Timing of intradialytic exercise and its impact on intradialytic hypotension: a randomized crossover study

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Intradialytic hypotension (IDH) is a common complication during hemodialysis, occurring in 20-30% of HD treatments.[1,2] The Kidney Disease Outcomes Quality Initiative defines IDH as a decrease in systolic blood pressure by ≥20 mmHg or a decrease in Mean Arterial Pressure by ≥ 10 mmHg associated with the following symptoms: abdominal discomfort, yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness or fainting, and anxiety.[3] IDH is caused by factors that reduce cardiac output and peripheral resistance, including high ultrafiltration rate, arterial stiffness, abnormal baroreflex sensitivity, ineffective vasoregulation and left ventricular hypertrophy.[4,5]

Intradialytic hypotension can cause unpleasant symptoms for HD patients including dizziness, cramps and nausea, which lead to interruption of HD and inadequate dialysis.[4,6,7] IDH can also lead to decline in residual kidney function, vascular access thrombosis, ischemic damage to white matter of the brain, volume overload, increased risk of cardiovascular events and increased mortality risk.[4,5] Research conducted by Iseki et al. on HD-associated hypotension showed an inverse correlation between death rate and diastolic blood pressure.[8] Shoji et al. looked further into HD-associated hypotension and discovered that there was an increased two-year mortality risk in HD patients who experienced IDH.[9]

Intradialytic exercise has been shown to improve physical function and health-related quality of life and may ameliorate several dialysis-related symptoms. In addition, studies have demonstrated improved cardiac function, including increased left ventricular ejection fraction and decreased systolic pulmonary artery pressure and right ventricle size with intradialytic exercise.[10] Initial concerns regarding the potential for intradialytic exercise to increase the rate of IDH have been mitigated by multiple interventional studies in which intradialytic exercise has been shown to be safe with minimal adverse effects.[11] In addition, Leung et al demonstrated no increased IDH with intradialytic cycling when exercise was performed in the first half of HD as compared to no exercise.[12] However, concerns regarding the potential of intradialytic exercise to increase frequency of IDH if exercise is performed in second half of HD remain. This is due to the potential risk of exacerbating intradialytic hypotension with post-exercise reductions in blood pressure in the latter half of dialysis when blood pressure (BP) and cardiac output may be lowest. This potential risk has not been rigorously studied prospectively and increased cardiac output and venous return associated with exercise may mitigate the effects of post-exercise hypotension in this setting.[13,14] Farese et al. observed a significant (11 mmHg) increase in overall dialysis treatment systolic blood pressure with 3 weeks of passive cycling movement during HD (as compared to a non-intervention dialysis treatment), but the study did not comment on timing of intradialytic exercise.[15] Rhee et al. found that decreases in systolic blood pressure improved as

exercise, completed in first half of dialysis, progressed over a 6-month period. In addition to improvement in systolic blood pressure, a significant reduction ($p<0.05$) in IDH episodes was observed.[16] Conversely, in a cross-sectional study conducted by Dungey et al, exercise that commenced 60 minutes after dialysis start significantly increased systolic blood pressure immediately post-exercise but SBP significantly decreased (106 vs. 117 mmHg; $p<0.001$) 1hour post exercise as compared to no exercise.[17] Many previous studies investigating the effects of intradialytic exercise have limited exercise sessions to the first half of HD due to concerns of potentiating IDH if exercise is performed in the latter half of an HD session. Anecdotally, a number of individuals in our clinical intradialytic cycling program have cycled during the last half of HD with no ill effects. The ability to safely perform intradialytic exercise in the second half of HD would allow more flexibility in exercise timing and facilitate availability of exercise equipment and staff to help with exercise by potentially avoiding exercise at the beginning of HD (often the busiest time with the most nursing tasks). Timing of exercise later in HD treatment may also decrease frequency of cramping and restless legs symptoms, which have a propensity to occur in the latter part of HD sessions.

No study has specifically compared the frequency IDH episodes when exercise is performed during second half of HD as compared to that when exercise is performed during the first half of a HD session to fully characterize the effect of timing of intradialytic exercise and its effect on IDH.

