

## Effect of Exercise Training on Left Ventricular Remodeling in Diabetic Patients with Diastolic Dysfunction: Rationale and Design

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### ABSTRACT

**INTRODUCTION:** This study will examine the effects of combined aerobic and resistance training on left ventricular remodeling in diabetic patients with diastolic dysfunction. This is the first randomized controlled trial to look for effects of combined strength training and aerobic exercise on myocardial function as well as other clinical, functional, or psychological parameters in diabetic patients with isolated diastolic dysfunction, and will provide important insights into the potential management strategies for heart failure with preserved ejection fraction.

**METHODS AND ANALYSIS:** This is a prospective, randomized controlled investigator initiated single center trial. Diabetic patients with LV diastolic dysfunction suitable for exercise training intervention will be randomized to three months of a supervised combination of aerobic and strength training exercises, or supervised light stretching (control arm). Pre and post intervention assessment will include stress echocardiography, peak aerobic power with 12-lead ECG, dual-energy X-ray absorptiometry, muscle strength, the capacity to perform activities of daily living (ADLs), and questionnaires to assess self-perceived quality of life and symptoms of depression. The primary endpoint is to compare any change in tissue Doppler-derived LV systolic and early diastolic velocities.

**ETHICS AND DISSEMINATION:** The current trial protocol has been approved by the Human Research Ethics Committee of Austin Health and the University of Melbourne, Melbourne. The study will be performed in accordance with the Declaration of Helsinki. The investigator, regardless of the outcome, will publish the results of the study.

**TRIAL REGISTRATION:** Australian New Zealand Clinical Trials Registry: ACTRN12610000943044.

**KEYWORDS:** cardiomyopathy, heart failure, echocardiography

**CITATION:** Asrar ul Haq et al. Effect of Exercise Training on Left Ventricular Remodeling in Diabetic Patients with Diastolic Dysfunction: Rationale and Design. *Clinical Medicine Insights: Cardiology* 2014;8:23–28 doi: 10.4137/CMC.S14089.

**RECEIVED:** January 2, 2014. **RESUBMITTED:** January 27, 2014. **ACCEPTED FOR PUBLICATION:** January 28, 2014.

**ACADEMIC EDITOR:** Thomas E. Vanhecke, Editor in Chief

**TYPE:** Research Proposal

**FUNDING:** Author(s) disclose no funding sources.

**COMPETING INTERESTS:** Author(s) disclose no potential conflicts of interest.

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### Introduction

An increase in physical activity level is an important goal in the rehabilitation of patients with chronic heart failure (CHF).<sup>1,2</sup> It has been shown that exercise training can improve peak aerobic power ( $V_{O_{2peak}}$ ),<sup>3,4</sup> muscle strength and mass,<sup>3–5</sup> New York Heart Association (NYHA) functional class,<sup>6</sup> and quality of life<sup>7</sup> in this population.

Most existing CHF management recommendations are based on information obtained from patients with reduced

(heart failure with reduced ejection fraction, HFREF) rather than preserved (heart failure with preserved ejection fraction, HFPEF) ejection fraction. However, it is now well established that at least one-half of the patients presenting with symptoms and signs of CHF will have a normal left ventricular ejection fraction (LVEF).<sup>8–10</sup> Apart from some limited evidence that exercise might improve  $V_{O_{2peak}}$  in patients with HFPEF,<sup>11</sup> there is no data for improvement in other clinical, functional, or psychological parameters. This study will examine the



effects of combined aerobic and resistance training on left ventricular remodeling in a diabetic population with diastolic dysfunction.

**Methods.** This is a prospective, randomized controlled investigator initiated single center trial based at Austin Hospital in Melbourne (Australia), where the patients will be recruited from. Diabetic patients with LV diastolic dysfunction suitable for exercise training intervention will be included according to the inclusion and exclusion criteria specified in Table 1. Patients will be randomized to three months of either a training (exercise) or control (stretching) group after baseline stress echocardiography to exclude patients with coronary artery disease. Echocardiography assessment of LV systolic and diastolic velocities will be done in a blinded fashion (exercise vs. stretching group, as well as the baseline values) to evaluate the effects of the exercise program on myocardial function.

