Effect of Intradialytic Exercise on Left Ventricular Diastolic Function in Hemodialysis Patients *(EXE-HDF)*

ClinicalTrials.gov Identifier: NCT06584734

Version: September 2, 2024

STUDY PROTOCOL

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Sponsor: Instituto Nacional de Cardiología Ignacio Chávez

Collaborator: Instituto Mexicano de Investigaciones Nefrológicas

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Ethics Approval Number: PT-23-1378

Document Note:
This revised version reflects the study procedures as implemented and incorporates the statistical analysis plan

1. Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients undergoing hemodialysis, largely due to structural cardiac changes associated with left ventricular diastolic dysfunction. In addition, this population has a high prevalence of sedentary behavior, which has been associated with increased cardiovascular mortality. Recent studies in patients with chronic kidney disease have shown that structured exercise interventions improve several parameters related to cardiovascular health.

Left ventricular diastolic function worsens during the hemodialysis session mainly due to preload effects associated with volume removal. Studies in patients with advanced CKD (pre-dialysis) have shown benefits in diastolic function when subjected to exercise programs. Based on this, implementing a standardized and protocolized exercise regimen during the hemodialysis session could provide cardiovascular benefits, specifically in terms of improving left ventricular diastolic function in this population.

The implementation of intradialytic exercise in the hemodialysis unit of the Instituto Nacional de Cardiología Ignacio Chávez began in 1994; however, there is no standardized or systematic process for intradialytic exercise. This leads us to ask the following research question: What is the effect of performing systematic intradialytic exercise on the echocardiographic parameters of left ventricular diastolic function in hemodialysis patients?

2. Objectives

2.1 Primary Objective

To evaluate the effect of implementing systematic, prescribed, and supervised intradialytic exercise on left ventricular diastolic function — assessed through the classification of left ventricular diastolic dysfunction grade per ASE/EACVI 2016 guidelines and left atrial reservoir strain (LASr) — in prevalent hemodialysis patients.

2.2 Secondary Objectives

- To assess changes in the ratio of early mitral inflow to mitral annular velocity (E/e' ratio) as a non-invasive estimate of left ventricular filling pressure.
- To evaluate changes in the mitral inflow E/A ratio.
- To assess changes in the left atrial volume index (LAVi) as a marker of chronic elevation in LV filling pressures.
- To evaluate changes in tricuspid regurgitation velocity as an indicator of estimated pulmonary pressure.
- To assess changes in left ventricular global longitudinal strain (GLS) as a measure of myocardial deformation.

- To evaluate changes in automated left ventricular ejection fraction (AutoLVEF) as a measure of systolic function.
- To assess changes in right ventricular systolic function via tricuspid annular plane systolic excursion (TAPSE).
- To evaluate changes in physical activity level using the General Practice Physical Activity Questionnaire (GPPAQ).
- To assess changes in functional exercise capacity using the 6-Minute Walk Test (6MWT).
- To determine changes in peak workload (maximal power output, watts) during cardiopulmonary exercise testing.
- To evaluate changes in workload at the first ventilatory threshold (VT1) as a marker of aerobic fitness.
- To assess changes in peak oxygen consumption (VO_2max) as a measure of cardiorespiratory fitness.

3. Methodology

3.1 Study Design

This is a non-randomized clinical trial (quasi-experimental, before-and-after study) conducted at the Instituto Nacional de Cardiología Ignacio Chávez. The study will be conducted over a total period of 32 weeks, divided into two consecutive 16-week phases.

Study Type	Interventional (quasi-experimental, before-and-after)
Intervention Model	Single Group Assignment
Allocation	N/A
Masking	None (Open Label). Echocardiographic image acquisition and analysis will be performed by echocardiographers blinded to the study phase (baseline, control, and intervention).
Primary Purpose	Treatment
Temporal Sequence	Longitudinal, prospective
Actual Enrollment	30 participants
Study Start Date	September 17, 2023
Primary Completion	September 30, 2024
Study Completion	October 30, 2024
Registration	ClinicalTrials.gov: NCT06584734

3.2 Study Population

The target population consists of patients with chronic kidney disease who are currently receiving hemodialysis (prevalent hemodialysis patients) at the Instituto Nacional de Cardiología Ignacio Chávez. Eligible patients will be identified among those attending the hemodialysis unit between September 2023 and September 2024 who have left ventricular diastolic function determined by echocardiographic measurement within the 6-month enrollment period.

