal consensus on the ideal markers to assess RKF [23].
4. Open-label design: Blinding (of the intervention) was not technically feasible.
5. Conventional HD was prescribed to all participants; how much (HDF, ultrapure dialysate) would contribute to the RKF preservation remains to be answered in future studies.

The findings of the current study demonstrate that cooled dialysis can be safely advocated to preserve RKF in incident HD patients. This might have even further implications if data are confirmed in other settings where renal recovery is a crucial target, as in patients with acute kidney injury.

Conclusion

Taken together, our findings demonstrate that cooled dialysis is a safe modality in incident HD patients that can be used to preserve RKF. CD is a simple, cost-free and feasible adjustment that fits well into the current model of HD care. Nevertheless, these findings should be interpreted with great caution. This study is hypothesis generating/proof of concept, suggesting that individualization is key. Given the benefits of CD in the vulnerable HD population, further future studies are warranted to confirm the findings of this study.

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Nil.

Conflicts of interest
There are no conflicts of interest.

References