HEMODYNAMIC EFFECTS OF LOW VS. HIGH DIALYSATE TEMPERATURE OR BICARBONATE CONCENTRATION IN CHRONIC HEMODIALYSIS PATIENTS (TURBO)

Research team and contact information

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Background

Intradialytic hypotension (IDH) is a common complication of hemodialysis (HD) and is considered one of the most frequent complications with a prevalence between 10-12% depending on the definition of IDH (1). IDH has been associated with inefficient dialysis (2), vascular access thrombosis (3) and mortality (4,5).
Orthostatic hypotension (OH) is another common complication in HD with a prevalence around 42% in patients initiating HD treatment (6). OH is significantly associated with worse outcome in HD patients in terms of an increased two-year mortality (4) and increased risk of all-cause death (6).

Understanding the mechanisms underlying IDH and OH has the potential to optimize HD treatment, in order to minimize the occurrence of IDH and OH, potentially improving not only patient mortality and morbidity but also the everyday comfort of chronic HD patients when receiving dialysis treatment.

This study will investigate the hemodynamic effect of alterations in dialysate bicarbonate and dialysate temperature. Due to the different nature of the two interventions, they will be addressed separately in the following.

Dialysate temperature

Several clinical studies have examined the effect of low temperature dialysate (LTD) on IDH, but only few have examined the hemodynamic response in detail with intradialytic measurements of cardiac output (CO), central blood volume (CBV) and total peripheral resistance (TPR) (7–14). Generally, the studies confirm a blood pressure (BP) stabilizing effect of LTD, but diverse results are

found on changes in CO, CBV and TPR. Some studies found greater increase in TPR during dialysis with LTD compared to a higher dialysate temperature (8,9,11,14). Other studies found that intradialytic CBV (7,12) and CO (12) improved considerably with LTD.
To the best of our knowledge only one study (14) have examined OH in relation to use of LTD, but not with detailed intradialytic hemodynamic measurements. The study showed that both supine and upright MAP were significantly lower after dialysis with a dialysate temperature of 37°C compared to a dialysate temperature of 35°C. Furthermore, the increase in TPR was greater during dialysis with LTD.

Dialysate bicarbonate

Few studies have investigated the effect of dialysate bicarbonate (DB) concentration on intradialytic hemodynamics and results have been conflicting. Lower DB (from 32 to 26 mmol/L or a reduction of 6 mmol/L, respectively) was in two cross-over studies (15,16) shown to increase systolic BP by approximately 5 mmHg, whereas a third study reported no significant effect on BP (17). One of these studies also found an increase in TPR with lower DB (16). IDH has been associated with lower DB in one of the previously mentioned cross-over studies (15), but this association was not found by Gabutti et al in 2005 (17) or in larger observational studies (17–19). Manipulation of DB inevitably affects plasma pH of the patient during dialysis. Thus, if pH decreases with DB-induced acidosis, hydrogen ions displace cations such as calcium from protein binding sites. DB-induced alkalosis on the other hand increases pH, which promotes increased protein binding, which decreases free cation levels. At the same time, intracellular sequestration of potassium at high pH levels has also been speculated to lower plasma potassium levels (20). Consequently, by changing DB a range of electrolytes including calcium are potentially affected which could impact neuromuscular function and thereby intradialytic hemodynamic parameters and the frequency of IDH and OH (17,21–26).

Summary

To elucidate the role of dialysate temperature and bicarbonate on hemodynamic parameters, plasma pH and electrolytes that potentially mediate this effect, we wish to conduct a single-blinded, randomized, controlled, crossover study, specifically examining the effects of

- A fixed LTD of 35°C compared to a fixed dialysate temperature of 37°C.
- A low DB concentration of 30 mmol/L compared to a high DB concentration of 38 mmol/L.

