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Effects of intradialytic inspiratory muscle training at different intensities on diaphragm thickness and functional capacity: clinical trial protocol in patients undergoing haemodialysis

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ABSTRACT

Introduction Patients with end-stage renal disease (ESRD) undergoing haemodialysis (HD) commonly present with a sedentary behaviour and reduced functional capacity, factors that can compromise their prognosis. Intradialytic inspiratory muscle training (IMT) can increase respiratory muscle strength and, consequently, improve functional capacity, besides being easy to apply, cheap and performed in a supervised setting. However, few studies show the effects of this type of training applied at different intensities in this population. This study aims to compare the effects of IMT at different intensities in adults with ESRD undergoing HD.

Methods and analysis A randomised, double-blind, sham-controlled trial will be conducted on 36 subjects randomly allocated into three groups: IMT at intensities of 30% or 50% of maximal inspiratory pressure (intervention groups), or 10% of maximal inspiratory pressure (sham-IMT). All the interventions will be supervised and performed three times per week, for 12 weeks, totalling 36 sessions. The primary outcomes are the 6-minute walk test, diaphragm thickness and the response of VO_2peak post-intervention. Respiratory muscle strength, 24-hour ambulatory blood pressure measurement and the Kidney Disease Quality of Life 36-item short form survey will be evaluated as secondary outcomes.

Ethics and dissemination This study has been approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (ID: 2020-0458). The results of this study will be disseminated by conference presentations and peer-reviewed journal.

Trial registration number NCT04660383.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A strength of this study is the randomised, double-blind and placebo-controlled design.
- ⇒ The first study to assess the effect of inspiratory muscle training on diaphragm thickness of haemodialysis individuals.
- ⇒ The outcomes will be obtained through clinically validated and accurate tools.
- ⇒ Since this will be a study conducted in a single region, the results may not have external validity.

INTRODUCTION

Patients with chronic kidney disease may be at increased risk of cardiovascular diseases, hospitalisation and mortality.[1 2] This risk is gradually associated as the estimated glomerular filtration rate decreases.[1] Evidence shows that individuals more susceptible to worse outcomes, who show end-stage renal disease (ESRD), have reduced functional capacity and impairment of respiratory muscle function, both contributing to exercise intolerance and physical inactivity.[3–5]

Many randomised clinical trials (RCTs) have shown the benefits of physical exercise in patients with ESRD undergoing haemodialysis (HD). For example, improvement in functional capacity, lipid profile, blood pressure, heart rate variability and quality of life.[6–8] This evidence encourages regular exercise recommendations for this population unless there is some contraindication.[9]

Many exercise modalities are available for patients with ESRD, even during HD sessions (intradialytic exercise), which proved to be safe and can be performed in a supervised setting.[9] Recently published data from meta-analyses suggest that combined intradialytic exercise is the best strategy to promote the aforementioned benefits.[6 10 11]

Inspiratory muscle training (IMT) uses specific devices to strengthen the inspiratory muscles by applying resistance during inspiration. It is easy-to-apply and low-cost training, which can be attractive, especially for patients with motor function problems and functional limitations. Although still little studied in patients with ESRD undergoing HD, some promising results have been observed in the 6-minute walk test (6MWT),[10] regarding inspiratory muscle strength and pulmonary function.[12]

These benefits may be partly due to diaphragm hypertrophy, which can be achieved by applying IMT.[13] However, few studies show the possible benefits of different IMT intensities in HD patients and the possible effect on diaphragm hypertrophy.

In other chronic disease settings, such as heart failure, studies have found encouraging results when IMT was applied to patients with inspiratory muscle weakness (maximal inspiratory pressure (MIP) <70% of predicted).[14–16] Furthermore, Figueiredo *et al*[4] reported an association between reduction in MIP and decreased functional capacity in HD subjects. These data state that patients with HD and respiratory muscle weakness can be more benefited.

Thus, we designed an RCT to investigate the effects of IMT at different intensities in patients with ESRD undergoing HD: 6MWT, diaphragm thickness and VO_2peak (primary outcomes); respiratory muscle strength and 24-hour ambulatory blood pressure measurement (secondary outcomes). Besides, we aim to determine by a sensitivity analysis if the results differ regarding patients with or without inspiratory muscle weakness.

METHODS AND ANALYSIS

This trial protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. The filled SPIRIT checklist can be found in online supplemental material 1. This study was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA) (ID: 2020-0458) and is registered at ClinicalTrials.gov (NCT04660383). Furthermore, it will be conducted in accordance with Resolution no. 466/12 of the National Health Council. Any changes in the protocol will be subjected to institutional review board approval and will be updated on ClinicalTrials.gov.