**Primary endpoint.** Change in tissue Doppler-derived LV systolic (sm) and early diastolic (em) velocities after three months of exercise intervention will be the primary endpoint.

**Secondary endpoints.** Secondary endpoints will be the comparison of the difference in peak aerobic power ( $V_{O_{2peak}}$ ), (NYHA) class, diastolic function grades, glycated hemoglobin (HbA1c), LV filling pressure estimate (septal, lateral, and average E/e') at rest and post exercise, LV torsion post exercise, LA volume index, systolic pulmonary artery pressure, skeletal muscle inflammatory markers, sodium—potassium (Na/K) regulation, and insulin-signaling proteins.

**Procedures.** At baseline and after three months of intervention, participants will undergo the following assessments: stress echocardiography, peak aerobic power with 12-lead ECG, dual-energy X-ray absorptiometry (DXA), muscle strength, the capacity to perform activities of daily living (ADLs), and questionnaires to assess self-perceived quality of life and symptoms of depression. In addition, participants will be asked to undergo an optional skeletal muscle biopsy.

**Table 1.** Inclusion and exclusion criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
<ul style="list-style-type: none"> <li>Type 2 diabetes mellitus</li> <li>Peak early diastolic myocardial tissue velocity (septal e') &lt;8 cm/s</li> <li>Deceleration time (DT) &gt;220 msec OR E/e' &gt;10</li> <li>Age 18 years or older</li> </ul>	<ul style="list-style-type: none"> <li>Known coronary artery disease or evidence of ischaemia on baseline stress echocardiography</li> <li>Left ventricular ejection fraction &lt;45%</li> <li>Significant (moderate or severe) valvular disease</li> <li>Unstable heart failure requiring &gt;2 medication changes in last 3 months</li> <li>Unstable diabetes as evidenced by hypoglycaemic events &gt;1/week, or HbA1c <math>\geq</math>9.0%</li> <li>Atrial fibrillation</li> </ul>

**Stress echocardiogram.** All eligible participants will undergo pre and post intervention evaluation of diastolic function with conventional and the echocardiography imaging when they are in a stable state. Exercise stress echocardiography will be performed using symptom-limited graded exercise on a Cybex MET 100 cycle (Cybex Metabolic Systems, Ronkonkoma, NY, USA). Exercise capacity will be measured in metabolic equivalents (MET) and  $V_{O_2}$ . Images of the left ventricle in motion and hemodynamic measures will be recorded at rest and immediately after exercise.

**Peak aerobic power with 12-lead ECG.** Aerobic power ( $V_{O_{2peak}}$ ) will be assessed during the same symptom-limited graded exercise test performed for stress echocardiography. The test will start after a five-minute period of rest. The protocol will consist of an initial intensity of 25 W, then an increase to 40 W after one minute, followed by increments of 20 W minute<sup>-1</sup> for males and 10 W minute<sup>-1</sup> for females. The test will be terminated when a participant's rating of perceived exertion will reach "very hard" (Borg scale = 17),<sup>12</sup> or before that if clinical signs or symptoms of metabolic or cardio-respiratory abnormalities appear. Expired respiratory gases will be collected through a breath-by-breath (BxB) pneumotach system connected to gas analyzers. The BxB data will be integrated for each 15 second interval, and the mean values for  $V_{O_2}$ ,  $V_{CO_{2peak}}$ , and ventilation (VE) used for that interval were calculated. The gas analyzer will be calibrated immediately before each test using gases that had been calibrated at alpha standard. Heart rate will be measured at rest and during the incremental test by 12-lead electrocardiography (Mortara, X-Scribe II, Milwaukee, WI, USA). Participants will be asked not to consume caffeine or alcohol for a minimum of two hours before the exercise test.