Hypotheses and endpoints

Hypotheses

We hypothesize that hemodialysis or hemodiafiltration (HdF) sessions with a decreased dialysate temperature (35°C vs. 37°C) or decreased DB concentration (30 mmol/L vs. 38 mmol/L) will have the following effects:

- An increase in systolic blood pressure (SBP), mean arterial blood pressure (MAP) and orthostatic blood pressure (OBP).
- An increase in one or more of the following: TPR, CO, CBV, stroke volume (SV) and/or heart rate (HR).
- A decrease in the frequency of IDH and OH.

Primary and secondary endpoints
The primary endpoint for the study is BP (SBP, MAP and OBP)

Secondary endpoints are:
- Hemodynamic parameters: TPR, CO, CBV, SV and HR
- Electrolytes: Calcium, potassium and magnesium
- Frequency of IDH and OH

All endpoints are assessed as the difference between within-treatment changes during HD or HdF sessions when manipulating either dialysate temperature (35°C vs. 37°C) or DB concentration (30 mmol/L vs. 38 mmol/L).

Methodology

Study design

The study will be a single-blinded, randomized, controlled, crossover study with each participant being his or her own control (Figure 1). Participants will be blinded to the intervention and the order of the interventions will be random.
Participants will be randomized using bloc randomization. We will create two blocs (sequence 1 (Green) and sequence 2 (Yellow)) with 8 participants in each. The four dialysis sessions will be conducted on the same weekday each week, which results in a 1-week wash-out period with standard dialysis treatment between interventions.

Practical considerations

Dialysis machines, filters, and dialysate composition

Dialysis console Fresenius 5008F (Fresenius Medical Care, Bad Homburg, Germany) and HD or HdF filters regularly used for treatment of the patient will be used in all dialysis sessions.
The standard dialysate prescribed for each individual patient will be used in all dialysis sessions thereby maintaining similar composition regarding electrolytes such as sodium, potassium, calcium, magnesium and chloride. Bicarbonate concentration will only be adjusted in the sessions investigating low (30 mmol/L) and high (38 mmol/L) DB concentration, respectively. Dialysate will be prepared on-line by the dialysis machine. Blood flow rate and dialysate flow rate will be kept as usual and will remain equal in all sessions regardless of intervention. Ultrafiltration rate will be kept constant and equal in the two dialysis sessions. The same applies for the volume of substitution fluid in HdF.

Intradialytic restrictions regarding participants and their medications

In order to standardize intradialytic conditions as much as possible and in order to avoid splanchnic redistribution of blood volume, the participants will be asked not to eat, drink, or sleep during the dialysis session. Throughout the study period medications affecting hemodynamics (e.g. blood pressure medications) will not be changed. Patients are encouraged not to deviate from their regular schedule in terms of timing or dosage of medication.

