PROTOCOL TITLE:

Effects of high-intensity inspiratory muscle training as a pre-cardiac rehabilitation intervention on cardiovascular functions in patients with heart disease

PRINCIPAL INVESTIGATOR:

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	12/1/2023	1. Changed title to Effects of high-intensity muscle training as a pre-cardiac rehabilitation intervention on cardiovascular function in patients with heart disease 2. Expand participant population to include those with a history of percutaneous coronary interventions, heart failure, and/or myocardial infarction.	Yes Yes

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1.0 Study Summary

Background / aim: Endothelial function is closely associated with coronary artery health among individuals being treated for heart disease. An impairement in endothelial function promotes arterial stiffening that directoy contributes to elevated systolic blood pressure as a result of increased vascular resistance. Inspiratory muscle training is simply a form of training consisting of repeated inspirations against a resistance. Inspiratory muscle training has also been applied to patients with chronic disease or as an additional therapy for cardiac rehabilitation and it has proven to be safe in these groups. Few studies in the literature examined the effects of high intensity inspiratory muscle training in this population, however, these studies did not examine the direct effects of inspiratory muscle training on vascular function. To the best of our knowledge, the effects of inspiratory muscle training in patients with heart disease on endothelial function and arterial stiffness prior to starting cardiac rehabilitation have not been investigated.

Methods: The study was designed as a randomized controlled trial. The demographic and clinical characteristics of the patients will be recorded after consent is obtained from the volunteer patients who meet the inclusion criteria. Subsequently, patients will be randomly divided with into two groups (22 subjects in each group) for inspiratory muscle training (IMT) with 60% of maximum inspiratory pressure (MIP) or sham inspiratory muscle training (Sham-control), for 4 weeks. In both groups, before and after 4-week-training, resting blood pressure (systolic/diastolic), resting heart rate, endothelial function, arterial stiffness, functional exercise capacity, the severity of dyspnea and inspiratory muscle functions will be measured.

2.0 Objectives*

2.1 Objectives: The aim of this study is to investigate and interpret whether high-intensity inspiratory muscle training, beyond the usual care of heart disease, improves endothelial function and arterial stiffness.

2.2 Hypotheses: High-intensity inspiratory muscle training will improve endothelial function and arterial stiffness beyond the usual care of patients with heart disease.

3.0 Background*

Cardiovascular diseases (CVD) remains a leading cause of morbidity and mortality in both men and women in developed and developing societies (Joseph et al., 2017). Some degree of pulmonary dysfunction is highly likely in patients with heart disease compared to those without(Calles et al., 2016; Cahalin and Arena, 2015). This can affect pulmonary function, gas exchange, as well as decrease maximum inspiratory and expiratory pressures (MIP and MEP, respectively)(Dos Santos et al., 2019; Haeffener et al., 2008; Roncada et al., 2015; Cahalin and Arena, 2015).

Inspiratory muscle training has been shown to be an effective form of training that enhances lung function. It consists of repetitive breath cycles where one inspires against resistance placed by a device and expires against no resistance. Studies that have applied this form of training in patients with heart disease have found significant improvements in MIP-MEP, tidal volume, vital capacity, and 6-minute walking distance. Few studies have examined the effects of high-intensity (between 50-80% of MIP) inspiratory muscle training in patients with heart disease (Dos Santos et al., 2019; Dos Santos et al., 2021; Laoutaris et al., 2007; Miozzo et al., 2018; Sadek et al., 2022). This level of training has been associated with greater improvements in the aforementioned outcomes of interest, however, no study has explored the effects of high-intensity inspiratory muscle training in patients with heart disease on measures of cardiovascular function.

This study will therefore examine the effects of high-intensity inspiratory muscle training in patients with heart disease on cardiovascular function.

4.0 Study Endpoints*

4.1 Primary endpoints; inspiratory muscle function, endothelial function, arterial stiffness.

4.2 Secondary endpoints; dyspnea, functional exercise capacity.

5.0 Study Intervention/Investigational Agent

5.1 Description of the study intervention: Based on the findings of a systematic review (Z. Sadek et al., 2018), it has been determined that to achieve significant improvements in inspiratory muscle strength, the threshold pressure for inspiratory muscle training (IMT) should be set at 60% of the maximal inspiratory mouth pressure (MIP). Consequently, the intervention protocol for IMT involves using a threshold-loaded IMT device (Threshold IMT Philips® Respironics, Inc). In the IMT group, the initial intensity of the inspiratory threshold will be set at 60% of each patient's initial maximal MIP, which is then readjusted after 2 weeks of training to maintain the 60% of MIP throughout the 4-week period. Rates of perceived inspiratory effort on a modified Borg scale will also be used to determine the highest tolerable load for each patient (at the 4-6 level of 10) (Borg, 1982; Wilson and Jones, 1989). Patients will perform IMT for 2 sets of 30 repetitions, with one-minute intervals between each set (McConnell, 2013; Z. Sadek et al., 2018). Throughout the training sessions, patients will be instructed to maintain diaphragmatic breathing. On the other hand, the Sham-control group will follow the same training program using the same device, but without any inspiratory load. Both groups will perform the training program twice a day, five days a week, for a total of 4 weeks, under the supervision of a physiotherapist (McConnell, 2013). The supervision will be conducted remotely through telerehabilitation, utilizing video calls to connect with the patients without requiring them to physically visit the healthcare facility. To familiarize the participants with the training procedure, both the IMT and Sham-control groups will undergo a session without any load on the

day of the baseline assessments. Throughout the study, all participants will visit the healthcare facility for baseline assessments, final assessments, and an additional brief assessment session at the end of the second week of training to measure MIP and readjust the loading value. The assessment to be made at the end of the 2nd week of the 4-week training seasons will only include the assessment of inspiratory muscle function described in 11.1.5.

5.2 Device Handling: The Threshold IMT Philips products will be obtained by researchers and provided to patients without any cost. The Threshold IMT Philips products is a legally marketed device when used in accordance with its labeling. There are no expected adverse events based on the product label. They will be used only on subjects and be used only by authorized investigators. On the other hand, a patient who loses the product before the study ends will be notified that he or she will be excluded from the study.

6.0 Study Timelines*

- The duration of an individual subject's participation in the study will be 4 weeks.
- The duration anticipated to enroll all study subjects is 9 months.
- The estimated duration for the investigators to complete this study is 10 months.
- The estimated date for the investigators to complete this study is June 14, 2024.

7.0 Inclusion and Exclusion Criteria*

7.1 Inclusion criteria as follows;

- Aged >18 years old
- Be able to walk independently.
- Had coronary artery bypass graft (CABG) surgery, history of percutaneous coronary interventions, heart failure, and/or myocardial infarction.
- Sufficient English language comprehension and cognitive ability to understand the study protocol, give informed consent and follow instructions.