**Dual-energy X-ray absorptiometry.** DXA (GE Lunar Pxdigy, Software version 9.1, Madison, USA) will be used to assess total body fat percentages, total body fat, and lean body mass (LBM). In addition, the DXA and GE Lunar Pxdigy software will be used to assess fat mass in the abdominal region. The lower boundary of the abdominal region is defined as the pelvis cut. The upper boundary of the abdominal region is defined as 20% of the distance between pelvis and neck cut above the pelvis cut. All DXA measurements will be conducted by the staff at the Bone Density Unit, Repatriation Hospital, Austin Health. DXA is a fast, simple, and safe technique to evaluate body composition.<sup>13</sup> Although DXA was initially designed as a tool for the diagnosis of osteoporosis, it has been recognized also as a precise tool to evaluate fat and LBM.<sup>14,15</sup>

**Exercise training.** Participants will be randomized to three months of either a combination of resistance and aerobic training (exercise) or control (stretching). Both groups will train for three days/week under the supervision of an exercise physiologist. For the EXERCISE group, sessions will begin with five minutes of warm-up followed by 50 minutes of exercises (30 minutes aerobic and 20 minutes power), and 5 minutes of cool-down. Aerobic exercise intensity will be at



70–75% of the predetermined  $V_{O_{2peak}}$ . Resistance exercise: three different exercises using large muscle groups (chest, back, legs, and shoulders). Each exercise will be performed for three sets, 8–12 repetitions. During the first week, intensity will correspond to 60% one-repetition maximum test (1RM). At week 2, intensity will increase to 70% 1RM and from week 3 to 16, intensity corresponded to 70–75% 1RM. For each session, weights will be adjusted according to the current capacity of the individual. Participants will rest for 120 seconds between sets and for 120–150 seconds between exercises. Blood sugar levels (BSL) will be monitored by checking the levels before and after each session. The STRETCHING (control) group will perform 60 minutes of light stretching (sham exercise group).

**Muscle strength.** Four to eight days prior to the 1RM, participants will perform a familiarization session with the resistance training equipment. During the familiarization session, correct lifting and breathing techniques will be taught and practiced using sub-maximal and near maximal loads. 1RM is defined as the heaviest weight a participant is able to lift once, using a proper lifting technique, without compensatory movements.<sup>16</sup> 1RM strength will be assessed for two different exercises, including chest press and leg press. The tests will commence after a light warm-up (three-minute walking at self-selected speeds on a treadmill). The maximal strength test protocol includes one set of 10 repetitions at a relatively light load that serves as a specific warm-up, followed by a gradual increase in load until 1RM is achieved. The rate of the gradual increase in load will be dependent on the participant's self-perceived capacity. 1RM will be achieved within three to eight attempts. The rest period between attempts will be 60 seconds, and 120 seconds between each specific exercise. Studies have reported that 1RM method to assess muscle strength is safe for the elderly<sup>17,18</sup> and patients with cardiovascular disease (CVD).<sup>19,20</sup> 1RM test is reliable<sup>21</sup> and the protocol has been used previously by us to evaluate maximal strength in patients with CHF<sup>22,23</sup> and patients at a high risk for developing diabetes and CVD.<sup>24</sup>

**Functional tests.** The functional tests will be based on the methods of Reuben and Siu, with modifications by Brandon et al. and Nichols et al.<sup>25–27</sup> Participants will perform four tasks that represent ADLs: 15 m rapid walking test, chair rise test, walking up stairs, and walking down stairs. In the 15 m rapid walking test, the participant will be asked to cover the distance as fast as he/she can but at a safe pace. In the chair rise test, the participant will be asked to rise from a chair, walk 3 m, and return to the chair. The walking up and down stairs test will consist of climbing up and down 20 steps “as fast as possible” while carrying a weight that corresponds to 10% of their body weight, but in a comfortable and safe manner.<sup>24,28</sup>

**Questionnaires.** Short Form Healthy Survey (SF 36) and the Cardiac Depression Scale (CDS) will be completed before and after three months of intervention. We have used these questionnaires previously.<sup>24</sup>

**Muscle biopsy (optional).** Muscle biopsies will be taken from the vastus lateralis by a medical practitioner experienced in the technique before and after the three months of training. Histochemical and protein analysis will be used to determine muscle inflammatory markers, Na/K, insulin-signaling proteins, other proteins, and enzymes that regulate muscle function.