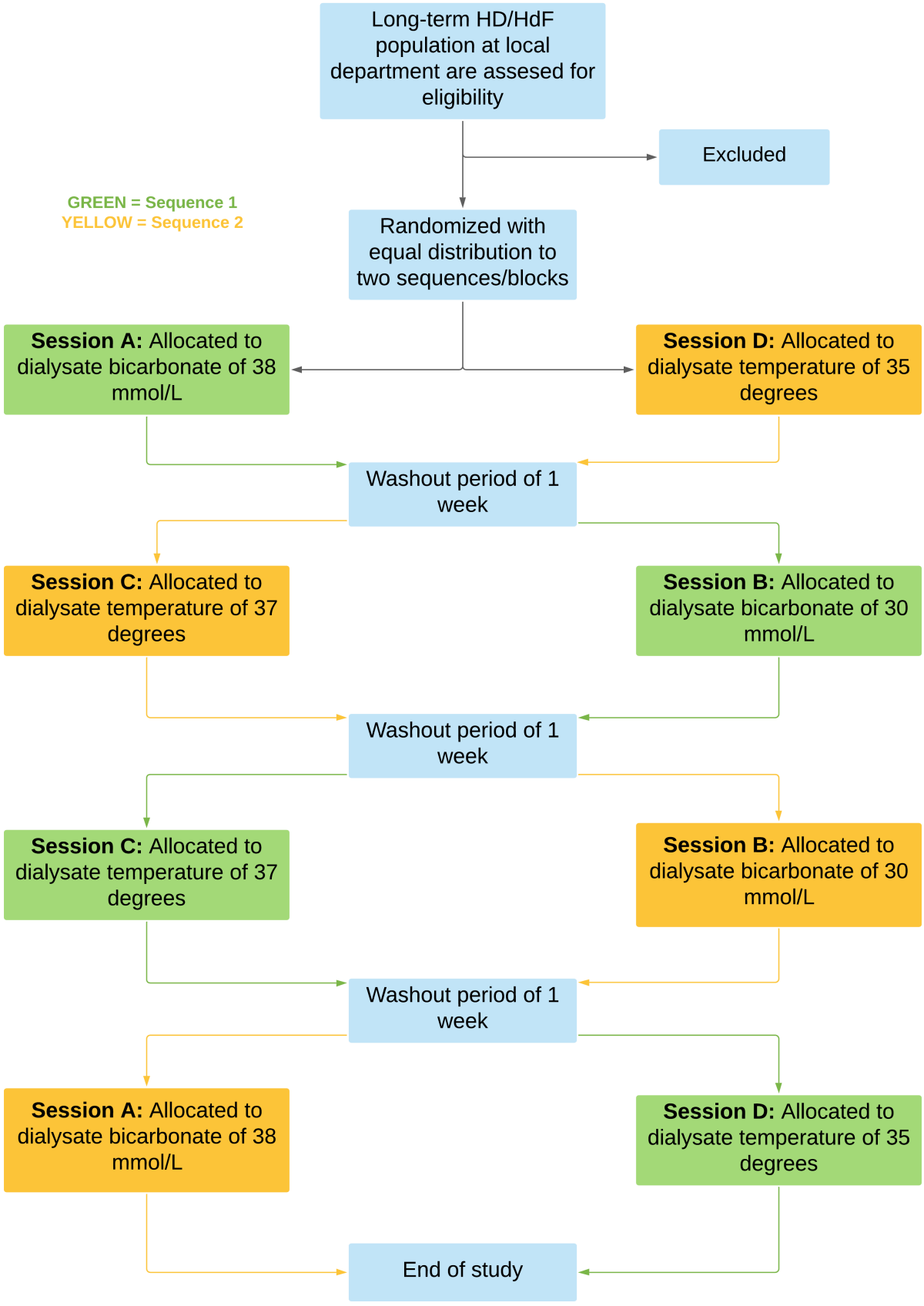

Figure 1: Study design

BP measurements

We will use the same automatic and validated BP device for all BP measurements (see Figure 2). The BP cuff will be chosen according to arm size and placed on the non-AV-fistula arm. The cuff should be positioned at the level of the heart, with the back and arm supported to avoid muscle contraction and isometric exercise-dependent increases in BP. Patient should be lying comfortably in a supine position for 5 minutes before beginning BP-measurements. Three BP measurements are recorded 1–2 min apart, and additional measurements only if the first two readings differ by >10 mmHg. BP is recorded as the average of the last two BP readings. The patient is not allowed to talk during the measurements.

OBP measurements

The patient will rest in bed for 5 minutes in the supine position, then HR (beats/min.) and BP (mmHg) are measured. The patient will then be asked to stand up beside the bed. BP and HR will be measured repeatedly with a 1-minute interval while standing for a minimum of 3 minutes. If BP declines at the third minute measurement, measurements can be continued for up to 10 minutes. The lowest BP while standing will be noted as the result for the orthostatic BP test.

Orthostatic hypotension (OH)

OH is defined as a reduction in SBP of at least 20 mmHg or in DBP of at least 10 mmHg within 3 minutes of standing (27).

Intradialytic hypotension (IDH)

IDH is defined as a decrease in systolic BP ≥20 mmHg or a decrease in MAP ≥10 mmHg associated with clinical events/symptoms (e.g. muscle cramps, abdominal discomfort, nausea or vomiting, dizziness or fainting, restlessness or anxiety, yawning or signing) and/or need for intradialytic interventions (Trendelenburg positioning, fluid administration, reduction in ultrafiltration rate, reduction of blood flow rate) or dialysis treatment cessation (28).