3.3 Inclusion Criteria

- Adults ≥ 18 years of age.
- Both sexes.
- Patients currently enrolled in the hemodialysis program at the Instituto Nacional de Cardiología Ignacio Chávez.
- Patients on hemodialysis for at least 3 months prior to enrollment.
- Echocardiographic evidence of left ventricular diastolic dysfunction.
- Good echocardiographic acoustic window that allows reliable determination of diastolic function parameters.
- Sufficient cognitive ability to understand and follow study instructions.
- Ability to perform lower-limb stationary cycling during hemodialysis sessions.
- Willingness to participate and provision of written informed consent prior to enrollment.

3.4 Exclusion Criteria

- Major cardiovascular event (myocardial infarction or stroke) within the 3 months prior to enrollment.
- Emergency room visit for symptoms of decompensated heart failure within the 3 months prior to enrollment.
- Diagnosis of atrial fibrillation and/or atrial flutter.
- Mechanical mitral valve prosthesis.
- Orthopedic conditions or physical limitations that preclude lower-limb stationary cycling.
- Pregnancy.

3.5 Study Arms and Phases

All participants will undergo the same two phases sequentially, serving as their own controls. Echocardiographic and functional assessments will be performed at three time points: T0 (Baseline, week 0), T1 (end of Control Phase, week 16), and T2 (end of Intervention Phase, week 32). All echocardiograms will be performed before the first dialysis session of the week (Monday or Tuesday, according to each patient's schedule).

Study Period / Arm	Description	Duration
Baseline (Week 0 — T0)	A baseline transthoracic echocardiogram (T0), 6-Minute Walk Test, and GPPAQ will be performed prior to commencing Phase 1. Patients undergo routine hemodialysis according to the center's standard of care. Patients will be instructed to discontinue any unstructured intradialytic exercise previously performed during their hemodialysis sessions.	Single time point (week 0)
Phase 1 — Control Period (Pre-Exercise)	Patients will receive standard hemodialysis treatment for 16	16 weeks

Weeks 1–16 (T1)	weeks without any type of structured, prescribed, or supervised exercise program within the study protocol. Hemodialysis sessions will continue unchanged according to the center's standard of care. An echocardiogram (T1), 6MWT, and GPPAQ will be performed at the end of this phase. This period serves as the internal control condition.	
Phase 2 — Intervention Period (Intradialytic Exercise) Weeks 17–32 (T2)	Patients will undergo 16 weeks of systematic, prescribed, and supervised intradialytic aerobic exercise (stationary cycling) during hemodialysis sessions, 3 times per week. Exercise intensity will be individualized based on a CPET performed at the start of Phase 2. A final echocardiogram (T2), 6MWT, GPPAQ, and a second CPET will be performed at the end of this phase.	16 weeks

4. Interventions

4.1 Control Period — "Not Exercise"

During the Control Period, patients will be instructed to discontinue any unstructured intradialytic exercise previously performed during their hemodialysis sessions for 16 weeks. Hemodialysis sessions will continue unchanged according to the center's standard of care. No exercise will be measured, quantified, or supervised during this phase. This phase is registered in ClinicalTrials.gov under the intervention name "Not exercise" (Other Names: Control Phase, Rest, Control Period, Pre-Exercise).

4.2 Intervention Period — Intradialytic Exercise

During the Intervention Period, patients will undergo a 16-week intradialytic exercise program performed using cycle ergometers during the hemodialysis session. The intervention is registered in ClinicalTrials.gov as "Exercise during hemodialysis session" (Other Names: Intervention period, Intradialytic Exercise).

Exercise intensity will be quantified in watts using power meters and will be individualized according to each participant's performance on cardiopulmonary exercise testing (CPET). The intradialytic exercise program will use a stationary bicycle model Urban Fit PRO SH-612. Power meters (Favero Assioma UNO) will be inserted into the pedals and connected

to a cycle computer (iGPSPORT BSC100S) to measure workload in watts. Each session will be supervised by a sports medicine specialist and two trained medical interns.