7.2 Exclusion criteria as follows;

- <18 years of age

- Being a current smoker (or tobacco).
- Having a diagnosed chronic disease such as inflammatory bowel disease/irritable bowel syndrome, cerebrovascular diseases, COPD, chronic kidney disease requiring dialysis, neurological disorders, or diseases that may affect motor/cognitive function [multiple sclerosis, Parkinson's disease, polio, Alzheimer's disease, dementia, or other brain diseases of ageing])
- Getting a score below 24 on the Standardized Mini Mental Test
- Using antipsychotic medications commonly used to treat schizophrenia or schizoaffective disorders (i.e., haloperidol)
- Having had any other previous thoracic operation except CABG (e.g. Pneumonectomy, lobectomy, etc.)
- Having a history of unstable-angina
- Having had pneumonia in the last 3 months

8.0 Vulnerable Populations*

8.1 The research not involves individuals who are vulnerable to coercion or undue influence.

- The research not involves pregnant women.
- The research not involves neonates of uncertain viability or non-viable neonates.
- The research not involves prisoners.
- The research not involves persons who have not attained the legal age for consent (“children”).
- The research not involves cognitively impaired adults.

9.0 Number of Subjects

9.1 For the required sample size; on the basis of prior studies (Hermes et al., 2015; Dos Santos et al., 2019; Dos Santos et al., 2021), the sample size was calculated as 20 subjects per group (n = 40 in total) for a significance level of 5%, a statistical power of 90%, and a difference in maximum inspiratory pressure (MIP) of at least 23 cmH2O between groups. However, to optimize the results, the required sample size was calculated as 44 participants, n=22 participants per group, with consideration of a 10% loss at follow-up. Separately, after ethical approval, the ClinicalTrials.gov study registration will be done before the study starts.

10.0 Recruitment Methods

For research purposes only, we propose to recruit patients that have undergone CABG surgery, history of percutaneous coronary interventions, heart failure, *and/or* myocardial infarction. Potential participants may be recruited at University of Illinois Health (UIH) clinics including Division of Cardiology (Dr. Ziccardi). Potential participants may *actively* be recruited from the Outpatient UIH Heart Center, and the Cardiac Rehabilitation (Dr. Ozemek) and Exercise Testing (Hannah Ozemek) Programs via clinician referral during patient's routine visit.

Patients may be identified via clinician referral during routine in person visits or phone calls used to schedule a cardiac rehabilitation orientation visit. Dr. Ziccardi and their staff may also notify Dr. Ozemek about whether and when any patients who meet the study criteria are scheduled to be seen in the clinic during the day or the following day. Patients that have received a referral to cardiac rehabilitation will be given the opportunity to take part in the study as long as the study requirements can be completed prior to their cardiac rehabilitation start date. Cardiac rehabilitation will not be delayed for the sole purpose of taking part in the study. Patients will not be able to do both study and cardiac rehabilitation at the same time as exercise is known to improve cardiovascular function.

The informed consent will be obtained from volunteer patients who meet the inclusion criteria. Patients will then be randomly assigned to a study or control group. The randomization sequence will generate from the www.randomizer.org website by an investigator not otherwise involved in the study, using a table of random numbers uniformly distributed and divided into 2 groups. No names or personal identification will be given out.

11.0 Procedures Involved*

This research will take place in the Physical Therapy Faculty Practice located at 1640 W. Roosevelt Road in Chicago, IL. It will be an interventional randomized controlled study. The data will be collected for research purposes only. We will ensure to participants that no new information (i.e., results from any study procedures) will be entered into or collected from patient's medical records. After eligibility is determined, those who agree to participate (provide oral consent) will be required to provide written informed consent statement before proceeding to subsequent data collection. All participants, both control and intervention, will be assessed with the following assessments.

Baseline Clinical Data collected will include demographics, level of educational attainment and past-medical history. Anthropometrics, Body Mass (kg) and height (m) will be assessed. **(visit #1)**

11.1 Assessments

11.1.1 Evaluation of mental state (visit #1)

A standardized Mini Mental Test (SMMT) will be used to evaluate the mental state. SMMT is a test with high sensitivity levels for moderate to severe cognitive impairment, as well as satisfactory reliability, internal consistency, and test-retest reliability, first developed by (Folstein et al., 1975) (Tombaugh & McIntyre, 1992). The test, which is one of the most widely used screening criteria for evaluating neuropsychological functions, is used in many patient groups, including heart diseases. SMMT is a scale that evaluates cognitive functions in orientation, registration, attention and calculation, recall and language sub-categories with a total of 30 points. Low scores indicate poor performance, while the cut-off point of the test is 24 for most patient populations (Nussmeier et al., 2010; Tombaugh and McIntyre, 1992). In our study, individuals who score below 24 in SMMT will be excluded from the study. The SMMT attached end of this document.

11.1.2 Questioning alcohol use (visit #1)

The alcohol use status of the participants will be evaluated by the American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). The DSM-5 evaluates an individual's alcohol use in the last 12 months with 11 items. Under the DSM-5, individuals who meet any 2 of 11 criteria within the last 12 months are diagnosed with alcohol dependence. The severity of the addiction (mild, moderate, or severe) depends on the number of criteria met. Participants meeting 2 or more of the 11 criteria defined in the DSM-5 in our study will be excluded from the study. The DSM-5 attached end of this document. Alcohol consumption is known to affect vascular function.

11.1.3 Dyspnea Evaluation (visit #1, 4-week visit)

The modified Medical Research Council (mMRC) dyspnea scale used in the evaluation of general dyspnea is a simple, valid and reliable five-item scale based on various physical activities that cause dyspnea. With this scale, patients are asked to mark the activity level that causes dyspnea (Bestall et al., 1999). There are many studies indicating that this scale is associated with dyspnea, arterial blood gases, health status, and lung function tests (Bausewein et al., 2007; Bestall et al., 1999; Wilson and Jones, 1989). The mMRC dyspnea scale attached end of this document.

11.1.4 Evaluation of Functional Exercise Capacity (visit #1, 4-week visit)

Submaximal functional exercise capacity will be evaluated with the 6-minute walking test (6MWT). 6MWT is a test that is frequently used in the evaluation of submaximal functional exercise capacity, has a low cost, provides important clinical results and is recommended by the guidelines

(ATS, 2002). As the standard protocol of the test, the person is asked to walk as fast as possible for six minutes in a continuous 30-meter corridor. Peripheral oxygen saturation, heart rate, perceived severity of dyspnea and leg fatigue (range 0-10) with the modified Borg scale are recorded before and after the test (ATS 2002; Borg, 1982). At the end of the test, the total distance walked is recorded in meters (Enright and Sherrill, 1998).

11.1.5 Inspiratory Muscle Function Evaluation (visit #1, 2-week visit, 4-week visit)

Inspiratory muscle function testing will be obtained from the PrO2Fit device (PrO2 Health Incorporated, Rhode Island, NE, USA) in which the maximal inspiratory pressure (MIP), total breath power and Fatigue Index Test (FIT) can be seen (McCreery et al., 2021). The PrO2Fit device incorporates a 2 mm leak to avoid glottal closure during maximal inspiration. The MIP is the highest pressure measured during inspiration and measured at residual volume (RV), with the unit of measure centimetres of water (cm H2O).