Before dialysis:

As the participant arrives in the hemodialysis clinic, he/she will be weighed (kg) with usual clothing. He/she will be followed to a bed and asked to lie down in a supine position and then a standard 12-lead electrocardiogram (ECG) is recorded. Followed by a bioimpedance measurement using the Body Composition Monitor (BCM, Fresenius Medical Care) for determination of fluid status and body composition. Subsequently an orthostatic BP test will be performed.

The nurse will then prepare the patient for dialysis treatment and will manage insertion of dialysis needles in the AV-fistula. Furthermore, the nurse will connect the extra tubes needed for the Transonic device. Fragmin (standard dose) is administrated, and the dialysate temperature/dialysate bicarbonate is regulated according to randomization.

Before the dialysis session is started blood samples on infectious parameters and magnesium and an arterial blood gas will be drawn from the arterial cannula.

Time course - from the participant arrives to the participant leaves the dialysis clinic

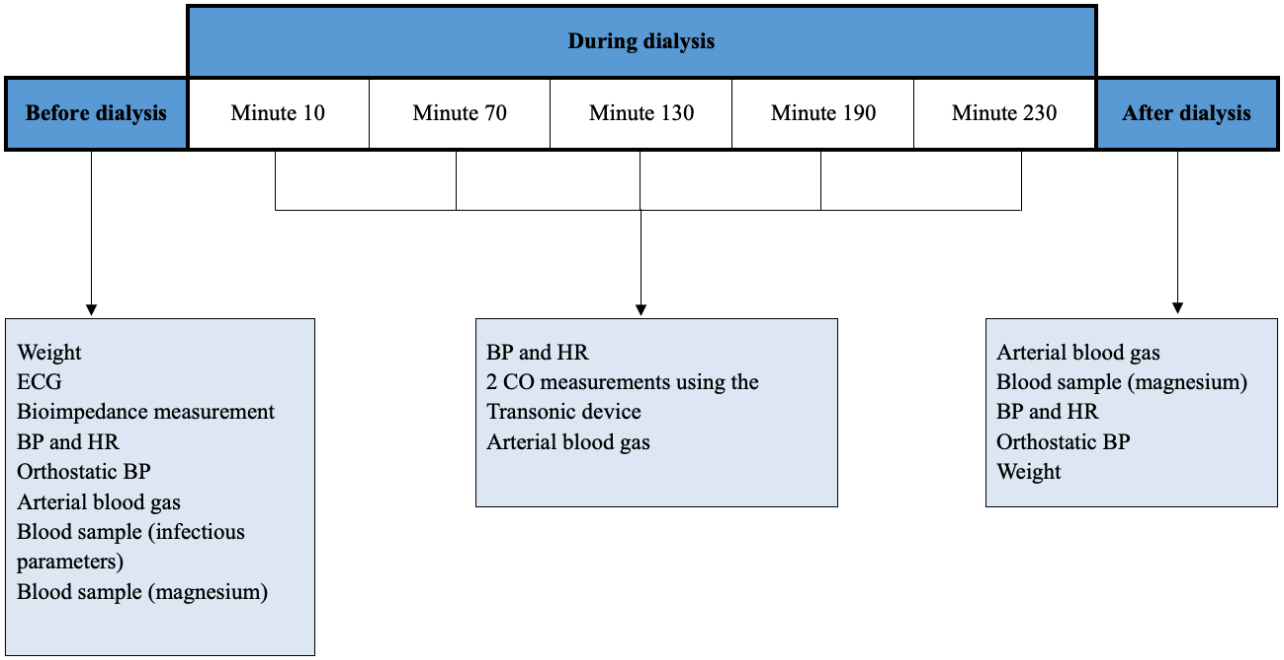

Figure 2 An overview of the time course. It illustrates what will occur before, during and after dialysis.

