Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

Ida Ormstad Nilsen

The Effect of Group-Based versus Individually Performed Exercise on Ventilatory Efficiency in Post-Myocardial Infarction Patients

A Randomized Controlled Trial

Master's thesis in Physical Activity and Health (Exercise Physiology)
Supervisor: Ulrik Wisløff
Co-supervisor: Alexander Robert Gran Svenningsen
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THE EFFECT OF GROUP-BASED VERSUS INDIVIDUALLY PERFORMED EXERCISE ON VENTILATORY EFFICIENCY IN SURVIVORS OF MYOCARDIAL INFARCTION

AIM ⟶ Investigate the effect of home-based peer-supported vs. individual exercise on ventilatory efficiency, measured as ventilatory equivalent for carbon dioxide at ventilatory anaerobic threshold ($Eq\dot{V}CO_{2VThan}$), in survivors of myocardial infarction (MI).

Randomized controlled trial

12 weeks intervention period

Cardiopulmonary exercise testing pre- and post-intervention

Did you know?

MI most common cause of death in Europe (~2M annually).

$Eq\dot{V}CO_{2VThan}$ is recognized as a significant prognostic factor.

Lack of research on the effect of peer-supported group exercise on $Eq\dot{V}CO_{2VThan}$ in survivors of MI.

Intervention group

n = 6

Age (years): 60.8±9.1

BMI (kg/m^2): 26.0±3.6

$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1}): 35.4±7.7

Peer-supported group exercise

Control group

n = 10

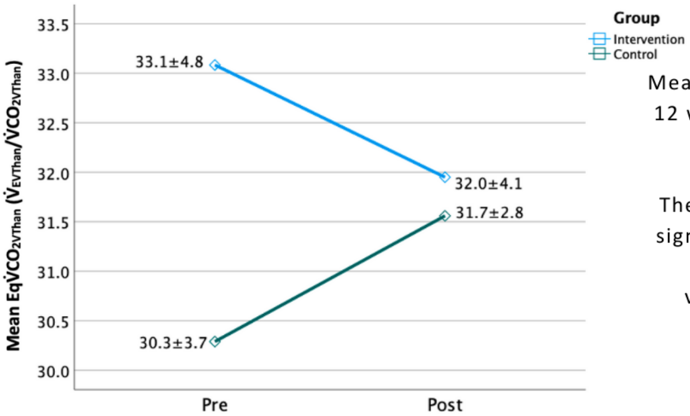
Age (years): 67.6±7.4

BMI (kg/m^2): 27.2±3.3

$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1}): 32.6±8.0

NorEx protocol, individual exercise

RESULTS AND CONCLUSION



Mean difference in ventilatory efficiency after 12 weeks between the respective groups was -2.4±1.5 (p = .119).

The study indicates, despite not statistically significant, that home-based peer-supported group exercise can result in enhanced ventilatory efficiency, in comparison to individually performed exercise.

NTNU

Ida Ormstad Nilsen

idaoni@stud.ntnu.no

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Abstract

Purpose: Investigate the effect of 12 weeks home-based peer-supported group exercise versus individually performed exercise on ventilatory efficiency, measured by ventilatory equivalent for carbon dioxide (Eq$\dot{V}CO_{2VThan}$), in survivors of myocardial infarction (MI).

Methods: Randomized controlled trial with participants included in The Norwegian Trial of Physical Exercise After Myocardial Infarction (NorEx). NorEx aim to determine whether four years of home-based exercise to increase cardiorespiratory fitness (CRF) reduces mortality and cardiovascular morbidity in MI survivors. We enrolled 24 participants from the NorEx intervention group with low adherence to prescribed exercise, randomly allocated to 12 weeks peer-supported home-based exercise (intervention group, n = 12) or individual home-based exercise training according to the NorEx protocol (control group, n=12). During the intervention, six participants in the intervention group and two participants in the control group were lost to follow-up. Complete case analyses were performed on six and ten participants in the respective groups. Ventilatory efficiency and peak oxygen uptake ($\dot{V}O_{2peak}$) were measured by cardiopulmonary exercise testing performed on a treadmill at baseline and after 12 weeks intervention period.

Results: The mean difference in Eq$\dot{V}CO_{2VThan}$ from baseline to post-test in the intervention group was -1.1±2.5 (p = .313), and 1.3±3.0 (p = .209) in the control group. The mean difference between the two groups was -2.4±1.5 (p = .119, 95% CI -5.51, 0.69). The mean difference in $\dot{V}O_{2peak}$ between the groups after 12 weeks was 1.7±0.8 $mL \cdot kg^{-1} \cdot min^{-1}$ (p = .04, 95% CI 0.09, 3.33); the intervention group improved (1.2±1.2 $mL \cdot kg^{-1} \cdot min^{-1}$, p= .053) and the control group slightly reduced (-0.5±1.6 $mL \cdot kg^{-1} \cdot min^{-1}$, p = .36) $\dot{V}O_{2peak}$.

Conclusion: The present study indicates, despite not statistically significant, that home-based peer-supported group exercise can result in enhanced ventilatory efficiency, in comparison to individually performed exercise. In the future, larger confirmatory studies should investigate this further.

Abstrakt

Hensikt: Undersøke effekten av 12 ukers hjemme-basert likemanns-trening i gruppe sammenliknet med individuell trening på ventilatorisk effektivitet, målt ved ventilatorisk ekvivalent for karbondioksid ($Eq\dot{V}CO_{2VThan}$), hos personer som har hatt hjerteinfarkt.

Metode: Randomisert kontrollert studie med deltakere inkludert i «The Norwegian Trial of Physical Exercise After Myocardial Infarction» (NorEx). NorEx har som mål å finne ut om fire år med hjemme-basert trening for å øke kardiorespiratorisk kondisjon reduserer dødelighet og kardiovaskulær sykelighet hos personer som har overlevd hjerteinfarkt. Vi inkluderte 24 deltakere fra intervensjonsgruppen i NorEx med lav overholdelse av foreskrevet trening, tilfeldig fordelt til 12 ukers hjemme-basert likemanns-trening i gruppe (intervensjonsgruppe, n = 12) eller hjemme-basert individuell trening i henhold til NorEx-protokollen (kontrollgruppe, n = 12). Under intervensjonen ble seks deltakere i intervensjonsgruppen og to deltakere i kontrollgruppen tapt for oppfølging. Komplett-data analyser ble utført på henholdsvis seks og ti deltakere i de respektive gruppene. Ventilatorisk effektivitet og maksimalt oksygenopptak ($\dot{V}O_{2peak}$) ble målt ved kardiopulmonal belastningstest utført på tredemølle ved baseline og etter 12 ukers intervensjonsperiode.

Resultater: Gjennomsnittlig forskjell i $Eq\dot{V}CO_{2VThan}$, fra baseline til post-test i intervensjonsgruppen var -1.1±2.5 ($p = .313$), og 1.3±3.0 ($p = .209$) i kontrollgruppen. Gjennomsnittlig forskjell mellom de to gruppene var -2.4±1.5 ($p = .119$, 95% KI -5.51, 0.69). Den gjennomsnittlige forskjellen i $\dot{V}O_{2peak}$ mellom gruppene etter 12 uker var 1.7±0.8 $mL \cdot kg^{-1} \cdot min^{-1}$ ($p = .04$, 95 % KI 0.09, 3.33); intervensjonsgruppen forbedret (1.2±1.2 $mL \cdot kg^{-1} \cdot min^{-1}$, $p = .053$) og kontrollgruppen reduserte (-0.5±1.6 $mL \cdot kg^{-1} \cdot min^{-1}$, $p = .36$) $\dot{V}O_{2peak}$.