5. Study Procedures

5.1 Cardiopulmonary Exercise Testing (CPET)

A cardiopulmonary exercise test (CPET) will be performed by a sports medicine specialist using a cycle ergometer for all study participants, at the beginning of Phase 2 (T1) and at the end of Phase 2 (T2). The following parameters will be determined:

- Peak oxygen consumption (VO_2max), expressed in mL/kg/min.
- Workload at the first ventilatory threshold (VT1), expressed in Watts, according to Skinner's three-phase model.
- Peak workload (maximal power output), defined as the highest power output in watts achieved during the test (last fully completed stage, or highest workload maintained for ≥30 seconds).

The VT1 will determine the individualized exercise intensity for the intradialytic exercise prescription, corresponding to the boundary between training zones 1 and 2.

5.2 Prescription of Intradialytic Exercise (FITT-VP Protocol)

Exercise prescription will be based on the FITT-VP framework validated by the American College of Sports Medicine, applied as follows:

F – Frequency	3 sessions per week, during each hemodialysis session (all patients).
I – Intensity	Low resistance, maintaining the VT1 watts throughout the session.
T – Time	Initially 45 minutes per session, increasing by 5 minutes each week, targeting 90 minutes (1 hour 30 minutes) by the end of the intervention phase.
T – Type	Aerobic exercise — stationary cycling (Urban Fit PRO SH-612).
V – Volume	Continuous pedaling during the hemodialysis session with workload monitored continuously in watts using power meters.
P – Progression	Time and workload progression will be individually monitored and recorded throughout the 16-week intervention phase.

Heart rate reserve will be monitored using the modified Karvonen method ((HRmax – HRrest) × (40–80%) + HRrest) and perceived exertion using Borg's Rating of Perceived Exertion Scale. A standardized exercise log will be maintained for each patient and each session.

5.3 Evaluation of Left Ventricular Diastolic Function (Echocardiography)

Diastolic function will be evaluated in accordance with the 2016 recommendations of the American and European Societies of Echocardiography (ASE/EACVI). Two-dimensional echocardiographic studies will be performed by two experienced cardiologists with current certification in echocardiography, using the Vivid Q GE ultrasound machine with a 3.5 MHz transducer. Echocardiographers will be blinded to the study phase (baseline, control, and intervention) at the time of image acquisition and analysis.

The following measurements will be obtained:

- Early transmitral flow velocity (E wave) and late diastolic transmitral flow velocity (A wave), with the E/A ratio, recorded in an apical 4-chamber view with pulsed Doppler (sample volume at mitral valve leaflet tips).
- Tissue Doppler imaging (TDI): septal e' and lateral e' velocities, with the pulsed Doppler sample volume placed 5 mm at the medial and lateral regions of the mitral annulus. The average E/e' ratio (mean of septal and lateral E/e') will be calculated.
- Left atrial volume indexed to body surface area (LAVi), measured by the biplane Simpson method in apical 4-chamber and 2-chamber views (mL/m^2).
- Tricuspid regurgitation velocity (TR Vmax), measured by continuous-wave Doppler in the apical 4-chamber view focused on the right ventricle (m/s).
- Based on the above four parameters (E/A ratio, average E/e' ratio, LAVi, and TR velocity), left ventricular diastolic dysfunction will be classified per ASE/EACVI 2016 guidelines into: Grade 1 (mild, impaired relaxation), Grade 2 (moderate, pseudonormal filling), Grade 3 (severe, restrictive filling), or Indeterminate.
- Left atrial reservoir strain (LASr), conduit strain (LAScd), and contractile strain (LASct), measured by 2D speckle tracking echocardiography in an apical 4-chamber view (expressed as %).
- Automated left ventricular ejection fraction (AutoLVEF), calculated using automated contour detection software (Vivid Q GE system).
- Left ventricular global longitudinal strain (GLS), assessed by 2D speckle tracking echocardiography (expressed as negative %; more negative = better longitudinal contraction).
- Tricuspid annular plane systolic excursion (TAPSE), measured by M-mode in the apical 4-chamber view (mm).