11.1.6 Endothelial Function Assessment (visit #1, 4-week visit)

A standard non-invasive method will be used to assess endothelial function. For this, flow-mediated dilation (FMD) ultrasound measurements of brachial artery flow-mediated dilatation will be performed according to standard methods with ultrasonography (ProSound α7; Aloka, Tokyo, Japan) using a multifrequency linear array transducer as previously described (Ozemek et al., 2020; Thijssen et al., 2011). Briefly, a cuff will be placed on the upper forearm and brachial artery images will be taken ~3–6 cm above the antecubital fossa. After taking simultaneous measurements of 1-min baseline brachial artery diameter and blood flow velocity, forearm occlusion will be produced by inflating the cuff to 250 mmHg for 5 minutes and then rapidly deflating it. After the release of the artery occlusion, Doppler blood flow velocity will be obtained and B-mode ultrasound brachial artery diameter images will be measured continuously for 3 minutes. Brachial artery diameter and blood flow velocity will be analyzed using an available software package (QUIPU SRL, Cardiovascular Suite 4.5.0, Italy). All procedures will be performed following published guidelines for the assessment of FMD in human participants (Corretti et al., 2002; Thijssen et al., 2011).

11.1.7 Evaluation of Arterial Stiffness (visit #1, 4-week visit)

Arterial stiffness will be assessed by measuring pulse wave velocity with a dedicated system (Noninvasive hemodynamics (NIHem) workstation, Cardiovascular Engineering, Inc. Norwood, MA) according to the methods

previously described (Mitchell et al., 2010). Arterial tonometry of the brachial, radial, femoral and carotid artery will be performed with a custom transducer and waveforms were signal-averaged and gated to the ECG R-wave (NIHem, Cardiovascular Engineering, Inc. Norwood, MA) as previously described (Mitchell et al., 2010). Measurements will be made after a four-hour fast and before any other exercise test to be performed on the same day (Scalzo et al., 2017; Mitchell et al., 2010).

11.2 Inspiratory Muscle Training Protocol:

Based on the findings of a systematic review (Z. Sadek et al., 2018), it has been determined that to achieve significant improvements in inspiratory muscle strength, the threshold pressure for inspiratory muscle training (IMT) should be set at 60% of the maximal inspiratory mouth pressure (MIP). Consequently, the intervention protocol for IMT involves using a threshold-loaded IMT device (Threshold IMT Philips® Respironics, Inc). In the IMT group, the initial intensity of the inspiratory threshold will be set at 60% of each patient's initial maximal MIP, which is then readjusted after 2 weeks of training to maintain the 60% of MIP throughout the 4-week period. Rates of perceived inspiratory effort on a modified Borg scale will also be used to determine the highest tolerable load for each patient (at the 4-6 level of 10) (Borg, 1982; Wilson and Jones, 1989). Patients will perform IMT for 2 sets of 30 repetitions, with one-minute intervals between each set (McConnell, 2013; Z. Sadek et al., 2018). Throughout the training sessions, patients will be instructed to maintain diaphragmatic breathing. On the other hand, the Sham-control group will follow the same training program using the same device, but without any inspiratory load. Both groups will perform the training program twice a day, five days a week, for a total of 4 weeks, under the supervision of a physiotherapist (McConnell, 2013). The supervision will be conducted remotely through telerehabilitation, utilizing video calls to connect with the patients without requiring them to physically visit the healthcare facility. To familiarize the participants with the training procedure, both the IMT and Sham-control groups will undergo a session without any load on the day of the baseline assessments. Throughout the study, all participants will visit the healthcare facility for baseline assessments, final assessments, and an additional brief assessment session at the end of the second week of training to measure MIP and readjust the loading value. The assessment to be made at the end of the 2nd week of the 4-week training seasons will only include the assessment of inspiratory muscle function described in 11.1.5.

The Threshold IMT products will be obtained by researchers and provided to patients without any cost. A patient who loses the product before the study ends will be notified that he or she will be excluded from the study. The enrolled research subject is not responsible for returning the

Threshold IMT product upon completion of the research activities. There are no expected adverse events based on the product label.

12.0 Data and Specimen Banking*

12.1 The data will be banked for future use by sharing with all researchers for 5 years at least without any personal information of patients. All written data collection forms and digital data will be hendled by principal investigator.. The principal investigator will be the person contacted and the authorizing authority in this regard.

12.2 **The data to be stored:** All written data collection forms, in addition to digital data that prepared for analysis.

12.3 **The procedures to release data:** Before using the data, those wishing to use it should contact the principal investigator via e-mail. In this e-mail, a state in general what the data will be used for and how it will be shared with whom. The principal investigator will be able to authorize the use of the data by providing a digitally signed pdf letter. Only academic researcher can obtain data.

13.0 Sharing of Results with Subjects*

13.1 Results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will not be shared with subjects or others (e.g., the subject's primary care physicians). Only the involved researchers will be informed. Patients will not be informed about the change in MIP values.

14.0 Withdrawal of Subjects*

14.1 Subjects will be withdrawn from the research without their consent according to the rules as follows; 1. Not attending more than 20% of supervised intervention sessions. 2. Not perform the measurements after the intervention (at the end of the 4th week). 3. Losing the product (Philips IMT) before the study ends. 4. Consent in writing that who wishes to end the study at any stage of the study.

14.2 For patients meeting any of 14.1 (one of the above), the principal investigator will be notified. The principal investigator will notify that he/she has been terminated from the study by obtaining verbal consent from the relevant patient.

14.3 Should the subject choose to withdraw, the health information already collected will continue to be used for research, however, no further health information will be collected. All health information and collected data will be stored coded on paper, electronically on UIC Health Data Box Folder. Only the PI and Co-Is will have access

to the key to the code that links coded data with the identity of the subject (which will be password protected).

15.0 Risks to Subjects*

15.1 Confidentiality and privacy: A risk of this research is a loss of privacy or confidentiality. To minimize this risk and protect the participant's identity, we will store health information coded, using a subject ID # instead of the participant's name. Coding and locking of data will minimize the risk of confidentiality loss. All data collected during visits linking study and health information will also be coded and stored in the PI's laboratory. Only the PI and limited research personnel will have access to the key to the code that links coded data with the identity of the participant (which will be password protected) and this key will be stored in the PI's locked office (Rm 308A).

15.2 Questionnaires: Participants may feel uncomfortable providing any personal information to questions. Subject will be advised to skip any questions they do not wish to answer.

15.3 Cardiovascular function: There are no known risks associated with the process of measuring endothelial function or arterial stiffness. Subjects may however feel uncomfortable when the blood pressure cuffs are inflated.