Study design

This is a double-blind, sham-controlled, randomised superiority clinical trial with a 1:1:1 allocation with a follow-up period of 12 weeks, from December 2022 to June 2023. The study will be conducted primarily in the Nephrology Department of HCPA (Porto Alegre, Brazil).

Eligible participants will be randomised to receive IMT or sham-IMT during the first and second hours of HD.

Patient timeline

Patients will be recruited at the HCPA Nephrology Department and by the public health network. Those eligible to participate will be contacted in person or via telephone call by the responsible researcher, who will explain the nature of the study and verify the patient's interest in participating. In case of interest, the patient will be referred to the Physiatrist and Rehabilitation Department of the HCPA to sign the informed consent form and start data collection. A copy of the informed consent form translated into English can be found in the online supplemental material 2. The estimated time to complete this research is 18 months. Figure 1 shows the schedule of enrolment, interventions and assessments. Figure 2 shows the allocation of participants and timeline.

Eligibility criteria

Inclusion criteria

- Patients with chronic kidney disease who are on HD for at least 3 months.
- With stable chronic kidney disease for at least 30 days (with no hospitalisation).
- Patients must be aged 18 years.
- Authorised by their attending physician and be able to exercise.
- Have provided a written consent term accepting participation in the study.

Exclusion criteria

- History of arrhythmias (6 months).
- Recent hospitalisation (<3 months).
- Recent acute myocardial infarction (<6 weeks).
- HD routine <3×/week.
- Muscle or respiratory disorders (eg, chronic obstructive pulmonary disease).
- Unstable angina.
- Severe valve disease.
- Uncontrolled hypertension.
- Haemoglobin concentration <10 g/dL.
- Who have not participated in a study with intradialytic exercise 6 months before this study.
- Refusal to participate in the study.

Sample size calculation

The results obtained in the study by Campos *et al*[17] were inserted using the WINPEPI software. They found a difference of 50% in the increase in functional capacity measured by the 6MWT in the training group with 50% of MIP, with 20% SD. Based on these data, the minimum need for a sample with 30 individuals was identified using 80% power and 5% significance, that is, 10 for each group. The sample size will be increased by 20% to control possible losses in the follow-up, thus finalising a sample of 36 individuals, 12 for each group.

Screening, randomisation and blinding

Eligible participants will be randomised by a sequence generated by the 'Random Allocation Software' with an allocation of 1:1:1 to receive an IMT intervention at one of three different intensities during the HD period. All patients who signed the informed consent form and fulfilled the inclusion criteria will be randomised. The research group will be blinded to the randomisation sequence and blinded by the researchers who enrolled and evaluated the patients. Patients will receive intervention with visually identical equipment, but with specific adjustments for each group, being blinded to which intervention they were assigned.

	STUDY PERIOD			
	Enrollment	Allocation	Post-allocation	Close-out
TIMEPOINT (weeks)	-4	0	12	13
ENROLLMENT:				
Eligibility screen	X			
Informed consent form	X			
Allocation		X		
INTERVENTIONS:				
IMT 30% of MIP			↔	
IMT 50% of MIP			↔	
IMT 10% of MIP			↔	
ASSESSMENT:				
Anthropometric measurements	X			X
Six-minute walk test	X			X
Diaphragm muscle thickness	X			X
Cardiopulmonary exercise test	X			X
Manovacuometry	X			X
24-hour ambulatory blood pressure monitoring	X			X
KDQOL-36	X			X
Adverse events questionnaire			X	X

Figure 1 The schedule of enrolment, interventions and assessments. IMT, inspiratory muscle training; KDQOL-36, Kidney Disease Quality of Life 36-item short-form survey; MIP, maximal inspiratory pressure.

Interventions

Patients will be subjected to threeweekly IMT sessions at three different intensities for 12 weeks, totalling 36 sessions, as follows: (a) intervention groups: 30% or 50% of MIP; (b) control group: 10% of MIP (sham-IMT). Patients who do not attend three consecutive sessions or four non-consecutive sessions will be withdrawn from the research.

The IMT will be applied by an electronic device (Power Breathe K1, POWERbreathe International) with a linear pressure load of respiratory incentives. The patient will use a nose clip and will breathe by a mouthpiece with resistance in the inspiratory branch, using the respective MIP.