We aim to address this knowledge gap with a randomized crossover study examining the rate of IDH when individuals in a clinical intradialytic cycling program exercise during the first half of their hemodialysis session as compared with the IDH rate when exercise is performed during the second half of hemodialysis.

METHODS

Research Question: In individuals on maintenance HD, does cycling exercise performed during the second half of HD result in a higher rate of intradialytic hypotension than exercise performed in the first half of HD?

Objectives:

1. To compare the rate of IDH when intradialytic exercise is performed in the first half of the HD session as compared with that when intradialytic exercise is performed in the second half of HD.

2. To compare the prevalence of hemodialysis related symptoms when intradialytic exercise is performed in the first half of the HD session as compared with symptom prevalence when exercise is performed in the second half of HD.

3. To compare recovery time post HD when intradialytic exercise is performed in the first half of the HD session as compared with recovery time post HD when exercise is performed in the second half of HD.

Study Design: Multi-centre randomized crossover study comparing the rate of IDH over a 2-week period in 90 individuals on chronic HD when intradialytic cycling is performed in the first half of HD as compared with the rate of IDH when intradialytic cycling is performed in the second half of HD for 2 weeks.

Population/Setting: Adults with end-stage renal disease on chronic (>3 months) in-centre HD who are already participating in the *Northern Alberta Renal Program* (University of Alberta Hospital, Grey Nuns Hospital, Edmonton General Hospital, and St. Paul's Dialysis Unit); *Southern Alberta Renal Program* (Sheldon Chumir Hemodialysis Unit, South Calgary Hemodialysis Unit, Peter Lougheed Centre, North East Dialysis Centre, Northland Dialysis Centre); or the *Manitoba Renal Program* (Sherbrook Centre Dialysis Unit, Central Dialysis Unit and Seven Oaks Hemodialysis Unit) clinical intradialytic cycling programs are eligible to participate. Participants will act as their own comparisons.

Inclusion criteria: adult (≥ 18 years old); receiving three times per week intermittent hemodialysis sessions; able to communicate in English; able to provide informed consent

Exclusion criteria: dialysis frequency not three times per week

Recruitment, Enrolment and Assessments:
Individuals receiving HD at SCDU and SOGH who are currently participating in the Manitoba Renal Program's clinical intradialytic cycling program (see below) will be contacted by dialysis unit staff regarding their interest in being approached to participate in this study. If agreeable to initial approach, study staff will visit patients during their usual HD session, provide information about the study and obtain written consent. We plan to recruit a total of 30 patients from Winnipeg. These patients will act as their own comparisons. All recruited patients are already cycling during their regularly scheduled HD sessions as part of the MRP clinical intradialytic cycling program. No new intervention will be applied as part of this study. Participants will simply change the timing of their intradialytic cycling for 2 out of the 4 weeks of the study. Participants will be randomly assigned (computer generated randomization list generated by a third party) to study Group 1 or Group 2 with even distribution between each group.Similar recruitment procedures will occur in Calgary and Edmonton.

Withdrawal of subjects:
Patients may withdraw from the study at any time with or without giving a reason. If the reason is given, it will be recorded on the case report form and primary investigator will be notified of withdrawal.

Intervention:
To facilitate study implementation and optimize use of exercise resources and equipment, participants at each site will be randomly split into 2 groups. Group 1 will perform 2 weeks of their usual intradialytic cycling (6 sessions) during the first half of their usual HD and then perform 2 weeks of intradialytic cycling (6 sessions) during the second half of their usual HD. Group 2 will perform the intervention in reverse order to Group 1 (See Figure 1). No washout period is required as there is no biological plausibility for carry over effect. However, as participation in the cycling program is voluntary, some participants may choose not to exercise during some of their HD sessions. We will monitor these non-cycling sessions for IDH as well and will compare IDH rate in these non-exercise sessions with IDH rate during sessions when intradialytic exercise was performed.
Participants will perform their usual duration and intensity of intradialytic cycling at each HD session as per clinical intradialytic cycling protocol procedures (see below). Prescribed exercise time and intensity will remain unchanged over the course of the study.