5.4 Six-Minute Walk Test (6MWT)

The 6-Minute Walk Test will be administered to assess functional exercise capacity. The test will be conducted on the first hemodialysis day of the week (Monday or Tuesday), before the dialysis session, at baseline (T0), end of Control Period (T1), and end of Intervention Period (T2). Additionally, the test will be repeated every 4 weeks throughout both phases to monitor longitudinal changes.

The test will be performed in accordance with the guidelines of the American and European Thoracic Societies by two medical interns trained to administer the test. Total distance walked in meters will be recorded.

5.5 General Practice Physical Activity Questionnaire (GPPAQ)

The GPPAQ is a validated, self-administered questionnaire for adults consisting of three questions: (1) type and amount of physical activity at work; (2) time spent on different types of physical activity during the previous week; and (3) usual walking pace. It classifies patients into four physical activity (PA) levels:

- Inactive: sedentary work and no physical exercise or cycling.
- Moderately inactive: sedentary work and <1 hour/week of physical exercise or cycling; or standing work without physical exercise or cycling.
- Moderately active: sedentary work and 1–2.9 hours/week of exercise or cycling; or standing work and <1 hour/week; or physically active work without additional exercise.
- Active: sedentary work and ≥3 hours/week of exercise or cycling; or standing work and 1–2.9 hours/week; or physically active work and <1 hour/week; or work with vigorous PA.

The GPPAQ will be administered at baseline (T0), every 4 weeks thereafter, and at T1 and T2, on the same day and before the 6MWT.

6. Safety Monitoring and Adverse Event Management

Adverse events will be monitored exclusively during the Intradialytic Exercise Phase (Intervention Period, Phase 2, 16 weeks). No exercise-related adverse events are expected during the Control Phase, as no structured exercise will be performed during that period.

All exercise sessions will be supervised by trained medical staff present during and immediately after each session. Adverse events will be classified by organ system (using MedDRA-aligned categories) and reported as frequency (n) and percentage (%) among participants. Any adverse event requiring session discontinuation will be documented and reported. Predefined adverse events to be monitored include:

- Intradialytic hypotension: decrease in systolic blood pressure ≥20 mmHg or mean arterial pressure ≥10 mmHg associated with clinical symptoms requiring nursing intervention. Will be managed per standard unit protocols without long-term complications or study withdrawal.
- Nausea: subjective sensation of abdominal discomfort with an urge to vomit during the physical exertion phase. Classified as mild, typically self-limiting; resolved by reducing exercise intensity.
- Muscle cramps: episodes of involuntary and painful skeletal muscle contractions primarily affecting the lower extremities, occurring during or immediately following the intradialytic pedaling session.

- Dizziness: sensation of unsteadiness, lightheadedness, or spinning during or shortly after the exercise intervention.
- Headache: cephalalgia occurring during or following the exercise component of the hemodialysis session.

Any serious adverse event (SAE) — life-threatening event, event requiring hospitalization, or event resulting in permanent disability — will be reported to the Ethics Committee and the principal investigator within 24 hours. Exercise will be discontinued in any patient experiencing an SAE, and study continuation will be assessed on a case-by-case basis.

7. Ethics and Regulatory Considerations

The study protocol has been approved by the local Research and Ethics Committees of the Instituto Nacional de Cardiología Ignacio Chávez under approval number PT-23-1378. This study has been registered at ClinicalTrials.gov (NCT06584734). The study will be conducted in full compliance with the principles of the Declaration of Helsinki and applicable national regulations.

Written informed consent will be obtained from all participants prior to enrollment. Participation is voluntary and patients may withdraw at any time without consequences for their ongoing medical care. All data will be handled confidentially and anonymized for analysis and publication. Individual participant data (IPD) will not be shared.