15.4 Lung/Respiratory Muscle Function and Inspiratory Muscle Training: There is risk of dizziness, coughing, and/or feeling short of breath during the tests.

15.5 Functional Status: Participants may experience muscle tightness, muscle soreness and fatigue, shortness of breath, and lightheadedness. A research staff member will stand an arm's length away while you are performing the balancing portion of the test for precautionary measures.

16.0 Potential Benefits to Subjects*

16.1 Individual subjects who take part in this research may or may not experience improvements in pulmonary and/or physical functions.

Information acquired during this study will contribute to the literature that seeks to determine the efficacy of this form of training.

17.0 Data Management* and Confidentiality

17.1 All statistical analyses will be performed using SPSS 21.0 (SPSS, Chicago, Illinois). The Shapiro–Wilk test will be used to evaluate the normality of the data distribution for each variable, and the natural

logarithmic transformation will be applied when necessary. The continuous variables will be reported as a mean (standard deviation) and 95% confidence interval (95% CI), and the categorical variables will be presented in absolute frequencies and percentages. Nominal data will be compared using a chi-square test. An independent T-test will be used to compare groups for baseline characteristics. The treatment effect will be assessed using analysis of covariance (ANCOVA) with baseline values entered as covariates. The estimated marginal means will be saved from the ANCOVA model and will compare main effects with Bonferroni correction (Van Breukelen G. J., 2006) The significance level was set at 5% for all analyses. The necessary sample size based on Praveen et al. study examining the effects of inspiratory muscle training performed after CABG (Praveen et al., 2009), was calculated to be 14 participants per group (total n=28), with a significance level of 5%, statistical power of 80%, and a minimum difference of 54 m in 6-minute walking distance (6MWD), taking into account the change in maximum inspiratory pressure (MIP) after training. However, to optimize the results, a 20% loss was anticipated during follow-up, resulting Erdfelder et al., 1996).

17.2 To ensure the confidentiality, integrity, and availability of the data collected during the study, the following steps will be taken:

- Authorization of Access: Access to the data will be limited to authorized personnel only, such as the study coordinator and principal investigator. The study participants' data will be anonymized, and any identifiable information will be stored separately from the study data.
- Password Protection: All electronic data will be password-protected, with access restricted to authorized personnel only. Passwords will be required to access electronic files and folders containing the data.
- Encryption: All electronic data collected during the study will be encrypted to ensure its security during transmission and storage. Data will be transmitted securely using encrypted methods and stored on secure hard drives.
- Physical Controls: All physical documents and materials containing patient data will be stored in locked cabinets or rooms with access restricted to authorized personnel only.
- Separation of Identifiers and Data: Identifiers, such as names and, will be stored separately from study data to ensure the privacy and confidentiality of participants. Identifiers will only be used to link study data to the participants, and they will be removed once the data analysis is complete.

17.3 The data will be handled study-wide as follows: All written data collection forms and electronic data will be handled and stored by principal investigator. The written data collection forms will be stored in PI's locked office in a locked filing cabinet. The research electronic data will be stored using the UIC Health Box Data Folder electronic database.

Authorized research personnel will maintain a master sheet which has the subject's name linked to their code. This sheet will be maintained within the UIC Health Box Data Folder designated for the study. All personal identifiable data will be destroyed 10 years after study completion. Results published will not include names of subjects. Some personal health information will be collected during the screening process, including name, contact information, and for individuals who meet the inclusion and exclusion criteria, dates of birth and CABG.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

The principal investigator will be primarily responsible for monitoring the safety of participants, and the safety and confidentiality of data. This will be done by following the best practices to ensure that we strictly adhere to the inclusion and exclusion criteria, and protections against risks outlines. The safety of each participant will be assessed on an individual basis throughout their involvement with the study. Any decline in function or participant responses that indicates a potential adverse effect will be reviewed individually and events will be reported to the IRB per UIC policy in a timely manner.

A member of the study personnel will be available to each participant throughout testing and will be monitoring participant safety. Participants will be instructed to immediately inform study personnel if any adverse effects of treatment are experienced. We will ask the participant to provide us with a phone number of a caregiver (or friend or family member) to contact in case of emergency. Any adverse events or unanticipated problems will be recorded and communicated to all study personnel as soon as possible. Study personnel will be trained to identify and manage adverse events or unanticipated problems involving risks to subjects or others. The PI will be notified immediately. Serious adverse events, study-related adverse events, and unanticipated problems will be reported within 24 hours to the UIC IRB. Participants will be removed from the study if the study procedures threaten the participants' safety or study procedures are unbearable. Any adverse events will be noted within the subject file.

In the event of injury related to this research, treatment will be available. However, the subject or his/her third party payer, if any, will be responsible for payment of this treatment. In the unlikely event that the subject requires emergency medical care during a study visit, 911 will be called

immediately. There is no compensation and/or payment for such medical treatment for such injury except as may be required by law.

19.0 Provisions to Protect the Privacy Interests of Subjects

Confidentiality and privacy: A risk of this research is a loss of privacy or confidentiality. To minimize this risk and protect the participant's identity, we will store health information coded, using a subject ID # instead of the participant's name. Coding and locking of data will minimize the risk of confidentiality loss. All data collected during visits linking study and health information will also be coded and stored in the PI's laboratory, in addition to a UIC Health Box Data Folder. Only the PI and limited research personnel will have access to the key to the code that links coded data with the identity of the participant (which will be password protected) and this key will be stored in a UIC Health Box Data Folder.

20.0 Compensation for Research-Related Injury

Compensation for research-related injury is not available.

21.0 Economic Burden to Subjects

Participants will only be invited to the institution where the study will be conducted for measurement at the beginning, middle and end of the study. In total, each patient will have come 3 times. Participants will cover their own travel expenses. It is not foreseen that there will be any other expenses. This information will be stated in the consent form, and patients who volunteered to participate in this study must have accepted it.

22.0 Consent Process

Informed consent will be obtained from the participant by the PI and/or research personnel according to UIC policy at the screening.
Proper informed consent will be given according to previous training in responsible conduct of research, protection of human research participants, and good clinical practice. Participants will be be given a sufficient amount of time to review the consent document and ask any questions that they may have prior to providing their consent for participation.

- Informed consent and authorization will be obtained after eligibility screening has been confirmed, either during the routine patient visit at the outpatient Exercise Testing or Cardiac Rehabilitation Programs.

  - Subjects expressing interest in participating in the study will communicate to key research personnel conducting the screening and consenting process. During the routine visit, oral consent will be obtained so that eligibility screening.
  - An alteration of consent and a waiver of documentation of consent will be obtained for the eligibility screening.

- All investigators/study personnel carrying out recruitment will follow a detailed informed consent process that will include a careful review study requirements and explanation of the study protocol
- PI, and Key Research Personnel (research assistants) will obtain consent. Beside the PI and Co-Is, study staff thoroughly trained by the PI in the consenting process, and who have completed their CITI and HIPPA training may also obtain consent from subjects.