Within the first 2 hours of HD, all individuals must perform three sets of 15 repetitions, with a 60-second rest interval. The intensity of the three initial sessions will be reduced to familiarise the patients with the equipment and routine, and guidance related to the training procedure. The IMT will comply with the principle of overload evolution with reassessments every 15 days for adequate load readjustment. Similar to training, all reassessments will be performed during HD sessions.

Primary outcomes

Six-minute walk test

The 6MWT is a useful, validated and well-tolerated tool that requires no specialised equipment, used to determine the functional capacity of individuals with chronic kidney disease.[18] In addition, the 6MWT is able to represent the submaximal level of functional capacity (eg, daily physical activity). The results will be defined as the difference in metres in distance covered at weeks 0 and 12. Participants will be instructed to walk on a flat, straight corridor, and will be told that the objective of the test is to walk as far as possible for 6 min at a self-selected speed.

Diaphragm thickness

Diaphragm thickness will be assessed by B-mode ultrasound (EnVisor C, Philips, Bothell, Washington, USA) with a 12.0 MHz ultrasound probe (L12-3, Philips)

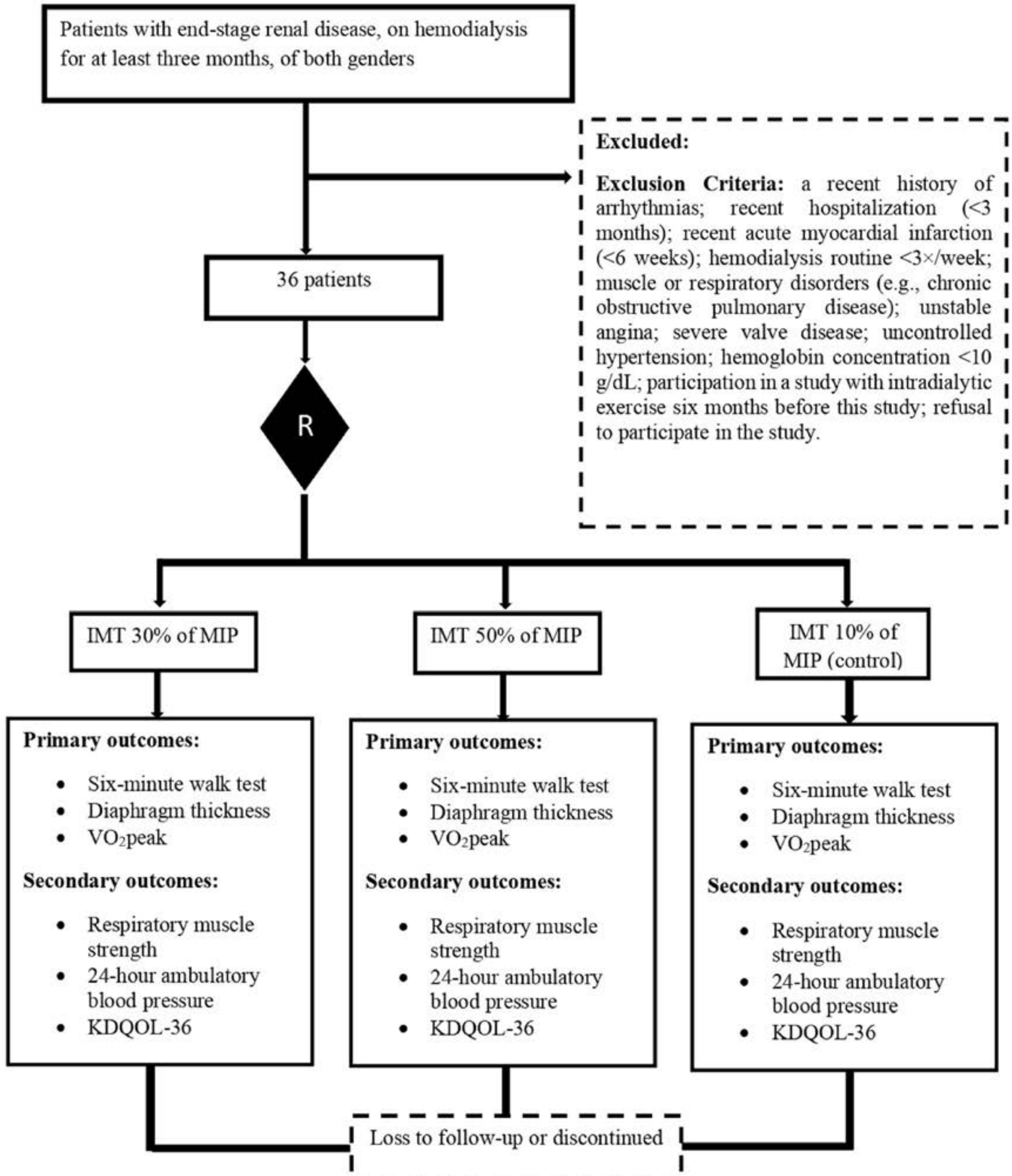

Figure 2 Allocation of participants and timeline. IMT, inspiratory muscle training; KDQOL-36, Kidney Disease Quality of Life 36-item short-form survey; MIP, maximal inspiratory pressure.