Principal Investigators are not employed by the organization sponsoring the study. There is no agreement between the Principal Investigator and the sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

8. Study Outcomes

8.1 Primary Outcomes

Outcome Measure	Description	Time Frame
1. Left Ventricular Diastolic Function Category	Classification of left ventricular diastolic function into ordinal grades based on the 2016 ASE/EACVI guidelines. Grading is determined by integrating four parameters: E/A ratio, average E/e' ratio, indexed left atrial volume (LAVi), and tricuspid regurgitation (TR) velocity. Grading criteria: • Grade 1 (mild — impaired relaxation): E/A <0.8, average E/e' ≤14, LAVi ≤34 mL/m², TR velocity ≤2.8 m/s; fewer than 2 positive criteria.	16 weeks (end of control period) and 32 weeks (end of intervention)

	• Grade 2 (moderate — pseudonormal filling): E/A 0.8–2.0, with ≥2 of the following positive: average E/e' >14, LAVi >34 mL/m², TR velocity >2.8 m/s. • Grade 3 (severe — restrictive filling): E/A >2.0, or E/A 0.8–2.0 with all three criteria positive. Grade 1 = least severe; Grade 3 = most severe.	
2. Left Atrial Reservoir Strain (LASr)	Peak longitudinal deformation of the left atrium during the reservoir phase, measured by 2D speckle tracking echocardiography in an apical 4-chamber view. Expressed as a percentage (%). Higher values indicate better left atrial reservoir function and, indirectly, less elevation in left ventricular filling pressures.	16 weeks (end of control period) and 32 weeks (end of intervention)

8.2 Secondary Outcomes

Outcome Measure	Description	Time Frame
1. Left Ventricular Global Longitudinal Strain (GLS)	Assessment of myocardial deformation using 2D speckle tracking echocardiography. Values are expressed as a negative percentage (%); more negative values indicate better longitudinal contraction (e.g., −17.4% is better than −15.5%).	16 weeks (end of control period) and 32 weeks (end of intervention)
2. Automated Left Ventricular Ejection Fraction (AutoLVEF)	Automated left ventricular ejection fraction (%), calculated using automated contour detection software applied to 2D echocardiographic images. Represents the proportion of blood ejected from the left ventricle with each heartbeat. Higher values indicate better systolic function; values ≥52% are within the normal range.	16 weeks (end of control period) and 32 weeks (end of intervention)
3. Tricuspid Annular Plane Systolic Excursion (TAPSE)	Displacement of the tricuspid annulus toward the cardiac apex during systole, measured in millimeters (mm) by M-mode echocardiography at the lateral tricuspid annulus.	16 weeks (end of control period) and 32 weeks (end of intervention)

	Reflects right ventricular longitudinal systolic function. Higher values indicate better RV function; values ≥17 mm are within the normal range.	
4. Ratio of Early Mitral Inflow to Mitral Annular Velocity (E/e' Ratio)	Non-invasive estimate of left ventricular filling pressure calculated as the ratio of early diastolic mitral inflow velocity (E wave, pulsed-wave Doppler) to the average of septal and lateral mitral annular early diastolic velocities (e', tissue Doppler imaging). Higher values indicate elevated filling pressures.	16 weeks (end of control period) and 32 weeks (end of intervention period)
5. Mitral Inflow E/A Ratio	Ratio of early diastolic (E wave) to late diastolic (A wave) mitral inflow velocities measured by pulsed-wave Doppler echocardiography with the sample volume placed at the mitral valve leaflet tips, apical four-chamber view. Reflects left ventricular relaxation and filling patterns.	16 weeks (end of control period) and 32 weeks (end of intervention period)
6. Left Atrial Volume Index (LAVi)	Left atrial volume indexed to body surface area (mL/m²), measured by the biplane Simpson method using apical four-chamber and two-chamber views. Reflects left atrial structural remodeling as a marker of chronic elevation in LV filling pressures. Values ≤34 mL/m² are within the normal range per ASE 2016 guidelines.	16 weeks (end of control period) and 32 weeks (end of intervention period)
7. Tricuspid Regurgitation Velocity	Peak tricuspid regurgitation velocity (m/s) assessed by continuous-wave Doppler echocardiography. Used to estimate right ventricular systolic pressure and pulmonary artery pressure per the 2016 ASE/EACVI diastolic function guidelines. Values ≤2.8 m/s are within the normal range.	16 weeks (end of control period) and 32 weeks (end of intervention period)
8. Physical Activity Level (GPPAQ)	General Practice Physical Activity Questionnaire. Self-administered questionnaire classifying patients into 4 levels: Inactive, Moderately	16 weeks (end of control period), and 32 weeks (end of intervention)