Konklusjon: Denne studien indikerer, til tross for at den ikke er statistisk signifikant, at hjemme-basert likemanns-trening i gruppe kan resultere i økt ventilatorisk effektivitet sammenlignet med individuelt utført trening. I fremtiden bør større bekreftende studier undersøke dette nærmere.

Acknowledgments

First, I would like to thank my supervisor professor Ulrik Wisløff for giving me the opportunity to be a part of NorEx and sharing his vast experience and knowledge. I am very proud to have been involved in this important project and experienced the work of the Cardiac Exercise Research Group (CERG). People at CERG have been kind, considerate, helpful, and I am thankful for all the extra opportunities my involvement with the research group has given me. I would also like to express my appreciation to my co-supervisor Alexander Robert Gran Svenningsen for sharing his knowledge and always answering the questions and challenges I encountered.

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Abbreviations

CAD	Coronary Artery Disease
CO_2	Carbon Dioxide
CRF	Cardiorespiratory Fitness
CVD	Cardiovascular Disease
HR_{peak}	Peak Heart Rate
MI	Myocardial Infarction
PA	Physical Activity
RCP	Respiratory Compensation Point
RER	Respiratory Exchange Ratio
$\dot{V}_E$	Minute Ventilation
$\dot{V}_E/\dot{V}CO_2$, $Eq\dot{V}CO_2$	Ventilatory Equivalent for Carbon Dioxide (Ventilatory Efficiency)
$\dot{V}_E/\dot{V}O_2$, $Eq\dot{V}O_2$	Ventilatory Equivalent for Oxygen (Ventilatory Efficiency)
$\dot{V}CO_2$	Expired Carbon Dioxide
$\dot{V}O_2$	Oxygen Uptake
$\dot{V}O_{2max}$	Maximal Oxygen Uptake
$\dot{V}O_{2peak}$	Peak Oxygen Uptake
V_{Than}	Ventilatory Anaerobic Threshold

Definitions

Cardiorespiratory Fitness (CRF): The ability of the respiratory, circulatory, and muscular systems to consume, distribute, and utilize oxygen to perform physical work. The gold standard for measuring cardiorespiratory fitness is peak- or maximal oxygen uptake (1).

Cardiopulmonary Exercise Test: Exercise testing with ventilatory expired gas analysis, which allows for the concomitant assessment of three prognostic/functional parameters: Oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation (V_E) (1).

Exercise Training: Refers to planned, structured, and purposefully performed physical activity (PA) aiming to improve or maintain CRF (2).

Maximal Oxygen Uptake ($\dot{V}O_{2max}$): Refers to the highest rate at which an individual can transport and utilize oxygen during the performance of dynamic exercise involving a large part of total muscle mass. To reach the true $\dot{V}O_{2max}$ the $\dot{V}O_2$ must reach a plateau despite increased workload during an ergospirometry test (2).

Peak Oxygen Uptake ($\dot{V}O_{2peak}$): A term commonly used instead of $\dot{V}O_{2max}$ because maximal effort does not necessarily always give a plateau in $\dot{V}O_2$ during an ergospirometry test (due to lack of motivation, general discomfort, not able to push to maximum etc.). Hence, it is common to refer to $\dot{V}O_{2peak}$ attained during volitional incremental exercise (2).

Personal Activity Intelligence (PAI): Algorithm which considers an individual's sex, age, resting and maximal heart rate, and heart rate fluctuations during daily activity, and translates into a weekly score which reflects the individual's cumulative weekly physical activity (PA). Obtaining a weekly PAI score ≥100 is associated with reduced risk of premature morbidity and mortality from cardiovascular diseases (3).

Physical Activity (PA): Defined as any bodily movement, produced by skeletal muscles, that require energy expenditure above resting metabolism (4).

Respiratory Compensation Point (RCP): The point at which the ventilation increase faster relative to expired carbon dioxide ($\dot{V}CO_2$), marking the onset of hyperventilation (5).

Ventilatory Anaerobic Threshold (V_{Than}): Reflection of anaerobic threshold, assessed by ventilatory expired gas. Defined as the beginning of excess CO_2 output generated from buffering of H+ due to transitioning from aerobic to anaerobic metabolism (5).

Ventilatory Efficiency: The relationship of the liters of ventilation required to consume a liter of oxygen or eliminate a liter of CO_2 (5).

$\dot{V}_E/\dot{V}CO_2$ slope: The relationship between minute ventilation ($\dot{V}_E$) and $\dot{V}CO_2$ reported by plotting $\dot{V}_E$ (y-axis) relative to $\dot{V}CO_2$ (x-axis). The $\dot{V}_E/\dot{V}CO_2$ relationship during exercise can then be determined by analyzing the slope of this regression line (6). Provided the subject can tolerate high levels of exercise, $\dot{V}_E/\dot{V}CO_2$ virtually equals (i.e., "asymptotes") to the slope of the $\dot{V}_E/\dot{V}CO_2$ relationship (7).

Introduction

The most common cause of death in Europe with about two million deaths annually is myocardial infarction (MI) (8). The European Society of Cardiology (ESC), American College of Cardiology Committee (ACC), American Heart Association (AHA) and the World Heart Federation (WFA) states that the universal clinical definition of MI "*denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia" (9).* Around 20% of the survivors of MI experience a new cardiovascular event within the first year (10). Therefore, it is imperative to find effective secondary prevention strategies for this population. Physical activity (PA) and exercise training has been recognized as having a primary role in preventing chronic disease and in maintaining health throughout the age span (2). Epidemiological studies indicate that if the population adhered to official guidelines for PA, 30% of deaths caused by MI could have been prevented (8).

Maximal oxygen uptake ($\dot{V}O_{2max}$) is recognized as the gold standard measure of cardiorespiratory fitness (CRF) (2), and peak oxygen uptake ($\dot{V}O_{2peak}$) has traditionally been utilized in prognostic evaluation in systolic heart failure (11). Mancini et al. found in the early nineties that cardiac transplantation can be safely postponed in ambulatory patients with severe left ventricular dysfunction if their $\dot{V}O_{2peak}$ were above 14 $mL \cdot kg^{-1} \cdot min^{-1}$ (12). This work led to the establishment of 14 $mL \cdot kg^{-1} \cdot min^{-1}$ in $\dot{V}O_{2peak}$ as a cut-off value where below this, mortality significantly increased. However, advances in heart failure treatment have resulted in significant improvement in survival. For example, beta-blockers reduce mortality in patients with heart failure, but do not influence $\dot{V}O_{2peak}$ (13). Therefore, multiple authors have questioned the ability of $\dot{V}O_{2peak}$ to predict mortality, and especially its cut-off value (11).