to show the diaphragm in the apposition zone; the vertical section resting against the lateral portion of the right rib cage, using the method described by Wait *et al*.[19] Measurements will be taken at end-inspiration (Tdi) and end-expiration (Tde) to estimate the relative fractional thickness (TFrel [Tdi Tde]/Tdi) in the functional residual capacity.

VO_2peak

Patients will undergo a cardiopulmonary exercise test on a stationary bicycle (Vmax Encore, Oxycon and MasterScreen), using an incremental loading protocol according to guidelines published by the American Thoracic Society/American College of Chest Physicians.[20] Examinations will be performed by a cardiologist blinded to patient allocation. The absolute and relative VO_2peak (L/min and mL/kg/min) and the percentage of its predicted value for sex and age group by the Wasserman equation, the minute ventilation (VE) in L/min and its predicted value will be recorded: tidal ventilation (mL) at rest and at peak exercise, carbon dioxide production (VCO_2), oxygen saturation, percentage of maximum heart rate, respiratory rate and respiratory quotient. Carbon dioxide tension (mm Hg) at rest, the slope of the VE/VCO_2 ratio (VE/VCO_2 slope), the oxygen uptake efficiency slope and recovery variables such as the reduction in frequency in the first minute and T1/2 will also be evaluated.

Secondary outcomes

Respiratory muscle strength

MIP and maximal expiratory pressure (MEP) measurements will be conducted by a manovacuometry equipment (MVD 300, Globalmed, Porto Alegre, Brazil). MIP will be measured based on residual volume and MEP from total lung capacity.

The 24-hour ambulatory blood pressure measurement

Blood pressure will be assessed by ambulatory blood pressure measurement (ABPM). This method allows indirect and intermittent recordings of blood pressure for 24 hours while patients conduct their daily activities. This monitoring requires patients to maintain their normal daily activities, being automatically measured at 15-minute intervals (daytime) and 20-minute intervals (night-time). Systolic and diastolic blood pressure will be obtained by ABPM with mean values for the 24-hour, daytime and night-time periods. Participants will be evaluated by ABPM at the beginning and at the end of the study, using the equipment BPLab Vasotens technology (Petr Telegin).

Quality of life

Each participant will complete a paper questionnaire to assess the quality of life after 12 weeks of follow-up, evaluated by the Kidney Disease Quality of Life 36-item short form survey, which is considered one of the most used tools to assess the quality of life of individuals undergoing HD.[21] Overall scores range from 0 to 100, with higher scores indicating better quality of life.

Additional analysis

Patients with or without inspiratory muscle weakness (<70% of predicted) will be considered eligible. Thus, if possible, a sensitivity analysis will be performed to assess possible differences between the results regarding these patients.

Adverse events

All subjects will be interviewed at each training session regarding the occurrence of any adverse event using open-ended questions or structured questionnaires. All information will be stored with the participant's data. The relationship of events with the study intervention will be evaluated by the research team. Serious adverse events must be reported to the institutional review board by the main researcher within 24 hours after such events are identified. The participant will be informed of the importance to adhere to the study and encouraged to complete all intervention sessions. However, they may decline to participate at any time without harming their conventional treatment.

The research team will be trained to apply the assessments and the questionnaires. An independent trained researcher will conduct the cardiopulmonary exercise test assessments.

Data collection forms

The data will be collected and administered in a Microsoft Excel spreadsheet, then inserted and managed using REDCap tools hosted at HCPA. REDCap is a secure, web-based application designed to support data capture for research studies. For data analysis, subject-related data from REDCap will be exported to the SPSS statistical analysis program (V.20.0; IBM). All identifiable patient data will be removed before the data are exported.

Statistical methods

To preserve the benefits of randomisation, all data will be analysed according to the intention-to-treat principle, that is, considering the group that the individuals were originally assigned. Categorical variables will be presented with absolute and percentage values and compared using Fisher's exact or X^2 test. The continuous quantitative variables will initially be compared with the Gauss curve using normality tests (Shapiro-Wilk and Kolmogorov-Smirnov) and determined as parametric or non-parametric. Variables will be described as mean and SD, or median and IQR (P25%–P75%), according to their distribution. Analysis of covariance will be used to compare continuous variables between groups. Logistic regression analysis can be used to assess the association between variables. P values of <0.05 will be considered significant.