- The PI will keep the original signed consent form, and the subject will receive a copy.

- All consent documents and tracking sheets will be stored in Dr. Ozemek's locked office in a locked filing cabinet.

- All data collected for the current research purposes will be stored coded.

- Subjects who do not speak English will be excluded (please see our inclusion and exclusion criteria for details). The process of recruitment, enrollment and obtaining written informed consent will only be in English. Lay language will be used to describe technical and medical terms

Non-English Speaking Subjects

- Subjects who do not speak English will not be enrolled (please see our inclusion and exclusion criteria for details).

***Request for Waiver or Alteration of Consent Process (If you will not obtain written consent, required information will not be disclosed, or the research involves deception)**

- Written consent will be obtain

***Subjects who are not yet adults (infants, children, teenagers)**

- NA

***Cognitively Impaired Adults**

- The Standardized Mini-Mental Test will be applied to the patients as in the heading 11.1.1 and anyone with a score below 24 will be excluded from the study.

***Adults Unable to Consent**

- Adults Unable to Consent will not be involved in study.

23.0 Process to Document Consent in Writing

Informed consent will be obtained from the participant by the PI and/or research personnel according to UIC policy at the screening.
Proper informed consent will be given according to previous training in responsible conduct of research, protection of human research participants, and good clinical practice.

- Informed consent and authorization will be obtained after eligibility screening has been confirmed, either during the routine patient visit at the outpatient HF, Exercise Testing or Cardiac Rehabilitation Programs.
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- The PI will keep the original signed consent form, and the subject will receive a copy.

- All consent documents and tracking sheets will be stored in Dr. Ozemek's locked laboratory in a locked filing cabinet in Room 422 within the Applied Health Sciences Building.

- All data collected for the current research purposes will be stored coded.

- Subjects who do not speak English will be excluded (please see our inclusion and exclusion criteria for details). The process of recruitment, enrollment and obtaining written informed consent will only be in English. Lay language will be used to describe technical and medical terms

24.0 Setting

This research will take place in the Physical Therapy Faculty Practice located at 1640 W. Roosevelt Road in Chicago.

Informed consent and authorization will be obtained after eligibility screening has been confirmed, either during the routine patient visit at the outpatient Exercise Testing or Cardiac Rehabilitation Programs.

Subjects expressing interest in participating in the study will communicate to key research personnel conducting the screening and consenting process. During the routine visit, oral consent will be obtained so that eligibility screening.

An alteration of consent and a waiver of documentation of consent will be obtained for the eligibility screening.

All investigators/study personnel carrying out recruitment will follow a detailed informed consent process that will include a careful review study requirements and explanation of the study protocol

PI, and Key Research Personnel (research assistants) will obtain consent. Beside the PI and Co-Is, study staff thoroughly trained by the PI in the consenting process, and who have completed their CITI and HIPPA training may also obtain consent from subjects.

After consent obtaining the first appointment for baseline measurements will be determined and research procedures detailed in section 11.0 will be carried out.

25.0 Resources Available

25.1 Dr. Ozemek runs UIC's Cardiac Rehabilitation program and sees patients undergoing CABG, history of percutaneous coronary interventions, heart failure, and/or myocardial infarction on a daily basis. This service line will provide the volume of participants to complete the study. Dr. Ridvan Aktan is a visiting international scholar that has 100% of his time dedicated to this study and will therefore be able to oversee study visits and collect data.

26.0 Multi-Site Research*

This is a single site study.

27.0 References

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub.

American Thoracic Society / European Respiratory Society. 2002. "ATS/ERS Statement on respiratory muscle testing", American journal of respiratory and critical care medicine, 166(4), 518-624.

Barros, G. F., Santos Cda, S., Granado, F. B., Costa, P. T., Límaco, R. P., Gardenghi, G. 2010. "Respiratory muscle training in patients submitted to coronary arterial bypass graft", Rev Bras Cir Cardiovasc, 25(4), 483-490.

Bausewein, C., Farquhar, M., Booth, S., Gysels, M., Higginson, I. 2007. "Measurement of breathlessness in advanced disease: a systematic review", Respiratory medicine, 101(3), 399-410.

Bautista, L. E. 2003. "Inflammation, endothelial dysfunction, and the risk of high blood pressure: epidemiologic and biological evidence", J Hum Hypertens, 17(4), 223-230.

Bestall, J., Paul, E., Garrod, R., Garnham, R., Jones, P., Wedzicha, J. 1999. "Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease", Thorax, 54(7), 581-586.

Bisconti, A. V., Devoto, M., Venturelli, M., Bryner, R., Olfert, I. M., Chantler, P. D., Esposito, F. 2018. "Respiratory muscle training positively affects vasomotor response in young healthy women", PloS one, 13(9), e0203347.

Borg, G. A. 1982. "Psycho-physical bases of perceived exertion", Med sci sports Exerc, 14(5), 377-381.

Brevetti, G., Silvestro, A., Schiano, V., Chiariello, M. 2003. "Endothelial dysfunction and cardiovascular risk prediction in peripheral arterial disease: additive value of flow-mediated dilation to ankle-brachial pressure index", Circulation, 108(17), 2093-2098.

Cahalin, L. P., & Arena, R. A. 2015. Breathing exercises and inspiratory muscle training in heart failure. Heart Fail Clin, 11(1), 149–172.

Caliskan, E., de Souza, D. R., Böning, A., Liakopoulos, O. J., Choi, Y. H., Pepper, J., Gibson, C. M., Perrault, L. P., Wolf, R. K., Kim, K. B., Emmert, M. Y. 2020. "Saphenous vein grafts in contemporary coronary artery bypass graft surgery", Nat Rev Cardiol, 17(3), 155-169.

Calles, A. C. d. N., Lira, J. L. F., Granja, K. S. B., Medeiro, J. D. d., Farias, A. R., Cavalcanti, R. C. 2016. "Pulmonary complications in patients undergoing coronary artery bypass grafting at a hospital in Maceio, Brazil", Fisioterapia em Movimento, 29(4), 661-667.

Campos, N. G., Marizeiro, D. F., Florêncio, A. C. L., Silva Í, C., Meneses, G. C., Bezerra, G. F., Martins, A. M. C., Libório, A. B. 2018. "Effects of respiratory muscle training on endothelium and oxidative stress biomarkers in hemodialysis patients: A randomized clinical trial", Respir Med, 134, 103-109.

Chrysant, S. G., Chrysant, G. S. 2014. "The age-related hemodynamic changes of blood pressure and their impact on the incidence of cardiovascular disease and stroke: new evidence", J Clin Hypertens (Greenwich), 16(2), 87-90.

Cohen-Solal, A., Tabet, J. Y., Logeart, D., Bourgoin, P., Tokmakova, M., Dahan, M. 2002. "A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure", Eur Heart J, 23(10), 806-814.