Efficient pulmonary gas exchange is characterized by uniform matching of lung ventilation with perfusion. In contrast, mismatching is marked by inefficient pulmonary gas exchange, requiring increased ventilation for a given CO_2 production (14). During exercise, ventilation increases in proportion to metabolic demand. Meaning, CO_2 production ($\dot{V}CO_2$) to maintain arterial blood gas and acid-base balance (6). The response of minute ventilation ($\dot{V}_E$) in relation to $\dot{V}CO_2$ is commonly termed ventilatory efficiency ($\dot{V}_E/\dot{V}CO_2$). The $\dot{V}_E/\dot{V}CO_2$ response to exercise is often elevated in conditions such as heart failure, and serves as an independent predictor of poor outcomes and mortality in many diseases (6). Research has shown that patients with coronary artery disease (CAD) exhibit ventilatory inefficiency (15), with dyspnea and reduced aerobic performance being two hallmarks (16).

In cardiopulmonary exercise tests, $\dot{V}_E$ increases within three phases: first up to the anaerobic threshold, second between the anaerobic threshold and the respiratory compensation point (RCP) known as the isocapnic buffering period, and third from RCP to maximal exercise exertion. The first phase is linked to oxygen uptake ($\dot{V}O_2$), second to $\dot{V}CO_2$, and third to unbuffered acidosis (pH reduction) (17). Ventilatory anaerobic threshold (V_{Than}) is thought to reflect the anaerobic threshold, assessed by ventilatory expired gas, whereas RCP are the point where $\dot{V}_E$ increases faster relative to $\dot{V}CO_2$, thus marking the onset of hyperventilation (5). The ventilatory equivalent for CO_2 at V_{Than} ($Eq\dot{V}CO_{2VThan}$) is considered the most common measure of ventilatory efficiency. The reason is that ventilation varies least in the range between V_{Than} and RCP, and ventilation is more closely related to expired CO_2 than inspired oxygen (5). The $\dot{V}_E/\dot{V}CO_2$ slope is another key indicator of ventilatory efficiency and is the relationship between $\dot{V}_E$ and $\dot{V}CO_2$ during exercise determined by analyzing the slope of its regression line (6). Provided the participant can tolerate high levels of exercise, $\dot{V}_E/\dot{V}CO_2$ virtually equals to the $\dot{V}_E/\dot{V}CO_2$ slope (7). The $\dot{V}_E/\dot{V}CO_2$ slope does not need maximal test conditions in contrast to $\dot{V}O_{2peak}$, which makes it attractive for clinical application in patients presenting limitations to strenuous stress testing (11).

A meta-analysis by Cahalin et.al state that both $\dot{V}O_{2peak}$ and the $\dot{V}_E/\dot{V}CO_2$ slope are robust and highly significant prognostic values in patients with heart failure (18). In addition, the meta-analysis supports the view that the $\dot{V}_E/\dot{V}CO_2$ slope has a greater prognostic strength in comparison to $\dot{V}O_{2peak}$ (18). A scientific statement from American Heart Associations (AHA) states that both $\dot{V}O_{2peak}$ and the $\dot{V}_E/\dot{V}CO_2$ slope provide prognostic and functional indices that are responsive to numerous therapeutic interventions in patients with cardiovascular disease (CVD) (1). However, research regarding the effect of exercise intervention on ventilatory efficiency in patients with a history of CVD appear mixed and non-conclusive (16, 19, 20).

Dibben et al. performed a Cochrane meta-analysis of exercise-based rehabilitation for coronary heart disease and found a large reduction in fatal or non-fatal MI, and likely reductions in all-cause mortality and all-cause hospital admissions up to 12 months follow-up (21). However, the results are inconclusive and there is still a need for large randomized controlled trials (21). NorEx, The Norwegian Trial of Physical Exercise After Myocardial Infarction, is an ongoing randomized controlled trial initiated to provide quality cause evidence for secondary prevention and rehabilitation in patients with a history of MI. NorEx aim to investigate if 4 years supervised moderate to vigorous exercise training will lower mortality and cardiovascular morbidity compared to standard care in post-MI patients (8). Martin et al. found that among patients with CAD referred to cardiac rehabilitation, completion is associated with improved survival and decreased hospitalization (22). However, a substantial proportion of referred patients never attend, which is a concerning finding that requires exploration (22).

Research shows that home-based aerobic interval training can be as effective as a center-based approach in cardiac rehabilitation (23-26). A review by Anderson et al. state that the availability of home-based exercise programs may widen the access, uptake, adherence, and increase participation in cardiac rehabilitation in patients with heart disease (26). Social support and companionship have been identified as powerful motivators and facilitators for maintaining PA long-term in survivors of MI (27, 28). Therefore, it can be beneficial to implement these factors into a home-based peer-supported group exercise program in the hope of increasing adherence.

There is a lack of evidence for the effect of home-based peer-supported group exercise in survivors of MI on ventilatory efficiency. The aim of the present study was to investigate the effect of 12 weeks of home-based peer-supported group exercise versus individually performed exercise on ventilatory efficiency in people with a history of MI. The primary outcome was assessment of $Eq\dot{V}CO_{2VThan}$. Secondary outcomes were supplementary measures of ventilatory efficiency ($Eq\dot{V}O_{2VThan}$, $Eq\dot{V}CO_{2peak}$ and $Eq\dot{V}O_{2peak}$), cardiorespiratory fitness ($\dot{V}O_{2peak}$) and ventilatory thresholds (V_{Than} and RCP). The hypothesis was that the participants in the intervention group would enhance ventilatory efficiency at both V_{Than} and RCP. In addition, it was hypothesized that $\dot{V}O_{2peak}$ would improve among the intervention group compared to the control group after 12 weeks.

Methods

NorEx

NorEx is an ongoing three-armed multicenter randomized controlled trial. All participants were screened by nurses prior to enrollment to ensure safe participation. The intervention is home-based and semi-supervised by a personal trainer. Consists of an intensity, duration and frequency that accumulates to at least 115 minutes exercise per week, and comprises minimum 20 minutes vigorous intensity (~85% of peak heart rate (HR_{peak}) or rate of perceived exertion of ~16 on the Borg scale (29)) and 95 minutes of moderate intensity (~70% of HR_{peak} or rate of perceived exertion of ~13 on the Borg scale (29)). Alternatively, continuous heart rate measurements amounting to at least 100 Personal Activity Intelligence (PAI) equivalents per week (8). Table 1 lists the inclusion and exclusion criteria for participants in NorEx.

Table 1: Inclusion and exclusion criteria for NorEx (The Norwegian Trial of Physical Exercise After Myocardial Infarction (8).