**Randomization.** Randomization will take place immediately after the collection of baseline data is completed. The twenty patients will be allocated to exercise or stretching groups according to computer generated random numbers held in sealed envelopes by a third party. The randomization will be stratified according to muscle biopsy/no muscle biopsy and balanced after every two patients using the method of Peto et al.<sup>29</sup>

**Sample size.** The sample size for the fully powered randomized controlled trial (RCT) will be 48 participants for the intervention group, taking into account our preliminary data where the  $em = 6.6 \pm 1.6$  (cm/second), and assuming that we achieve an expected 15% change in the myocardial measures (indicated by a difference in myocardial torsion or diastolic tissue velocities) in response to intervention, it is estimated that a minimum of 44 subjects will be required in each group to deliver a statistical power greater than 0.8 with a  $P$ -value of  $<0.05$ . A total of 48 subjects will be enrolled in the treatment arm to account for an anticipated dropout of 10%. A pilot study will be conducted initially with an estimated enrollment of 20 patients to assess the preliminary results before continuing further enrollment.

**Statistical analysis.** All patients who undergo randomization will be included in the primary analysis in the groups to which they were originally allocated (intention-to-treat principle). Multivariate analysis of variance (MANOVA) will be used to examine physiological and functional differences between groups at baseline. A repeated measure ANOVA model will be used to analyze the effect of primary interest by time (pre, post), treatment (training and control), and time-by-treatment (effect over time). A Spearman rho correlation will be conducted to assess the relationship between selected variables. Paired  $t$ -test will be used to compare pre and post training echo values. Data will be reported as mean  $\pm$  standard deviation (SD) and all statistical analyses will be conducted at the 95% level of significance.

**Ethical considerations.** The study will be performed in accordance with the Declaration of Helsinki. The protocol, informed consent form, and other study-related documents were submitted to the local Human Research Ethics Committee and approved. A written informed consent was obtained from each participant. The trial has been registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) with a trial ID ACTRN12610000943044. The investigator, regardless of the outcome, will publish the results of the study.



## Discussion

Exercise training can restore the abnormal autonomic, neurohormonal, hemodynamic, and functional abnormalities in patients with HFREF.<sup>3,6,30,31</sup> Some investigators have shown that exercise can reverse LV remodeling in clinically stable HFREF patients,<sup>32</sup> that is, the left ventricle can again become smaller and contract more efficiently. One recent study<sup>11</sup> showed improvement of diastolic function in subgroups of patients with significant increase in moderate and vigorous activity, after one year of supervised and home based exercise intervention. However other investigators<sup>33,34</sup> have reported no benefits with exercise training on LV end-diastolic volume, end-systolic volume, or ejection fraction. Thus, uncertainty remains regarding the effects of exercise training on LV remodeling in patients with HFPEF.

*Aerobic exercise vs. resistance training.* There is controversy regarding the level and format of exercise that can yield optimal beneficial effects in CHF. Exercise intensity has been reported as an important factor for reversing LV remodeling and improving aerobic capacity.<sup>35</sup> Similarly, resistance training has been shown to be safe and to improve skeletal muscle strength, peak oxygen consumption, and quality of life in patients with CHF.<sup>5,22,36</sup> However a recent meta-analysis<sup>37</sup> of 14 randomized trials to determine the effect of exercise training and type of exercise (aerobic vs. strength vs. combined training) on LV remodeling in clinically stable patients with HFREF indicated no confirmed benefit with combined aerobic and strength training despite reversal of LV remodeling with aerobic training.