We will attempt to keep dialysate composition, dialyzer, dialysate temperature, HD access, dialysis duration and medications unchanged over the course of the study, but will not intervene/interfere with usual clinical care. The research assistant will record any changes to dialysis prescription related to routine clinical care on a weekly basis.

Manitoba Renal Program's Clinical Intradialytic Cycling Program:
In this pre-existing clinical program, individuals cycle on a stationary ergometer during their regular HD sessions while supervised by a kinesiologist. At present, 60 individuals are participating in this program at SCDU and SOGH. Participants cycle in the first half of each HD session (usually 30-60 minutes) on TherapyCycle™ (Greely, CO) ergometers modified for dialysis chairs with a target exercise intensity of 3-4/10 on the Borg Rating of Perceived Exertion (RPE), which is considered to be moderate intensity.[18] Rest periods are provided as needed if participants are unable to complete their target duration of continuous exercise. Duration of total exercise time and self-reported exercise intensity (Borg RPE) is recorded by participants/kinesiologist for each exercise session. The study kinesiologist adjusts cycling duration and ergometer resistance in consultation with each individual patient. HD unit staff assist with set up and monitoring of exercise sessions. In addition to routine HD monitoring (blood pressure and pulse before, after and every 30 min during HD and glucose pre and post HD in diabetics) participants have blood pressure, pulse and glucose (in individuals with diabetes) measured before and after completion of each intradialytic exercise session. The program is voluntary and participants choose not to cycle during some HD sessions. Program participants have physical function (4 metre gait speed, grip strength, shuttle walk test), health-related quality of life (EQ5D-3L) and self-reported physical activity level (Godin Leisure Time Exercise Questionnaire) measured prior to participating in the intradialytic program and every 6 months thereafter while enrolled in the exercise program.
Calgary and Edmonton have similar clinical intradialytic cycling programs from which

participants will be enrolled. Those 2 sites will receive ethics approval for their site through their respective University ethics boards.

BP Measurement:
We will use the initial BP measurement obtained once the patient has commenced HD (i.e. patient "hooked up" and blood present in both venous and arterial lines) for the *baseline BP*. Blood pressure will be measured as per routine procedures used in the participants' HD units (usual arm/leg, usual BP cuff). Pre and post HD BP will be collected as per usual HD Unit practice. During HD, BP will be collected more frequently than the usual HD routine (q30 min) at q15min intervals or more frequently when clinically indicated based on patient symptoms or status. This timing will be pre-programed into HD machines to minimize work for bedside HD nurses. However, bedside HD nurses will need to record each BP measurement on the HD run sheet. Research assistant and/or clinical exercise program kinesiologist will be present at each cycling session to ensure outcome data is being collected.

Primary Outcome: *Difference in rate of intradialytic hypotension* between the 2 study time periods (early and late intradialytic exercise). Rate of IDH will be reported as episodes of intradialytic hypotension per 100 hours of HD. Intradialytic hypotension will be defined as the composite of >20 mmHg drop from baseline BP OR a drop in systolic BP to <90 mmHg during HD. A >20 mmHg reduction in blood pressure is justified as this magnitude of reduction from baseline BP has been associated with occurrence of HD-induced cardiac injury.[19,20] In addition, a nadir BP of <90mmHg is the only definition of IDH associated with increased risk of mortality.[21]

Secondary Outcomes:

1. Difference in rate of intradialytic hypotension (episodes of hypotension per 100 hours of HD) between the 2 study time periods (early and late dialytic exercise) as defined by a >20 mmHg drop from baseline BP AND associated with symptoms (abdominal discomfort, yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness or fainting, and anxiety) or requiring intervention. Although this definition is proposed by KDOQI, practically it is harder to capture for research purposes.[3] Nonetheless, we will capture as a secondary outcome to ensure no difference in rate between two groups.
2. Difference in frequency and severity of dialysis related symptoms during the weeks that incorporate intradialytic cycling in the first part of the HD sessions as compared with symptoms when intradialytic cycling is performed during the second half of HD will be measured using the symptom burden score as measured by the Dialysis Symptom Index (DSI). The DSI (Appendix 1) is a 30-item self-administered questionnaire with low administrative burden that measures the presence (yes/no) and severity (5 point Likert-scale) of common symptoms in HD patients (cramping, nausea, dizziness, fatigue, chest pain, and shortness of breath) and has been shown to be reliable and valid.[22,23] Participants will complete the DSI at time of consent and then weekly at the end of the

midweek HD session (on Wed for MWF HD shifts and on Thurs for TTS HD shifts) for the duration of the study (i.e. each participant will complete the DSI a total of 5 times over the study).