Protocol amendments

Any change in the protocol that could affect the conduct of the study or change the benefit or harm to the participant will require formal information to the HCPA Research Ethics Committee prior to implementation.

Ancillary and post-trial care

Interventions with IMT are conducted with patients with many diseases and are considered safe. The risks of the study are low, with a small possibility of adverse effects. The most frequent adverse effects are hypotension, nausea, headache and fatigue, usually not requiring treatment discontinuation. In case of adverse effects or problems related to participation in the study that require medical treatment, the researchers will be responsible for providing medical care so that the participant does not incur costs.

Patient and public involvement

Patients have not been involved in the study design.

Ethics and dissemination

This study will be conducted according to Resolution no. 466/12 of the National Health Council and approved by the Research Ethics Committee of the HCPA (ID: 2020-0458). The results of this study will be submitted to a peer-reviewed journal.

DISCUSSION

In recent decades, regular physical exercise has emerged as an essential non-pharmacological intervention for patients with ESRD undergoing HD. Thus, it is recommended integrating physical exercise into these individuals' routine unless there is contraindication.[4]

Some studies have suggested that HD patients with decreasing functional capacity have a worse prognosis and high mortality risk.[22 23] Evidence from RCTs and meta-analyses of RCTs indicate relevant benefits of intradialytic exercise, such as improvement in functional capacity, muscle strength and quality of life.[10 24–26] However, these studies mainly assessed aerobic, resistance and combined exercises. On the other hand, although few RCTs have studied IMT during HD, improvements have been reported. Figueiredo *et al*[27] found that IMT at 50% intensity of MIP improved functional capacity and inflammatory biomarkers in HD subjects, which is comparable with the group that practised low-intensity aerobic exercise (between 3 and 5 points on the modified Borg scale). Pellizzaro *et al*[28] found significant improvement in the 6MWT in patients who underwent IMT in 50% of MIP versus the control group. Yuenyongchaiwat *et al*[29] observed improvements in respiratory fitness and shortness of breath after IMT at 40% intensity of MIP for 3 days/week, for 2 months. These results are essential because patients with chronic kidney disease commonly have decreased inspiratory muscle strength or muscle weakness compared with predictive values.[30] Despite encouraging results from IMT in the HD scenario, applying different intensities can generate different responses in this population. Thus, differences in IMT intensities regarding its benefits have not yet been assessed.

The IMT is an easy-to-apply intervention and relatively cheap. Furthermore, it may be attractive to include patients with diabetes complications (such as lower extremity amputation), which reduces the chance of non-participation in a training intervention. On the other hand, aerobic training requires an adapted cycle ergometer, which may be unavailable in HD centres. Besides, resistance training with free weights can raise concerns regarding the safety of overloading the arteriovenous fistula arm, the amount of weight that can be maintained or the need to avoid exercising the fistula arm.[31]

Besides assessing the functional capacity measured by the cardiopulmonary exercise test (the gold standard for this outcome), blood pressure, MIP and MEP, we evaluated the effect of IMT at different intensities on diaphragm thickness. Since inspiratory muscles can be considered skeletal muscles, they tend to respond to training,[13] and these effects can positively influence the improvement of functional capacity. Chiappa *et al* observed diaphragmatic hypertrophy in patients with chronic heart failure and reduced ejection fraction.[15] However, the effects of IMT on diaphragm thickness in patients with ESRD undergoing HD remain unknown.

We intend to compare the responses of interventions between individuals with or without inspiratory muscle weakness. Despite more consistent IMT results found in patients with heart failure and inspiratory muscle weakness, there are no data on patients with ESRD and HD.[14–16]

Finally, if the results of this RCT can be applied on daily basis, many HD patients may benefit from a patient-centred, easy-to-apply and low-cost type of intervention.

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Contributors MdST, FF, MS and RS designed the trial protocol, drafted this manuscript, collected data, and will perform data analysis and interpretation. FF, TD and MS offered suggestions on trial design and data analysis, collaborated in the writing and critical review of this manuscript, and will collaborate in data interpretation. MdST, FF, GC, EdSB, MS and RS contributed to the protocol development and writing of this manuscript; they will perform data analysis and interpretation, critical review and final approval of future research communications. All authors read and approved the final version of this manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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