Inclusion criteria	Exclusion criteria
• Age 18 years to 79 years • Can communicate in Norwegian or another Scandinavian language • Hospitalized in a Norwegian hospital with type 1 acute myocardial infarction during 2013-2022 • Signed consent form • Norwegian national identification number • Being able to be physically active according to study protocol	• Regular physical activity level above the exercise intervention or participating in endurance sport competitions • Cognitive impairment or dementia • Known drug or alcohol abuse • Serious psychiatric disease • Renal insufficiency requiring dialysis • Cardiac disease contradicting moderate or high intensity physical activity • Uncontrolled hypertension (> 210/110 mmHg) • End-stage somatic disease with reduced life expectancy or which prevents following the exercise intervention • Residing in a nursing home or other institution • Participate in another exercise intervention study

Participants

A sample size calculator from ClinCalc LLC (30) was used to determine the minimum number of participants required to have sufficient statistical power, and estimated 14 participants with seven in each group. The estimated sample size is based on a statistical power of 0.8 and significance level of 0.05. In addition, a hypothesis of a possible clinically significant group difference in change in $\dot{V}O_{2peak}$ of 3 mL·kg^{-1}·min^{-1}, with an assumption of a standard deviation of 2 mL·kg^{-1}·min^{-1}, were taken into calculation (31). Due to the risk of drop-outs, we aimed to include 24 participants, 12 in each group.

Participants were selected from the participants enrolled in NorEx intervention group. Table 2 lists the exclusion and inclusion criteria of the present study. Due to the study leaders place of residence, resources, and number of available participants in NorEx, 112 participants from the central areas of Trondheim were selected. These participants were then distributed into groups according to their average activity level the two months prior, which has been documented through NorEx digital follow-up (8). The groups were high (> 23 days above 100PAI in one month), adequate (15-23 days above 100PAI in one month), low (< 15 days above 100PAI in one month) and unknown (registered PAI < 15 days in one month). The present study intended to identify participants struggling with adhering to prescribed levels of PA by NorEx. Thus, 71 participants constituted the groups adequate, low, and unknown, and this is the participant pool that was utilized. The randomization was carried out by the use of syntax in IBM SPSS (Statistical Package for Social Science v28, Chicago, IL, USA). From the participant pool of 71 participants, 36 were randomized (18 to each group) to receive invitation to participation in the present study.

The invitation process took place by contacting the participants by telephone. The intervention group received information about the project, while the control group was invited to an exercise test without any additional information. A supplementary randomization of 18 participants (6 to intervention group, 12 to control group) was necessary to reach the required sample size. Thus, a total of 54 participants were randomized to receive invitation, while 17 participants were in surplus. The final sample size was 12 participants in each group. Six participants from the intervention group and two participants from the control group were lost to follow-up. Figure 1 displays a flowchart of the randomization process and information regarding participants lost to follow-up.

Table 2: Inclusion and exclusion criteria for the present study.

Inclusion criteria	Exclusion criteria
• NorEx participant • < 23 days above 100 PAI monthly for the two months prior to inclusion • Residing in central areas of Trondheim	• Cardiac disease contradicting moderate or high intensity physical activity

Abbreviations: NorEx: The Norwegian Trial of Physical Exercise After Myocardial Infarction, PAI: Personal Activity Intelligence.

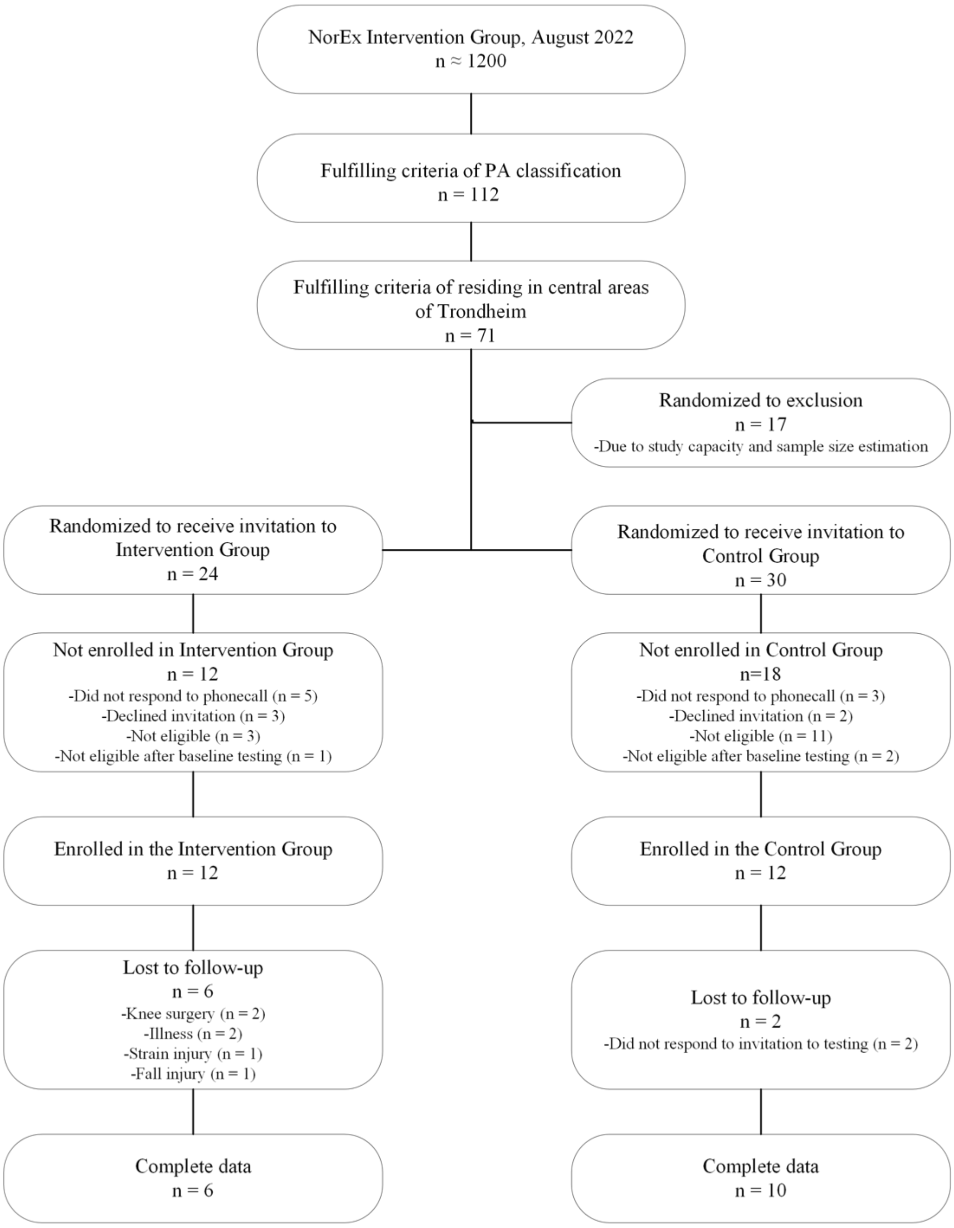

Figure 1: Flowchart of the randomization process and information regarding participants lost to follow-up. Abbreviations: NorEx: The Norwegian Trial of Physical Exercise After Myocardial Infarction, n: sample size, PA: Physical Activity.