3. Difference in time for recovery post-dialysis when exercise is performed during first half of dialysis as compared with time for recovery post-dialysis when exercise is performed during the latter half of HD: at each study assessment, participants will be asked to answer the question "Approximately how much time does it take to recover from a dialysis session". Answers will be recorded in minutes. Prolonged post-HD recovery time, defined as the answer to the question "How long does it take to recover from a dialysis session" has been identified as a troubling symptom complex and important outcome unique to individuals receiving HD.[24,25]

Data Collection and Management:

Baseline demographic and clinical data will be collected from the hemodialysis chart. This will include age, sex, race, time on hemodialysis, hemodialysis access, dialysis vintage, comorbidities (including hypertension, diabetes, congestive heart failure and ischemic heart disease), amount of fluid removed at each HD, hemoglobin, Kt/V (dialysis efficacy), medications and blood work results as measured on last monthly bloodwork. Each patient will be assigned a unique study identifier. Routine hemodialysis run sheets on which all BP measurements during HD are recorded will be copied after each treatment (with all identifying information removed) and labeled with only the patients' unique study identifier. The patient's identifying information with the coded study numbers will be stored in a hardcopy file in a locked filing cabinet. In addition, this information will also be stored in a password protected electronic file on a secure research server located at the University of Manitoba, Rady Faculty of Health Sciences, Max Rady College of Medicine that is accessible only to required study staff. Local research staff at each study site will enter de-identified study data from hard copy data collection sheets into a dataset that is housed on the secure research server. All electronic data files will be password protected. Datasets from Calgary and Edmonton will be password protected, combined together and analyzed in Winnipeg. Participant study questionnaires (completed as hard copies) will have no identifying information other than the unique study number. All hard copies will be stored in a locked filing cabinet in the primary investigator's office at each site. Both electronic and hard copy data will be destroyed after a period of 10 years.

Data analysis:

Demographic and baseline clinical data will be analyzed using the appropriate descriptive statistics and presented as mean (standard deviation), median (interquartile range), and proportion for parametric, non-parametric and categorical data, respectively. Linear mixed models will be used to analyze the associations between timing of exercise (first half or second half of HD) and intradialytic hypotension while accounting for duration of exercise, UF rate and

within patient data. Mean symptom burden score will be stratified by timing of intradialytic exercise and compared using paired Student's t-test. Similar analysis will be performed for time for recovery post HD.