	Inactive, Moderately Active, and Active. Higher activity levels represent better physical activity status; Active is the most favorable and Inactive the least favorable category.	
9. Distance Covered in the Six-Minute Walk Test (6MWT)	Total distance in meters (m) walked by the patient on a flat, hard surface over 6 minutes, performed according to ATS/ERS guidelines by two trained medical interns. Assesses functional exercise capacity. Greater distances indicate better functional capacity.	16 weeks (end of control period) and 32 weeks (end of intervention)
10. Peak Workload (Maximal Power Output)	Peak workload (maximal power output) defined as the highest power output (in watts) achieved during a symptom-limited incremental CPET on a cycle ergometer, corresponding to the last fully completed workload stage or the highest workload maintained for ≥30 seconds. Higher values indicate greater maximal aerobic exercise capacity.	16 weeks (end of control period), and 32 weeks (end of intervention)
11. Workload at First Ventilatory Threshold (VT1)	Power output (watts) achieved during a CPET at the point of the first ventilatory threshold (VT1) — the exercise intensity above which ventilation begins to increase disproportionately to oxygen consumption, determined per Skinner's three-phase model. Higher values indicate greater aerobic exercise capacity and improved cardiovascular fitness.	16 weeks (end of control period) and 32 weeks (end of intervention)
12. Peak Oxygen Consumption (VO_2max)	Maximum rate of oxygen consumption (VO_2max) measured during incremental exercise on a cycle ergometer (CPET), expressed in mL/kg/min. Reflects overall cardiorespiratory fitness and aerobic capacity. Higher values indicate better cardiovascular fitness; values <17.5 mL/kg/min in dialysis patients are associated with increased cardiovascular risk.	16 weeks (end of control period) and 32 weeks (end of intervention)

8.3 Pre-specified Sensitivity Analyses (Post-hoc)

As a pre-specified sensitivity analysis, the E/e' ratio and the E/A ratio will each be analyzed across all three study time points (T0, T1, T2) using a one-way ANOVA, in addition to the primary paired comparison approach. These analyses are intended to assess trends across the full study period. Time Frame: Baseline (week 0), 16 weeks (end of control period), and 32 weeks (end of intervention period).

9. Statistical Analysis Plan

This statistical analysis plan (SAP) is pre-specified as part of the study protocol approved under ethics approval number PT-23-1378 by the Comité de Ética e Investigación of the Instituto Nacional de Cardiología Ignacio Chávez. All analyses will be conducted using IBM SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY, USA).

9.1 Analysis Population

The analysis population will include participants who complete both study phases and have evaluable echocardiographic data at both T1 and T2. Participants who completed Phase 1 will constitute the analysis population; reasons for non-completion of Phase 1 will be documented (renal transplant, surgery, hospitalization, vascular access dysfunction).

9.2 Data Distribution

The distribution of all continuous variables will be assessed at each time point using the Shapiro-Wilk test and the Kolmogorov-Smirnov test. A p-value <0.05 will be considered indicative of non-normal distribution and will guide the selection of parametric or non-parametric tests.

9.3 Descriptive Statistics

- Normally distributed continuous variables: mean ± standard deviation (SD).
- Non-normally distributed continuous variables: median [interquartile range, IQR 25th–75th percentile].
- Categorical variables: absolute frequencies (n) and percentages (%).

9.4 Inferential Statistical Tests

Paired comparisons between study phases (T1 vs. T2) will be performed as follows:

- Parametric data (normal distribution): Paired Student's t-test.
- Non-parametric data (non-normal distribution): Wilcoxon Signed-Rank Test.

9.5 Pre-specified Sensitivity Analysis

A one-way ANOVA will be performed as a pre-specified sensitivity analysis to evaluate changes across the three study periods (T0, T1, T2) for the E/e' ratio and the E/A ratio.

9.6 Significance Level

All analyses will be two-tailed. Statistical significance will be defined as $p < 0.05$.

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