During dialysis:
CO will be obtained by a previously validated ultrasound dilution technique using Hemodialysis Monitor HD03, Flow-QC tubing sets, and clip-on flow/dilution sensors from Transonic Systems Inc., Ithaca, NY, USA (29–32). The ultrasound sensors will be positioned on the arterial and venous Flow-QC tubing set using standard ultrasound gel to secure good contact. Access recirculation in the AV-fistula can invalidate CO-measurements. A built-in recirculation protocol will be used to check for access recirculation using injection of 10 mL isotonic saline into the venous blood line prior to the first CO-measurement. If recirculation is detected the dialysis needles will most likely be reinserted. CO will be measured in duplicate by injecting a bolus of 30 mL 37°C isotonic saline into the venous blood line within 5 seconds. If results deviate more than 15% a third measurement will be done. The mean of the two closest recordings will serve as the result. With the Transonic device intradialytic hemodynamic parameters are obtained at 10, 70, 130, 190, and 230 minutes. Patients will be lying in a supine position with the head elevated 20 degrees. Before each CO measurement HR and BP will be measured.

Following the same time pattern as the Transonic measurements an arterial blood gas will be drawn from the arterial cannula.

Changes in relative blood volume (RBV) (%) during dialysis are monitored continuously by the module (blood volume monitor, Fresenius Medical Care) incorporated in the dialysis machine, which measures changes in RBV by measuring changes in hemoconcentration markers (hematocrit, hemoglobin or total blood protein concentration). Cumulative ultrafiltration volume (mL) is registered every 15 minutes during dialysis. Temperature and energy transfer in the arterial and

venous tubing will be recorded continuously by the blood temperature monitor mounted on the dialysis console (BTM, Fresenius Medical Care).

Generally, if a dialysis session is interrupted the participant will be given a replacement day on a corresponding weekday. In the event of IDH we will obtain a BP measurement and subsequently, the nurse will try to stabilize the patient with the necessary interventions.

After dialysis:
After dialysis an arterial blood gas will be taken from the arterial cannula for determination of the same parameters as before dialysis. Furthermore, a blood sample on magnesium will be drawn.

The hemodialysis nurse will stop the dialysis and remove the dialysis needles when the session is finished. Patients usually stay 10 minutes after removal of dialysis needles to ensure hemostasis/minimize the risk of bleeding from the AV-fistula. This time will be utilized for an OBP measurement, which will follow the same method as before dialysis. Lastly, the patient will be weighed and leaves the clinic.

Data from the dialysis session will be extracted from electronic patient journal, Therapy Data Management System (TDMS, Fresenius Medical Care) and Transonic HD03 Administrative Software (Transonic Systems Inc, Ithaca, NY). The mean arterial blood pressure (MAP), total peripheral resistance (TPR), and stroke volume (SV) are derived by the following equations:
MAP = diastolic BP + 1/3 x (systolic BP – diastolic BP)
CO = SV x HR = MAP/TPR

Central blood volume (CBV) is defined as the volume of blood in the heart, lungs and great vessels and is estimated with the Transonic device based on the CO measurement as previously described (29).

Dialytic Kt/V urea will be estimated by using Daugirdas formula (33) and urea reduction ratio will be calculated.

Dialysis sessions are expected to last 30 minutes longer than usual, and patients will be informed of this before agreeing to participate.

Statistical considerations

Statistical analysis

Within-treatment changes in hemodynamics and plasma concentrations of solutes will be calculated as differences (delta values), whereas between intervention comparisons (control vs. intervention) are performed by calculating the difference between within-treatment changes (“delta-delta values”). A two-tailed, paired Student’s t-test with no difference between the two treatments as the null hypothesis will be used to compare the two interventions. Statistical significance (α - level) will be set to 0.05. The paired t-tests require data to conform to a normal distribution. If this is not the case,

a logarithmic transformation of data can be performed to achieve a normal distribution. Alternatively, a non-parametric test (Wilcoxon Signed Rank test) can be performed to compare changes in relevant delta-values between the two groups.