Cordeiro, A. L., de Melo, T. A., Neves, D., Luna, J., Esquivel, M. S., Guimarães, A. R., Borges, D. L., Petto, J. 2016. "Inspiratory Muscle Training and Functional Capacity in Patients Undergoing Cardiac Surgery", Braz J Cardiovasc Surg, 31(2), 140-144.

Cordeiro, A. L. L., Mascarenhas, H. d. C., Landerson, L., Araújo, J. d. S., Borges, D. L., Melo, T. A. d., Guimarães, A., Petto, J. 2020. "Inspiratory Muscle Training Based on Anaerobic Threshold on the Functional Capacity of Patients After Coronary Artery Bypass Grafting: Clinical Trial", Braz J Cardiovasc Surg, 35(6), 942-949.

Cornelissen, V. A., Smart, N. A. 2013. "Exercise training for blood pressure: a systematic review and meta-analysis", J Am Heart Assoc, 2(1), e004473.

Corretti, M. C., Anderson, T. J., Benjamin, E. J., Celermajer, D., Charbonneau, F., Creager, M. A., Deanfield, J., Drexler, H., Gerhard-Herman, M., Herrington, D., Vallance, P., Vita, J., Vogel, R. 2002. "Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force", J Am Coll Cardiol, 39(2), 257-265.

Dall'Ago, P., Chiappa, G. R., Guths, H., Stein, R., Ribeiro, J. P. 2006. "Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial", J Am Coll Cardiol, 47(4), 757-763.

de Abreu, R. M., Rehder-Santos, P., Minatel, V., Dos Santos, G. L., Catai, A. M. 2017. "Effects of inspiratory muscle training on cardiovascular autonomic control: A systematic review", Auton Neurosci, 208, 29-35.

Del Buono, M. G., Arena, R., Borlaug, B. A., Carbone, S., Canada, J. M., Kirkman, D. L., Garten, R., Rodriguez-Miguelez, P., Guazzi, M., Lavie, C. J., Abbate, A. 2019. "Exercise Intolerance in Patients With Heart Failure: JACC State-of-the-Art Review", J Am Coll Cardiol, 73(17), 2209-2225.

DeLucia, C. M., De Asis, R. M., Bailey, E. F. 2018. "Daily inspiratory muscle training lowers blood pressure and vascular resistance in healthy men and women", Exp Physiol, 103(2), 201-211.

Dempsey, J. A., Romer, L., Rodman, J., Miller, J., Smith, C. 2006. "Consequences of exercise-induced respiratory muscle work", Respir Physiol Neurobiol, 151(2-3), 242-250.

Dipp, T., Macagnan, F. E., Schardong, J., Fernandes, R. O., Lemos, L. C., Plentz, R. D. M. 2020. "Short period of high-intensity inspiratory muscle training improves inspiratory muscle strength in patients with chronic kidney disease on hemodialysis: a randomized controlled trial", Braz J Phys Ther, 24(3), 280-286.

Dos Santos, T. D., Pereira, S. N., Portela, L. O. C., Cardoso, D. M., Lago, P. D., Dos Santos Guarda, N., Moresco, R. N., Pereira, M. B., de Albuquerque, I. M. 2019. "Moderate-to-high intensity inspiratory muscle training improves the effects of combined training on exercise capacity in patients after coronary artery bypass graft surgery: A randomized clinical trial", Int J Cardiol, 279, 40-46.

Dos Santos, T. D., Pereira, S. N., Portela, L. O. C., Pereira, M. B., Pasqualoto, A. S., da Silveira, A. D., de Albuquerque, I. M. 2021. "Influence of inspiratory muscle strength on exercise capacity before and after cardiac rehabilitation", International Journal of Therapy and Rehabilitation, 28(2), 1-12.

Drexler, H. 1999. "Nitric oxide and coronary endothelial dysfunction in humans", Cardiovascular research, 43(3), 572-579.

Enright, P. L., Sherrill, D. L. 1998. "Reference equations for the six-minute walk in healthy adults", American journal of respiratory and critical care medicine, 158(5), 1384-1387.

Erdfelder E., Faul F., Buncher A. 1996. “GPOWER: a general power analysis program”, Behav Res Meth Instrum Comput, 28(1), 1-11.

Ferreira, J. B., Plentz, R. D., Stein, C., Casali, K. R., Arena, R., Lago, P. D. 2013. "Inspiratory muscle training reduces blood pressure and sympathetic activity in hypertensive patients: a randomized controlled trial", Int J Cardiol, 166(1), 61-67.

Ferreira, P. E., Rodrigues, A. J., Evora, P. R. 2009. "Effects of an inspiratory muscle rehabilitation program in the postoperative period of cardiac surgery", Arq Bras Cardiol, 92(4), 275-282.

Flavahan, N. A., Vanhoutte, P. M. 1995. "Endothelial cell signaling and endothelial dysfunction", Am J Hypertens, 8(5 Pt 2), 28s-41s.

Folstein, M. F., Folstein, S. E., McHugh, P. R. 1975. ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician", J Psychiatr Res, 12(3), 189-198.

Gaudino, M., Bakaeen, F. G., Benedetto, U., Di Franco, A., Fremes, S., Glineur, D., Girardi, L. N., Grau, J., Puskas, J. D., Ruel, M., Tam, D. Y., Taggart, D. P. 2019. "Arterial Grafts for Coronary Bypass: A Critical Review After the Publication of ART and RADIAL", Circulation, 140(15), 1273-1284.

Gaudino, M., Taggart, D., Suma, H., Puskas, J. D., Crea, F., Massetti, M. 2015. "The Choice of Conduits in Coronary Artery Bypass Surgery", J Am Coll Cardiol, 66(15), 1729-1737.

Haeffener, M. P., Ferreira, G. M., Barreto, S. S., Arena, R., Dall'Ago, P. 2008. "Incentive spirometry with expiratory positive airway pressure reduces pulmonary complications, improves pulmonary function and 6-minute walk distance in patients undergoing coronary artery bypass graft surgery", Am Heart J, 156(5), 900.e901-900.e908.

Harms, C. A., Wetter, T. J., McClaran, S. R., Pegelow, D. F., Nickele, G. A., Nelson, W. B., Hanson, P., Dempsey, J. A. 1998. "Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise", J Appl Physiol (1985), 85(2), 609-618.

Haroun, M. K., Jaar, B. G., Hoffman, S. C., Comstock, G. W., Klag, M. J., Coresh, J. 2003. "Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland", J Am Soc Nephrol, 14(11), 2934-2941.

He, G. W. 2005. "Endothelial function related to vascular tone in cardiac surgery", Heart Lung Circ, 14(1), 13-18.

Hermes, B. M., Cardoso, D. M., Gomes, T. J., Santos, T. D., Vicente, M. S., Pereira, S. N., Barbosa, V. A., Albuquerque, I. M. 2015. "Short-term inspiratory muscle training potentiates the benefits of aerobic and resistance training in patients undergoing CABG in phase II cardiac rehabilitation program", Rev Bras Cir Cardiovasc, 30(4), 474-481.