Descriptive Variables

Data collection was performed at St. Olavs Hospital, Emergency and Cardiothoracic Centre, Next Move Core Facility, Trondheim, Norway from August 25th until December 06th 2022. Each participant underwent two days of data collection, one at baseline testing and one at post-testing. Height was reported in nearest whole centimeter and measured while the participant stood barefoot with straight legs, shoulder-width apart while looking straight forward (Seca 222, Hamburg, Germany). Body mass (kg) was measured by weighing scale Model DS-102 (Arctic Heating AS, Notteroy, Norway). Heart rate throughout the testing was provided by electrocardiography (Custo Cardio 100 BT, Custo Med GmbH, Ottobrunn, Germany). Heart rate recovery (HRR) was calculated as the decrease in HR_{peak} from peak exercise to 1 min after the exercise test while the participant remained standing. In case of significant disturbance to the electrocardiography signal, heart rate was also measured with the monitor Polar H10 (Polar Electro Oy, Kempele, Finland). Adherence was measured by registration of attendance at each session.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was used to test CRF. Participants completed an individualized graded protocol on a treadmill (Woodway PPS Med55, Waukesha, WI, USA) as described in Loe et al. (32). The participants could either walk or run and maintained the chosen movement during the entire test. They were instructed to avoid holding on to the handrails on the treadmill if possible. The exercise testing was conducted in accordance with American Heart Associations (AHA) guidelines for indications and contraindications for test termination in patients with CVD (33). Concurrent 12-lead electrocardiography was applied to monitor cardiac response.

The cardiopulmonary exercise test started with a 10-minute treadmill familiarization phase during warm-up, with electrocardiogram and without the mask. Participants managed this phase themselves, while study leaders supervised, and were instructed to reach an intensity corresponding 11-13 on the Borg Scale (29). Warm-up workload was based on self-reported PA level, monitoring of the heart rate, and feedback from the participant regarding rate of perceived exertion on the Borg scale. During this phase, participants were given information about the test´s three phases. The mask was mounted prior to phase one, which lasted for three minutes, and the initial speed and incline were determined by the individualized warm-up workload. Phase one was a submaximal workload, where participants' $\dot{V}O_2$ and heart rate stabilized after three minutes. Phase two was also submaximal workload and lasted another three minutes, with either 1 $km \cdot h^{-1}$ increase in speed or 2% increase in incline and obtained steady state after 2-3 minutes. In phase three, there was either a 1 $km \cdot h^{-1}$ increase in speed or 2% increase in incline approximately each minute until the participant reached volitional exhaustion (shortness of breath and leg fatigue). In this final phase the peak workload is located. Post-testing followed the same protocol as the baseline testing. Meaning, the participant began the post-test at same speed and incline as baseline test on phase one and followed the same increases in workload during the next phases.

The ergospirometry systems at the Next Move Core Facility at St. Olav´s Hospital was used to perform the testing, and these systems have been validated against Douglas-bag method and a Metabolic Calibration System (VacuMed, Ventura, CA, USA). The treadmill is regularly calibrated/controlled by Next Move engineers to ensure correct speed and inclination. A fitted face mask (Hans Rudolph, USA) was linked to the Metalyzer II (Cortex Biophysik GmBh, Leipzig, Germany) for mixing chamber gas analysis. The Metalyzer II was calibrated prior to the first test each day, with the use of a standard two-point gas calibration procedure. The calibration included measurements of ambient air and a gas mix of known content (15% oxygen and 5% CO_2 in nitrogen, accuracy ±1%) (HIQ Center, AGA A/S, Oslo, Norway), a calibration of the Triple-V volume transducer with a 3L Calibration Syringe (Cortex Biophysik GmBh, Leipzig, Germany), and barometric pressure control. Prior to each test ambient room air was measured, in addition to volume calibration. Two-point gas calibration was performed every third test.

Cardiorespiratory Variables from Cardiopulmonary Exercise Testing

If the participants reached a $\dot{V}O_2$ plateau that remained stable, increased ≤ 2 $mL \cdot kg^{-1} \cdot min^{-1}$, or decreased despite increased workload, and the respiratory exchange ratio (RER) ≥ 1.05, $\dot{V}O_{2max}$ was considered achieved (32). If these criteria were not met, the expression $\dot{V}O_{2peak}$ was used. Gas exchange variables were reported as an average of 10 second intervals. The mean of the three highest consecutive measurements was used to calculate $\dot{V}O_{2peak}$. Likewise, RER and $\dot{V}CO_{2peak}$ were determined as the mean of the three corresponding values. Ventilatory efficiency was calculated at V_{Than} as Eq$\dot{V}O_2$ ($\dot{V}_{EVThan}/\dot{V}O_{2VThan}$) and Eq$\dot{V}CO_2$ ($\dot{V}_{EVThan}/\dot{V}CO_{2VThan}$). Peak ventilatory efficiency was calculated at $\dot{V}O_{2peak}$ as Eq$\dot{V}O_2$ ($\dot{V}_{Epeak}/\dot{V}O_{2peak}$) and Eq$\dot{V}CO_2$ ($\dot{V}_{Epeak}/\dot{V}CO_{2peak}$).

Ventilatory Anaerobic Threshold (V_{Than}) and Respiratory Compensation Point (RCP)

To determine ventilatory anaerobic threshold (V_{Than}: L·min^{-1}, %$\dot{V}O_{2peak}$) and respiratory compensation point (RCP: L·min^{-1}, %$\dot{V}O_{2peak}$), the V-slope method was utilized. A regression analysis of the slopes of $\dot{V}CO_2$ and $\dot{V}O_2$ was performed in Microsoft Excel (v16.68), and the breakpoint where the slopes coincided was considered as V_{Than} (34). The same procedure was performed for detecting RCP, except that $\dot{V}_E$ and $\dot{V}CO_2$ plots were analyzed instead. RCP was not possible to identify among all the participants included in the present study. No more than four participants had identifiable RCP thresholds at both baseline- and post-test. Hence, it was not feasible to analyze and present absolute values for RCP. Two individual investigators visually inspected the data plots and corresponding slopes to strengthen accuracy of estimates.

Intervention

The intervention was a home-based peer-supported group exercise intervention. The participants in the intervention group were prescribed 12 weeks of group exercise, with two sessions each week. The study leaders supervised and joined the first four sessions and passively attended additional eight sessions sporadically. Weekly reminders of the exercise sessions were sent from study leaders to the participants via text messages. Study leaders introduced 4x4 high intensity intervals at the first session (four intervals with a duration of four minutes and intensity of ~85% of HR_{peak} or rate of perceived exertion of ~16 on Borg scale (8, 29), two minutes active break between each interval), and focused on transferring competence on key elements. The participants could choose what form of aerobic exercise they preferred for the remaining exercise sessions, and collectively chose to continue with 4x4 high intensity intervals. In preparation of the intervention period, the participants were asked to write down individual goals. An attendance form was brought and filled out at each session by the participants in order to document attendance. The attendance form was passed around within the intervention group from session to session, and the participant with the form were in charge of the respective session. The control group followed the original NorEx intervention.

Statistical Analysis and Data Visualization

Statistical analyses and creation of figures were performed in IBM SPSS, except Figure 1 which was created with the use of Microsoft 365 Visio (Standard, 2021). Complete case analyses were chosen, and data are presented as arithmetic mean ± standard deviation if not otherwise stated. The dataset was examined for errors such as correct number of decimals, variable category, variable name, etc. Tests of normality with histogram and QQ-plots was performed for each variable and confirmed normal distribution which led to the use of parametric analyses. A significance level of $p < 0.05$ was chosen. Independent-Samples T-test was utilized for each variable to compare the mean difference and establish level of significance between the intervention and control group. Paired-Samples T-test was utilized for each variable to establish level of significance within the respective groups.