Power and sample size

For estimation of standard deviation (SD) we used SBP measurements obtained before and after dialysis from 30 randomly selected patients undergoing HD or HdF treatment in the Dialysis Clinic at Aarhus University Hospital. Two treatment sessions were analyzed for each patient. The within treatment changes in SBP and mean differences between within-treatment changes in SBP (delta-delta values) and corresponding SD's were calculated, which yielded SD = 23 mmHg for the difference between within-treatment changes in SBP. This SD reflects non-standardized conditions in terms of dialysis treatment settings and BP-measurements in randomly selected patients not meeting the strict in-/exclusion criteria of the present study. Therefore, assuming a lower SD under standardized conditions we decided that SD = 12 mmHg was a reasonable estimate for the present study. Sample size calculation with Stata/IC 16.1 (StataCorp, 4905 Lakeway Dr, College Station, TX 77845, USA) using analysis for a one-sample mean test (t-test), assuming a minimal detectable difference in means (mean difference between the two within-treatment changes in systolic BP) = 10 mmHg; SD = 12 mmHg; two-sided significance level (alpha) = 0.05; power=0.80 resulted in 14 participants. However, to account for dropout of two participants, a sample size of 16 was chosen.

Study participants

Participants will be recruited from the maintenance HD and HdF population associated with the Department of Renal Medicine at Aarhus University Hospital in Denmark. These include the Dialysis Clinic at Aarhus University Hospital as the main hub and satellite dialysis clinics in Randers and Horsens. Inclusion- and exclusion criteria are listed below in table 1 and table 2, respectively.

Inclusion criteria
Regular dialysis (HD or HDF) therapy for $>$ 3 months
Age $>$ 18 years
Stable and functional arteriovenous fistula
Able to achieve a dialysis blood flow above 250 mL
Able to stand up for a minimum of 10 min
Able to undergo a 4 hour dialysis therapy without eating, drinking or sleeping
Proven capable of a cumulative ultrafiltration volume of 2% of end-dialytic-weight (EDW)
Able to give informed consent to participation in the study
Hematocrit $>$ 30%
BMI above 18 and below 35

Table 1 Inclusion criteria

Exclusion criteria
Central venous catheter for HD or HdF
Recirculation in arteriovenous fistula
Acute myocardial infarction within 3 months
Atrial fibrillation
Active malignant or infectious diseases
Cerebrovascular incident within 3 months
Pregnancy
Alcohol or drug abuse
History of interruptions during dialysis treatment or termination of dialysis before the scheduled time

Table 2 Exclusion criteria

Risks and side effects

Dialysis nurses will oversee the dialysis sessions and will connect the extra tubes needed for Transonic measurements. Saline injections are administered via dedicated injection ports for isotonic saline provided with the Transonic tubing set or via the dialysis machine using sterile technique after thorough training. If any unexpected events occur the dialysis nurse will intervene, and the principal investigator can be contacted if necessary.

Manipulation of DB is not considered to induce any significant side-effects for the participants apart from what is commonly seen following a standard dialysis session with HD/HdF. Accordingly, lowering of DB may induce a slight increase in BP and a slight decrease in postdialytic pH compared to standard conditions. Since these changes are transient, they are not expected to cause any detrimental long-term side-effects for the participants, as demonstrated by previous trials using similar interventions (15–17).

Participants might feel slightly discomfortable during intervention with LTD in terms of cold sensation or related symptoms (10), but could on the other hand also feel less fatigue and more energetic according to previous studies examining LTD (34,35).

Participant exclusion and discontinuation of the study

Should any serious known or unknown side effects or complications occur during the study, the study session will be discontinued, and the participant will receive treatment from a dialysis nurse or a medical doctor if deemed necessary. Following this, the investigators of the study in consultation with the patient will decide if the patients is to be excluded from the study or offered a replacement session on a corresponding weekday.

If blood samples obtained on a given study session show signs of infection, the data obtained in this study session will be deemed invalid and will not be used in the study. Strong suspicion of infection will be handled as per usual in the hospital setting and can potentially lead to hospitalization for further investigation. Once the infectious state has receded, the patient can continue in the study via

a replacement day on a corresponding weekday. In the case of protracted illness or hospitalization, the patient will be excluded from the study.