Hossen, A., Jaju, D., Al-Abri, M., Al-Sabti, H., Mukaddirov, M., Hassan, M., Al-Hashmi, K. 2017. "Investigation of heart rate variability of patients undergoing coronary artery bypass grafting (CABG)", Technol Health Care, 25(2), 197-210.

Hulzebos, E. H. J., van Meeteren, N. L. U., van den Buijs, B. J. W. M., de Bie, R. A., de la Rivière, A. B., Helders, P. J. M. 2006. "Feasibility of preoperative inspiratory muscle training in patients undergoing coronary artery bypass surgery with a high risk of postoperative pulmonary complications: a randomized controlled pilot study", Clinical rehabilitation, 20(11), 949-959.

Joseph, P., Leong, D., McKee, M., Anand, S. S., Schwalm, J. D., Teo, K., Mente, A., Yusuf, S. 2017. "Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors", Circ Res, 121(6), 677-694.

Jousilahti, P., Vartiainen, E., Tuomilehto, J., Puska, P. 1999. "Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland", Circulation, 99(9), 1165-1172.

Kalyani, R. R., Egan, J. M. 2013. "Diabetes and altered glucose metabolism with aging", Endocrinol Metab Clin North Am, 42(2), 333-347.

Kaminski, D. M., Schaan, B. D., da Silva, A. M., Soares, P. P., Lago, P. D. 2015. "Inspiratory muscle training in patients with diabetic autonomic neuropathy: a randomized clinical trial", Clin Auton Res, 25(4), 263-266.

Komine, H., Sugawara, J., Hayashi, K., Yoshizawa, M., Yokoi, T. 2009. "Regular endurance exercise in young men increases arterial baroreflex sensitivity through neural alteration of baroreflex arc", J Appl Physiol (1985), 106(5), 1499-1505.

Laboratories, A. C. o. P. S. f. C. P. F. 2002. "ATS statement: guidelines for the six-minute walk test", Am J Respir Crit Care Med, 166(1), 111-117.

Laizo, A., Delgado, F. E., Rocha, G. M. 2010. "Complications that increase the time of Hospitalization at ICU of patients submitted to cardiac surgery", Rev Bras Cir Cardiovasc, 25(2), 166-171.

Lakatta, E. G., Levy, D. 2003. "Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease", Circulation, 107(1), 139-146.

Langer, D., Charususin, N., Jácome, C., Hoffman, M., McConnell, A., Decramer, M., Gosselink, R. 2015. "Efficacy of a Novel Method for Inspiratory Muscle Training in People With Chronic Obstructive Pulmonary Disease", Phys Ther, 95(9), 1264-1273.

Laoutaris, I. D., Dritsas, A., Brown, M. D., Manginas, A., Kallistratos, M. S., Chaidaroglou, A., Degiannis, D., Alivizatos, P. A., Cokkinos, D. V. 2008. "Effects of inspiratory muscle training on autonomic activity, endothelial vasodilator function, and N-terminal pro-brain natriuretic peptide levels in chronic heart failure", J Cardiopulm Rehabil Prev, 28(2), 99-106.

Laoutaris, I. D., Dritsas, A., Brown, M. D., Manginas, A., Kallistratos, M. S., Degiannis, D., Chaidaroglou, A., Panagiotakos, D. B., Alivizatos, P. A., Cokkinos, D. V. 2007. "Immune response to inspiratory muscle training in patients with chronic heart failure", Eur J Cardiovasc Prev Rehabil, 14(5), 679-685.

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., Wilkinson, I., Struijker-Boudier, H. 2006. "Expert consensus document on arterial stiffness: methodological issues and clinical applications", Eur Heart J, 27(21), 2588-2605.

Matheus, G. B., Dragosavac, D., Trevisan, P., Costa, C. E., Lopes, M. M., Ribeiro, G. C. 2012. "Inspiratory muscle training improves tidal volume and vital capacity after CABG surgery", Rev Bras Cir Cardiovasc, 27(3), 362-369.

McConnell, A. 2013. Respiratory muscle training: theory and practice: Elsevier Health Sciences.

McCreery, J. L., Mackintosh, K. A., Mills-Bennett, R., McNarry, M. A. 2021. The Effect of a High-Intensity PrO2Fit Inspiratory Muscle Training Intervention on Physiological and Psychological Health in Adults with Bronchiectasis: A Mixed-Methods Study. Int J Environ Res Public Health, 18(6), 3051.

Mello, P. R., Guerra, G. M., Borile, S., Rondon, M. U., Alves, M. J., Negrão, C. E., Dal Lago, P., Mostarda, C., Irigoyen, M. C., Consolim-Colombo, F. M. 2012. "Inspiratory muscle training reduces sympathetic nervous activity and improves inspiratory muscle weakness and quality of life in patients with chronic heart failure: a clinical trial", J Cardiopulm Rehabil Prev, 32(5), 255-261.

Miozzo, A. P., Stein, C., Marcolino, M. Z., Sisto, I. R., Hauck, M., Coronel, C. C., Plentz, R. D. M. 2018. "Effects of high-intensity inspiratory muscle training associated with aerobic exercise in patients undergoing CABG: randomized clinical trial", Braz J Cardiovasc Surg, 33(4), 376-383.

Mitchell, G. F., Hwang, S. J., Vasan, R. S., Larson, M. G., Pencina, M. J., Hamburg, N. M., Vita, J. A., Levy, D., & Benjamin, E. J. 2010. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation, 121(4), 505–511.

Monahan, K. D., Dinenno, F. A., Tanaka, H., Clevenger, C. M., DeSouza, C. A., Seals, D. R. 2000. "Regular aerobic exercise modulates age-associated declines in cardiovagal baroreflex sensitivity in healthy men", J Physiol, 529 Pt 1(Pt 1), 263-271.

Ng, C. S., Wan, S., Yim, A. P., Arifi, A. A. 2002. "Pulmonary dysfunction after cardiac surgery", Chest, 121(4), 1269-1277.

Nussmeier, N. A., Miao, Y., Roach, G. W., Wolman, R. L., Mora-Mangano, C., Fox, M., Szekely, A., Tommasino, C., Schwann, N. M., Mangano, D. T. 2010. "Predictive value of the National Institutes of Health Stroke Scale and the Mini-Mental State Examination for neurologic outcome after coronary artery bypass graft surgery", J Thorac Cardiovasc Surg, 139(4), 901-912.

Ozemek, C., Hildreth, K. L., Blatchford, P. J., Hurt, K. J., Bok, R., Seals, D. R., Kohrt, W. M., Moreau, K. L. 2020. "Effects of resveratrol or estradiol on postexercise endothelial function in estrogen-deficient postmenopausal women", J Appl Physiol (1985), 128(4), 739-747.