Ethical Statement

NorEx has been approved by the Regional Committee for Medical Research Ethics (REK 2019/797). The approval also applies for sub-studies equivalent to the present study. Written informed consent was obtained from all participants prior to enrolment in NorEx, which also applies for the present study. Additionally, the present study complies with the Declaration of Helsinki and Vancouver recommendations for authorship.

Results

A total of 24 participants were enrolled between 23 and 29 August 2023, with 12 participants in each group. A total of eight participants were lost to follow-up due to medical procedures, illnesses, and not responding to post-test invitation. Thus, 16 participants were included in the complete case analyses. Baseline characteristics of the participants are presented in Table 3. The term $\dot{V}O_{2peak}$ is used in the present study since 19% of the participants did not reach the predefined criteria for $\dot{V}O_{2max}$ at baseline testing. Corresponding cardiorespiratory variables are also referred to as peak values.

Table 3: Descriptive data for the intervention group and control group at baseline.

	Intervention group (n = 6)	**Control group (n = 10)**
Age (years)	60.8±9.1	67.6±7.4
Male/female (no. Participants)	4/2	8/2
Height (cm)	170.0±5.8	173.7±9.6
Body mass (kg)	74.8±9.3	82.4±14.3
BMI (kg/m^2)	26.0±3.6	27.2±3.3

Data presented as arithmetic mean ± standard deviation. Abbreviations: BMI: Body Mass Index, n: sample size.

Primary Outcome: Mean Difference in Ventilatory Efficiency ($Eq\dot{V}CO_{2VThan}$)

Figure 2 and 3 show results for ventilatory efficiency measured as $Eq\dot{V}CO_{2VThan}$ before and after intervention for the respective groups and for each individual participant, respectively. At baseline, mean $Eq\dot{V}CO_{2VThan}$ was 9.2% higher ($p = .239$) among the intervention group compared to the control group (33.1±4.8 vs. 30.3±3.7). The intervention group improved ventilatory efficiency by 3.4% shown by a decrease in $Eq\dot{V}CO_{2VThan}$ (-1.1±2.5, $p = .313$), whereas the control group reduced ventilatory efficiency by 4.2% shown by an increase in $Eq\dot{V}CO_{2VThan}$ (1.3±3.0, $p = .209$). After 12 weeks intervention mean $Eq\dot{V}CO_{2VThan}$ was similar: 32.0±4.1 and 31.6±2.8 for the intervention and control group, respectively. The mean difference for change in ventilatory efficiency between groups was not statistically significant (-2.4 ±1.5, $p = .119$, 95% CI -5.51, 0.69).

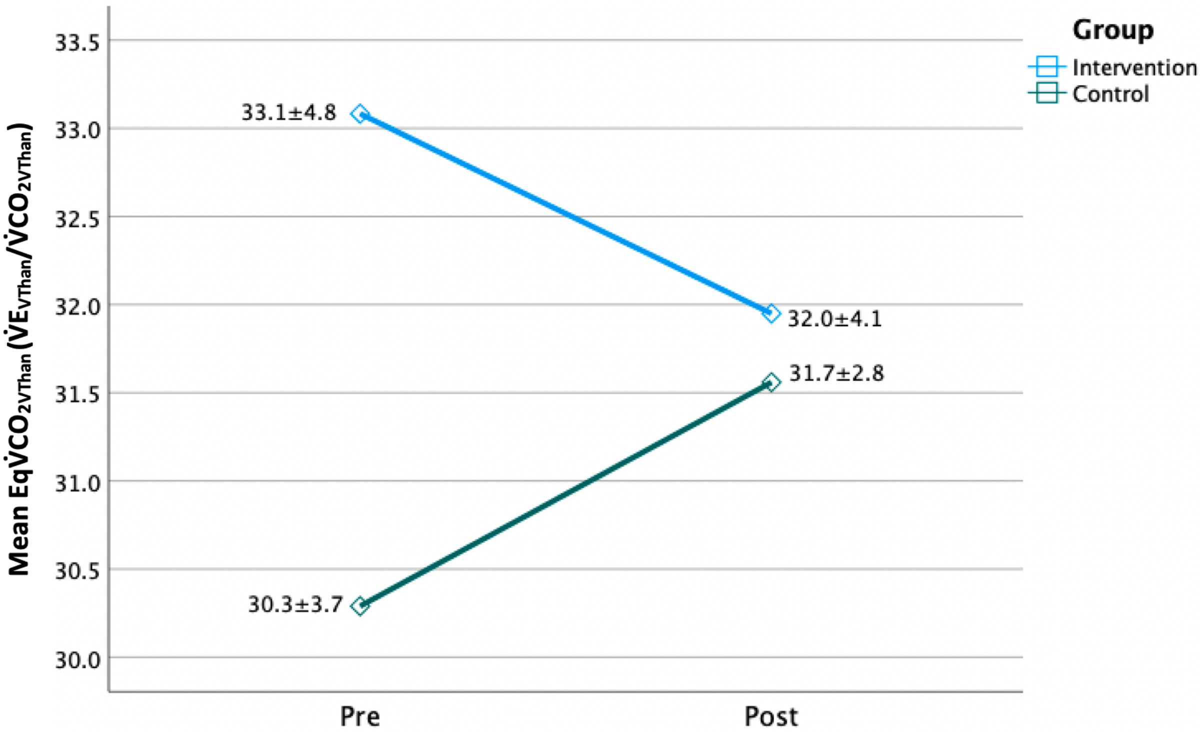

Figure 2: Comparison of mean change ± standard deviation in ventilatory efficiency measured by Eq$\dot{V}CO_{2VThan}$, before and after 12 weeks intervention period, between intervention group and control group. Abbreviations: Eq$\dot{V}CO_{2VThan}$: Ventilatory equivalent for carbon dioxide at ventilatory anaerobic threshold (ventilatory efficiency).