Blood sampling and handling of biological material

Eleven blood samples will be taken from the arterial blood line via the AV-cannula used for dialysis treatment. Four of the samples will be regular blood samples of 3-4 mL, whereas 7 of the samples will be arterial blood gases of 1 mL. Thus, per session 22 mL blood per participant is collected which adds up to a total of 88 mL for the entire study period. The purpose of this is to determine several essential parameters:

- Electrolytes such as calcium, magnesium, and potassium
- Acid-base status: pH, standard bicarbonate, standard base excess
- Hemoglobin, hematocrit
- Urea for the determination of Kt/V and URR.
- White cell count and C-reactive protein in the first blood sample in order to confirm the absence of infection

All blood samples will be transferred to the laboratory according to standard routine and analyzed according to current clinical standards at Department of Clinical Biochemistry, Aarhus University Hospital or local Department of Clinical Biochemistry normally servicing our satellite dialysis clinics in Randers and Horsens. Blood gas tests are analyzed using ABL blood gas analyzer (Radiometer, Radiometer Medical ApS, Brønshøj Denmark). All blood samples will be destroyed after analysis. No samples will be stored in a biobank.

Handling of personal information in the study

Information from patient records

For the purpose of recruitment, patient information regarding the inclusion- and exclusion criteria mentioned in table 1 and table 2 will be retrieved and assessed from the electronic medical record (MidtEPJ). Information retrieved before consent from patients only concerns the inclusion- and exclusion criteria and is fully contingent upon approval by the local ethics committee in Region Midtjylland (VEK) and authorization by the management of the Department of Renal Medicine, Aarhus University Hospital.

Following informed consent from participants, the results from blood samples taken during the study will be retrieved from the electronic medical record. In addition to this, intradialytic parameters such as Kt/V, blood flow rate, dialysate flow rate, ultrafiltration rate, cumulative ultrafiltration volume and relative blood volume are obtained from the Therapy Data Management System (Fresenius Medical Care) software, which is routinely used in the dialysis unit at the Department of Renal Medicine, Aarhus University Hospital.

The informed consent of study participants will grant investigators, potential trial sponsors and their representatives as well as any control authority direct access to obtain information in the patients' medical records etc. including the electronic medical record in order to obtain information about the participant's health conditions necessary for the execution of the study and for the purpose of control,

including self-regulation, quality control and monitoring, that the aforementioned parties are obliged to perform.

Personal information

The study will comply with The General Data Protection Regulation (GDPR) (Databeskyttelsesforordningen) and the Danish Data Protection Law (Databeskyttelsesloven).
The Central Denmark Region (Region Midtjylland) will be data controller and the present study will be reported to The Central Denmark Region (Region Midtjylland) by the principal investigator (Intern fortegnelse over forskningsprojekter med Region Midtjylland som dataansvarlig).
The personal information of participants will be protected according to "*Sundhedsloven"*. All study-related data will be coded and saved in an electronic case report form (CRF). All potentially identifiable records of the participants are confidential and will not be made publicly available. Only the number assigned to each participant is registered in the CRF. Data is stored in anonymized form for a minimum of 5 years after the project has been completed in accordance with the Danish Data Protection Agency's guidelines.

Financial aspects

The project is a result of a shared initiative between medical students Ina Ejsing Hunnerup Jørgensen and Jonas Schandorph Kaalund Jensen at Aarhus University and medical doctors at the Department of Renal Medicine, Aarhus University Hospital Jens Kristian Dam Jensen, Christian Daugaard Peters and Niels Henrik Buus. The study has no association with any private corporations, and the investigative team have no financial interests in the study.
Potential expenses of the study will be covered by the Dialysis Clinic, Department of Renal Medicine, Aarhus University Hospital with a potential for additional funding via public and private foundations. The latter includes expenses associated with biochemical analyses, publication of the study, travel expenses and congressional presentations.

Possible compensation to study participants

Participants will not be financially compensated for their participation.