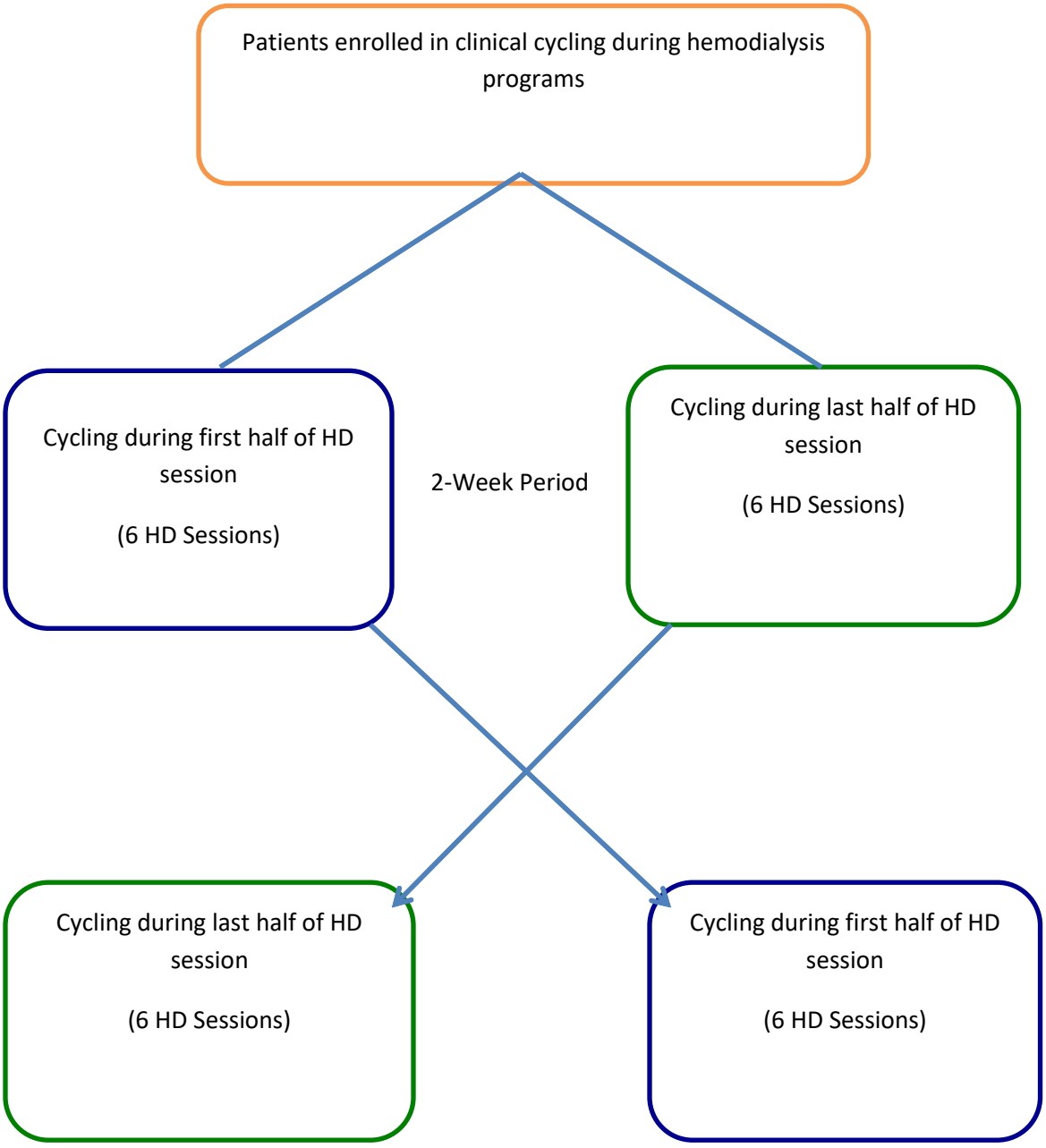
Data and Safety Monitoring:
This study is low risk and runs over a short time period (4 weeks). Intradialytic hypotension is a common complication of HD. Changing the timing of exercise during hemodialysis is unlikely to cause a significant increase in the number of episodes of hypotension based on the experience of our 3 centres and data on cardiac hemodynamics with exercise in HD. As such, no data safety monitoring committee has been convened.

Sample Size Estimation:
We consider a 20% increase in IDH rate with intradialytic exercise in the second half of HD to be clinically significant and unacceptable. A previous study of 42 HD patients who exercised in the first half of HD observed IDH rate was 130 episodes per 100 hours of HD.[12]
Assuming a standard deviation of 50, a sample size of 75 individuals (approximately 2250 hours of HD) will give us 80% power to observe a 20% increase in IDH rate with one-sided alpha 0.05. To account for study dropout, we will recruit a total of 90 individuals in total at the 3 sites (30 from each site Winnipeg, Calgary, Edmonton).

Feasibility:
Patients are currently participating and established in large clinical intradialytic cycling program in Winnipeg (65 patients), Calgary (200 patients) and Edmonton (130 patients). Therefore, there are currently 395 patients participating in the cycling program in our all 3 sites, all patients will be eligible for this study and we estimate no less than 50% will agree to participate, allowing us to achieve our target recruitment of 90 participants.

Anticipated outcome:
We anticipate that improved cardiac output and venous return will counteract post-exercise hypotension and that the rate of intradialytic hypotension when exercise is performed in the latter half of HD will not be significantly different than that when exercise is performed in the first half of HD.

Figure 1: Study Design



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