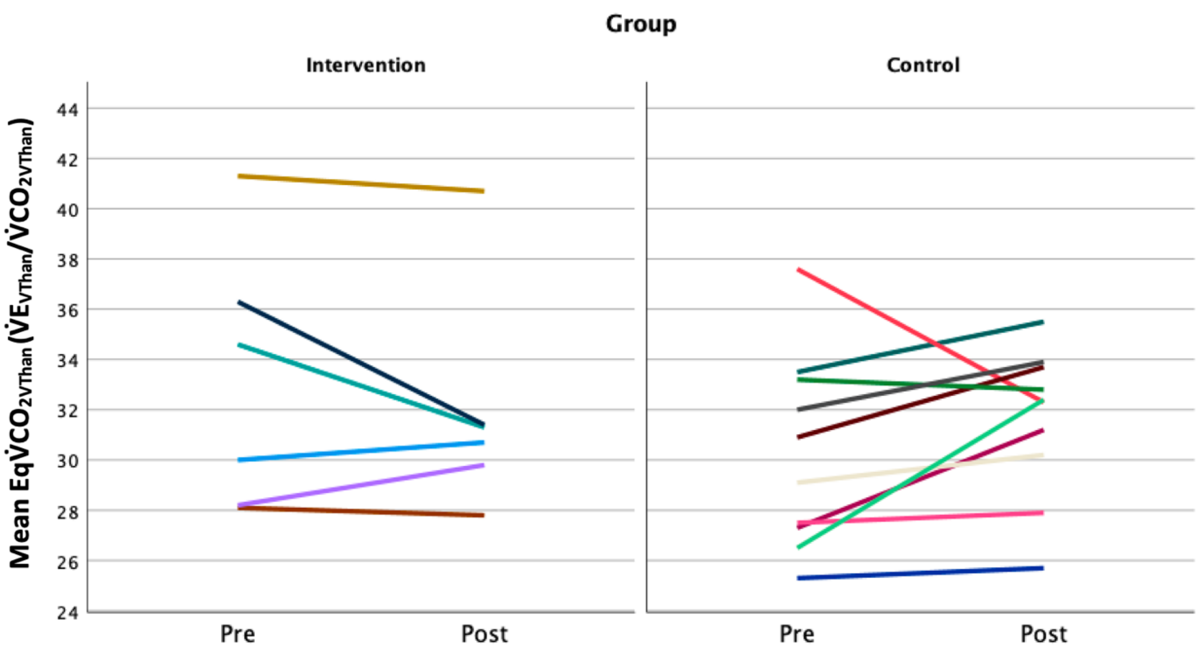

Figure 3: Comparison of individual change in ventilatory efficiency measured by Eq$\dot{V}CO_{2VThan}$, before and after 12 weeks intervention period, between intervention group and control group. Abbreviations: Mean Eq$\dot{V}CO_{2VThan}$: ventilatory equivalent for carbon dioxide at ventilatory anaerobic threshold (ventilatory efficiency).

Secondary Outcomes: Ventilatory Efficiency (Eq$\dot{V}O_{2VThan}$, Eq$\dot{V}CO_{2peak}$ and Eq$\dot{V}O_{2peak}$)

Results for ventilatory efficiency measured as Eq$\dot{V}O_{2VThan}$, Eq$\dot{V}CO_{2peak}$, and Eq$\dot{V}O_{2peak}$ before and after intervention are presented for the respective groups in Table 4. After 12 weeks the mean difference in change in Eq$\dot{V}O_{2VThan}$ between the two groups was 1.3±1.4 and not statistically significant (p = .373, 95% CI -4.28, 1.71). The intervention group decreased Eq$\dot{V}O_{2VThan}$ with -0.3±2.9 (p = .82), while the control group increased with 1.0±2.6 (p = .253).

The results of mean difference in change in both Eq$\dot{V}CO_{2peak}$ (-1.2±1.0, p = .259, 95% CI -3.39, 0.99) and Eq$\dot{V}O_{2peak}$ (-1.1±1.3, p = .425, 95% CI -3.85, 1.72) show no statistically significant difference after 12 weeks between the intervention group and the control group. Regarding Eq$\dot{V}CO_{2peak}$, the results show that the intervention group slightly decreased, while the control group slightly increased mean Eq$\dot{V}CO_{2peak}$ (-0.7±2.3 p = .514 vs. 0.6±1.8, p = .358). Regarding Eq$\dot{V}O_{2peak}$, the intervention group presented a decrease of -0.8±2.7 (p = .484), whereas the control group increased 0.3±2.4 (p = .753).

Ventilatory Threshold (V_{Than}) and Cardiorespiratory Fitness ($\dot{V}O_{2peak}$)

Results for CRF and V_{Than} before and after intervention are shown for each group in Table 4. The present study found no significant difference in change in V_{Than} between the respective groups after intervention (0.2±0.1 l/min, p = .129, 95% CI -0.07, 0.49). The control group had a decrease in V_{Than} after 12 weeks (-0.2±0.3 l/min, p= .129), whereas the intervention group´s V_{Than} remained nearly unchanged (0.1±0.2 l/min, p = .466). Expressed in percentage, $V_{Than}\%\dot{V}O_{2peak}$, the mean difference between the two groups was 4.4±4.6% and non-significant (p = .358, 95% CI -5.47, 14.19).

The present study found a statistically significant mean difference in change in $\dot{V}O_{2peak}$ from baseline to post-test between the respective groups (1.7±0.8 mL·kg^{-1}·min^{-1}, p = .04, 95% CI 0.09, 3.33). The intervention group improved $\dot{V}O_{2peak}$ with 1.2±1.2 mL·kg^{-1}·min^{-1} (p = .053), while the control group had a slight reduction of -0.5±1.6 mL·kg^{-1}·min^{-1} (p = .36).

Table 4: Outcome variables for intervention group and control group at baseline and after 12 weeks intervention period.

	Intervention group (n = 6)		Control group (n = 10)		Mean Difference
	Before	**After**	**Before**	**After**	
$Eq\dot{V}O_{2VThan}$ ($\dot{V}E_{VThan}/\dot{V}O_{2VThan}$)	30.7±4.7	30.4±3.6	27.5±3±4	28.5±3.3	1.3±1.4 (p = .373, 95% CI -4.28, 1.71)
$Eq\dot{V}CO_{2peak}$ ($\dot{V}E_{peak}/\dot{V}CO_{2peak}$)	34.1±3.7	33.5±3.2	31.1±2.9	31.7±3.1	-1.2±1 (p = .259, 95% CI -3.39, 0.99)
$Eq\dot{V}O_{2peak}$ ($\dot{V}E_{peak}/\dot{V}O_{2peak}$)	38.4±3.2	37.6±3.1	33.1±3.9	33.3±4.4	-1.1±1.3 (p = .425, 95% CI -3.85, 1.72)
V_{Than} ($L \cdot min^{-1}$)	1.94±0.36	2.01±0.43	1.99±0.60	1.85±0.59	0.21±0.13 (p = .129, 95% CI -0.07, 0.49)
V_{Than} $\%VO_{2peak}$	74.3±5.5	74.6±8.2	74.8±7.6	70.2±6.6	4.4±4.6 (p = .358, 95% CI -5.47, 14.19)
$\dot{V}O_{2peak}$ (L/min)	2.59±0.4	2.67±0.42	2.68±0.79	2.63 ±0.79	0.11±0.05 (p = .029, 95% CI 0.01, 0.21)*
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	35.4±7.7	36.7±7.7	32.6±8.0	32.1±8.2	1.7±0.8 (p = .04, 95% CI 0.09, 3.33)*
RER at $\dot{V}O_{2peak}$	1.14±0.67	1.13±0.04	1.06±0.07	1.06±0.05	
HRR, 1min ($beats \cdot min^{-1}$)	31±6	33±5	23±6	21±6	
HR_{peak} ($beats \cdot min^{-1}$)	170±13	167±17	151±21	149±25	

Data presented as arithmetic mean ± standard deviation. Abbreviations: n: sample size, CI: Confidence Interval, $\dot{V}O_{2peak}$: peak oxygen uptake, RER: Respiratory Exchange Ratio, HRR: Heart Rate Recovery (1min after completed test), HR_{peak}: peak Heart Rate, $Eq\dot{V}O_{2VThan}$: ventilatory equivalent for oxygen at ventilatory anaerobic threshold (ventilatory efficiency), $Eq\dot{V}CO_{2peak}$: ventilatory equivalent for carbon dioxide at $\dot{V}O_{2peak}$ (ventilatory efficiency), $Eq\dot{V}O_{2peak}$: ventilatory equivalent for oxygen at $\dot{V}O_{2peak}$ (ventilatory efficiency), V_{Than}: ventilatory anaerobic threshold.
* Statistically significant ($p < 0.05$).