Recruitment of participants and informed consent

Selection, initial contact and written material

Eligible patients will be selected by reading through the electronic patients records of maintenance HD or HdF patients at the Department of Renal Medicine, Aarhus University Hospital and associated satellite clinics and filtering out patients that do not meet the above-described inclusion- and exclusion criteria. This will only happen after approval by the local ethics committee (De Videnskabsetiske Komitéer for Region Midtjylland) and the authorization and disclosure of the management of the Department of Renal Medicine, Aarhus University Hospital.
Initial contact will happen while the selected patients are undergoing regular maintenance HD or HdF therapy at the Dialysis Clinic, Aarhus University Hospital and will be done by a member of the scientific team together with a dialysis nurse. Patients will receive a brief introduction to the study

and will be asked to consider participating, after which they will receive an invitation to a subsequent meeting at Aarhus University Hospital. Participants will be informed of their right to bring along a companion to the meeting and this will also be evident in the written material given to participants at initial contact, provided that patients express an interest in participating in the study. The written material handed out includes patient information(*"Deltagerinformation"*) which describes the project in layman terms and a pamphlet (*"Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt")* on general participants rights in medical research projects (36).

Informative meeting and consent

The informative meeting will take place after initial contact and will be held by one of the investigators of the scientific team (a medical student or a medical doctor) within approximately 1 week after initial contact. The patient is offered a choice between a telephone call or a private talk in a separate room to ensure the privacy of the conversation. Patients are advised to discuss participation with their relatives and can always be assisted by a person of their own choice for the informative meeting and are also advised about this possibility. The meeting will most likely take place in relation to the regularly scheduled dialysis treatments in the Dialysis Clinic. Participants will be asked for written consent at their next scheduled dialysis session, thereby securing a minimum of 24 hours to reflect on participation in the study prior to enrollment. Participants will be informed that they can withdraw from the study at any time if they should wish so, without this having any effect on their future treatment at the hospital.

Scientific research team

- Christian Daugaard Peters, Senior registrar, Post doc, PhD (Principal investigator)
- Jonas Schandorph Kaalund Jensen, Medical student
- Ina Ejsing Hunnerup Jørgensen, Medical student
- Jens Kristian Dam Jensen, Consultant, PhD
- Niels Henrik Buus, Professor, Consultant, Med.Sc.D, PhD
- Nurses from the Dialysis Clinic at Aarhus University Hospital or affiliated satellite units in Horsens and Randers and lab technicians from the Research lab affiliated with Department of Renal Medicine

Time plan and publication of results

The study will begin in July 2021, and it is expected to end by the end of January 2022.
Regardless of outcome, whether positive, negative or inconclusive, results will be published in international peer-reviewed journals. The study will also be registered at www.clinicaltrials.gov or www.clinicaltrialsregister.eu

Perspectives

The study is expected to provide valuable insights into the hemodynamic effects of changes in dialysate bicarbonate and dialysate temperature. This knowledge will potentially help clinicians when prescribing dialysis in order to alleviate patient discomfort and common side effects to dialysis

treatment such as IDH and OH. Ultimately, improvements in intradialytic hemodynamics may reduce morbidity and mortality for maintenance HD or HdF patients.

Research ethics

The study will be performed in accordance with the Helsinki Declaration per 2013. Patient autonomy and integrity will be respected, and identities will be protected and remain confidential in the publication of the study. Participants will only be included after informed consent is obtained by means of a written, signed and dated informed consent form. Moreover, participants will be informed that they can withdraw from the study at any time without consequences.

The LTD may cause slight discomfort such as cold sensations, whereas low dialysate bicarbonate potentially may cause brief transitory shifts in the plasma pH of patients. However, none of these side effects are considered unsafe, harmful or unpleasant enough to give serious cause for concern for the health and wellbeing of the participants. Based on the non-harmful nature of the study and the potential therapeutic gain for HD or HdF patients worldwide, we, therefore, consider this study to be ethically sound.

Insurance and compensation claims

Should study participants, contrary to expectation, be harmed or injured during the study, they will be covered by the publicly funded compensation (“Patienterstatningen”).

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