*Heart failure and diabetes.* LV systolic and diastolic dysfunction is a common feature in patients with type 2 diabetes mellitus (T2DM).<sup>38</sup> A recent RCT<sup>11</sup> investigated the effects of a one-year exercise intervention and failed to improve myocardial function in all patients. However, post-hoc analysis revealed that subgroups of patients who had the greatest increases in both moderate and vigorous activity significantly improved diastolic function, HbA1c, and cardio-respiratory fitness. This study involved an unselected group of patients since absence of LV dysfunction was not an exclusion criterion, which may have contributed to the lack of overall effect of the intervention on myocardial function. Furthermore, although based on current recommendations, the prescription used in this study may have had insufficient training dose (volume or intensity) to yield improvements in myocardial function in all subjects, when compared to some other studies.<sup>39–43</sup>

*Doppler tissue imaging and 2D speckle tracking.* 2D speckle tracking is a new technique that is able to quantify circumferential and radial motion, validated non-invasively by magnetic resonance imaging (MRI) tagging and invasively by sonomicrometry in animal models.<sup>44–46</sup> New developments in echocardiography enable a much fuller assessment of LV systolic and diastolic function, including measurement of

myocardial deformation or strain.<sup>44,45,47</sup> Stress echocardiography using these newer techniques to assess LV tissue velocities, strain, and torsion has been shown to have increased sensitivity to predict diastolic dysfunction.<sup>45,48–50</sup>

*Skeletal muscle function and metabolism.* The most common physical symptoms of patients with CHF are fatigue, shortness of breath and dyspnea, a decrease in work capacity and exercise intolerance, and muscle atrophy and strength reduction. These characteristics may be attributed to the changes in the structure, metabolism, and function of skeletal muscles that are an integral part of and an inseparable consequence of the progression of the disease.<sup>51,52</sup> Changes in skeletal muscle may also be due to deconditioning and disuse. The level of skeletal muscle impairment, the deficit in the skeletal muscle blood flow, and exercise intolerance are influenced by the severity of the MI and LV dysfunction.

People with type 2 diabetes also have altered muscle metabolism. It has been reported that the bioenergetic capacity of skeletal muscle mitochondria is impaired in patients with T2DM, compared to lean individuals. There is substantial evidence to indicate that alterations in skeletal muscle fiber types, mainly a reduction in percentage of type I fibers and an increase in percentage of type II fibers, are associated with obesity and T2DM. Studies have revealed that individuals with higher fat mass have higher percentages of fast twitch fiber types and lower percentages of type I fibers. As type I fibers are characterized by high capillary density, lipid storage capacity, insulin binding, insulin-stimulated glucose uptake, high GLUT4 content, and high oxidative enzyme activities, a reduction in type I fibers may contribute to prolonged recovery from peak exercise and early fatigue in obese patients and those with T2DM. Therefore, we will examine whether exercise training can, at least in part, restore muscle function and/or muscle metabolism.

## Conclusion

This is the first randomized controlled trial to look for the effects of combined strength training and aerobic exercise on myocardial function as well as other clinical, functional, or psychological parameters in diabetic patients with isolated diastolic dysfunction, and will provide important insights into the potential management strategies for HFPEF.

## Author Contributions

Conceived and designed the experiments: DLH, CW, MAH, SS, IL, GJ. Analyzed the data: MAH. Wrote the first draft of the manuscript: MAH. Contributed to the writing of the manuscript: MAH, CW, GJ, IT, DLH. Agree with manuscript results and conclusions: IL, PS, MS, DT, GJ, SS, CW, DLH. Jointly developed the structure and arguments for the paper: MAH, CW, GJ, DLH. Made critical revisions and approved final version: MAH, CW, GJ, DLH. All authors reviewed and approved of the final manuscript.





## Acknowledgment

Dr Itamar Levinger is supported by a Postdoctoral Research Fellow (PR 11M 6086) from the National Heart Foundation of Australia.

## DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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