Palau, P., Domínguez, E., Núñez, E., Schmid, J. P., Vergara, P., Ramón, J. M., Mascarell, B., Sanchis, J., Chorro, F. J., Núñez, J. 2014. "Effects of inspiratory muscle training

in patients with heart failure with preserved ejection fraction", Eur J Prev Cardiol, 21(12), 1465-1473.

Pinto, E. 2007. "Blood pressure and ageing", Postgrad Med J, 83(976), 109-114.

Pompilio, G., Rossoni, G., Alamanni, F., Tartara, P., Barajon, I., Rumio, C., Manfredi, B., Biglioli, P. 2001. "Comparison of endothelium-dependent vasoactivity of internal mammary arteries from hypertensive, hypercholesterolemic, and diabetic patients", Ann Thorac Surg, 72(4), 1290-1297.

Praveen, R., Swaminathan, N., Praveen, J. 2009. "Inspiratory muscle training is effective in improving respiratory muscle functions in patients who have undergone coronary artery bypass graft", Fizjoterapia Polska, 9(4), 285-292.

Qiu, C., Winblad, B., Marengoni, A., Klarin, I., Fastbom, J., Fratiglioni, L. 2006. "Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study", Arch Intern Med, 166(9), 1003-1008.

Roncada, G., Dendale, P., Linsen, L., Hendrikx, M., Hansen, D. 2015. "Reduction in pulmonary function after CABG surgery is related to postoperative inflammation and hypercortisolemia", International journal of clinical and experimental medicine, 8(7), 10938-10946.

Sadek, Z., Salami, A., Joumaa, W. H., Awada, C., Ahmaidi, S., Ramadan, W. 2018. "Best mode of inspiratory muscle training in heart failure patients: a systematic review and meta-analysis", Eur J Prev Cardiol, 25(16), 1691-1701.

Sadek, Z., Salami, A., Youness, M., Awada, C., Hamade, M., Joumaa, W. H., Ramadan, W., & Ahmaidi, S. (2022). A randomized controlled trial of high-intensity interval training and inspiratory muscle training for chronic heart failure patients with inspiratory muscle weakness. Chronic illness, 18(1), 140–154.

Saglam, M., Arikan, H., Vardar-Yagli, N., Calik-Kutukcu, E., Inal-Ince, D., Savci, S., Akdogan, A., Yokusoglu, M., Kaya, E. B., Tokgozoglu, L. 2015. "Inspiratory muscle training in pulmonary arterial hypertension", J Cardiopulm Rehabil Prev, 35(3), 198-206.

Scalzo, R. L., Moreau, K. L., Ozemek, C., Herlache, L., McMillin, S., Gilligan, S., Huebschmann, A. G., Bauer, T. A., Dorosz, J., Reusch, J. E., Regensteiner, J. G. 2017. "Exenatide improves diastolic function and attenuates arterial stiffness but does not alter exercise capacity in individuals with type 2 diabetes", J Diabetes Complications, 31(2), 449-455.

Seals, D. R., Jablonski, K. L., Donato, A. J. 2011. "Aging and vascular endothelial function in humans", Clin Sci (Lond), 120(9), 357-375.

Sistino, J. J., Fitzgerald, D. C. 2017. "Epidemiology of cardiovascular disease in the United States: implications for the perfusion profession. A 2017 update", Perfusion, 32(6), 501-506.

Smart, N. A., Giallauria, F., Dieberg, G. 2013. "Efficacy of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis", Int J Cardiol, 167(4), 1502-1507.

Thijssen, D. H., Black, M. A., Pyke, K. E., Padilla, J., Atkinson, G., Harris, R. A., Parker, B., Widlansky, M. E., Tschakovsky, M. E., & Green, D. J. 2011. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. Am J Physiol Heart Circ Physiol, 300(1), H2–H12.

Tombaugh, T. N., McIntyre, N. J. 1992. "The mini-mental state examination: a comprehensive review", J Am Geriatr Soc, 40(9), 922-935.

Van Breukelen G. J. 2006. "ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]", J Clin Epidemiol, 59(9), 920–925.

Vendemiale, G., Romano, A. D., Dagostino, M., de Matthaeis, A., Serviddio, G. 2013. "Endothelial dysfunction associated with mild cognitive impairment in elderly population", Aging Clin Exp Res, 25(3), 247-255.

Vranish, J. R., Bailey, E. F. 2015. "Daily respiratory training with large intrathoracic pressures, but not large lung volumes, lowers blood pressure in normotensive adults", Respir Physiol Neurobiol, 216, 63-69.

Vranish, J. R., Bailey, E. F. 2016. "Inspiratory Muscle Training Improves Sleep and Mitigates Cardiovascular Dysfunction in Obstructive Sleep Apnea", Sleep, 39(6), 1179-1185.

Wang, C. H., Li, S. H., Weisel, R. D., Fedak, P. W., Dumont, A. S., Szmitko, P., Li, R. K., Mickle, D. A., Verma, S. 2003. "C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle", Circulation, 107(13), 1783-1790.

Weiner, P., Zeidan, F., Zamir, D., Pelled, B., Waizman, J., Beckerman, M., Weiner, M. 1998. "Prophylactic inspiratory muscle training in patients undergoing coronary artery bypass graft", World J Surg, 22(5), 427-431.

Welch, J. F., Archiza, B., Guenette, J. A., West, C. R., Sheel, A. W. 2018. "Sex differences in diaphragmatic fatigue: the cardiovascular response to inspiratory resistance", J Physiol, 596(17), 4017-4032.

Whelton, S. P., Chin, A., Xin, X., He, J. 2002. "Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials", Ann Intern Med, 136(7), 493-503.

Wilson, R. C., Jones, P. 1989. "A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise", Clinical Science, 76(3), 277-282.

Wong, N. D., Lopez, V. A., Roberts, C. S., Solomon, H. A., Burke, G. L., Kuller, L., Tracy, R., Yanez, D., Psaty, B. M. 2010. "Combined association of lipids and blood pressure in relation to incident cardiovascular disease in the elderly: the cardiovascular health study", Am J Hypertens, 23(2), 161-167.

Yeboah, J., Folsom, A. R., Burke, G. L., Johnson, C., Polak, J. F., Post, W., Lima, J. A., Crouse, J. R., Herrington, D. M. 2009. "Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis", Circulation, 120(6), 502-509.

Zanini, M., Nery, R. M., de Lima, J. B., Buhler, R. P., da Silveira, A. D., Stein, R. 2019. "Effects of Different Rehabilitation Protocols in Inpatient Cardiac Rehabilitation After Coronary Artery Bypass Graft Surgery: A RANDOMIZED CLINICAL TRIAL", J Cardiopulm Rehabil Prev, 39(6), E19-e25.

Zeren, M., Demir, R., Yigit, Z., Gurses, H. N. 2016. "Effects of inspiratory muscle training on pulmonary function, respiratory muscle strength and functional capacity in patients with atrial fibrillation: a randomized controlled trial", Clin Rehabil, 30(12), 1165-1174.