Exercise Adherence

The intervention group originally consisted of 12 participants, with one participant dropping out in week seven, two participants in week 10 and three participants in week 12. With that in mind, the average number of participants per exercise session was 7.2±2.1, which equals 58% of the original 12 participants. When focusing on the six participants in the intervention group with complete data, the average attendance was 19±3 sessions per participant. This attendance rate equals 79% attendance per participant with complete data. Visual display of individual attendance and change in ventilatory efficiency among the intervention group is shown in Figure 4.

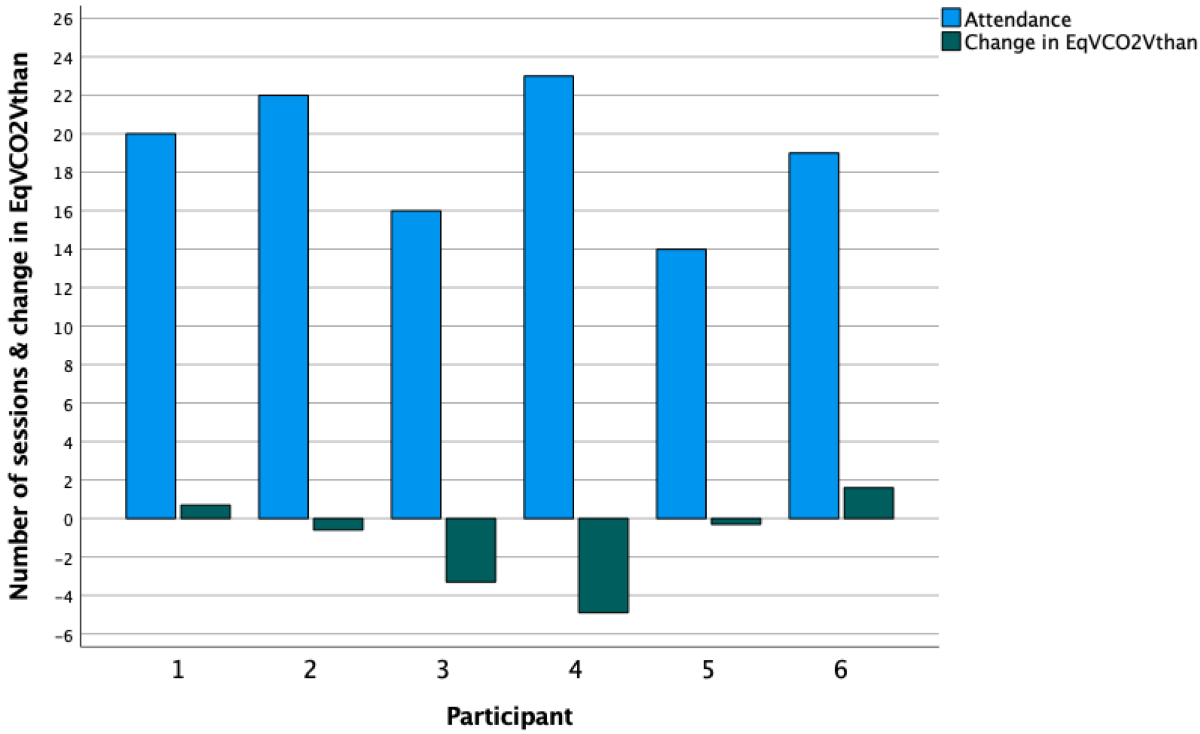

Figure 4: Display of attendance during the 12 weeks of intervention and change in $EqVCO_{2VThan}$ after 12 weeks intervention in the six participants with complete data. Abbreviations: $Eq\dot{V}CO_{2VThan}$: ventilatory equivalent for carbon dioxide (ventilatory efficiency).

Discussion

The main result of the present study was that mean difference in $Eq\dot{V}CO_{2VThan}$ from baseline to post-test between the intervention group and the control group was non-significant ($p = .119$), but may indicate a tendency towards a positive effect of the exercise intervention on ventilatory efficiency. Compared to the control group, the intervention group showed increased ventilatory efficiency measured as a reduction in $Eq\dot{V}CO_{2VThan}$, whereas the control group increased $Eq\dot{V}CO_{2VThan}$. Due to the small sample size, the results must be interpreted carefully.

Primary Outcome: Mean Difference in Ventilatory Efficiency ($Eq\dot{V}CO_{2VThan}$)

The findings of the present study were in line with a randomized controlled trial by Cardozo et al. who compared the effects of 16 weeks of high intensity interval training, moderate intensity training, and no exercise, on the $\dot{V}_E/\dot{V}CO_2$ slope in patients with coronary heart disease. They found no differences due to training in $\dot{V}_E/\dot{V}CO_2$ slope (19). However, both Gademan et al. and Guazzi et al. found that exercise training significantly decreased $\dot{V}_E/\dot{V}CO_2$ slope by 14% among patients with chronic heart failure (16, 20). Guazzi et al. had an intervention consisting of exercise training four times per week for eight weeks, while Gademan et al. intervention consisted of 30 exercise sessions with two to three sessions per week. Both studies had exercise interventions that consisted of activity below high intensity (16, 20).

Firstly, the discrepancy in previous findings may be a result of different CVDs being targeted. Neither of the mentioned studies targeted solely MI such as the present study. Further, the discrepancy may be partially explained by the fact that Cardozo et al., who did not find a significant decrease in the $\dot{V}_E/\dot{V}CO_2$ slope, excluded all participants with heart failure. Therefore, included participants were relatively healthy with a mean baseline $\dot{V}_E/\dot{V}CO_2$ slope below the usual threshold ($\dot{V}_E/\dot{V}CO_2$ slope < 34) for elevated risk (19). The participants in the present study had mean $Eq\dot{V}CO_{2VThan}$ baseline values below 34 in both intervention and control group (33.1 ± 4.8 vs. 30.3 ± 3.7), which leads to the speculation that they were relatively healthy and had less room for improvement in ventilatory efficiency (19). Further, mean $Eq\dot{V}CO_{2VThan}$ was 9.2% ($p = .239$) higher among the intervention group compared to the control group at baseline. This difference may suggest that the tendency towards a positive effect of the exercise intervention on ventilatory efficiency in the intervention group may be explained by the fact that the control group had higher ventilatory efficiency at baseline. Hence, the intervention group had more room for improvement.

Prado et al. compared the effect of aerobic exercise training in participants with CAD with three different levels of aerobic fitness and found that the group with initially lowest aerobic fitness experienced the greatest improvements in both $\dot{V}O_{2peak}$ and ventilatory efficiency (15). Thus, it could be expected that the participants in the intervention group in the present study would achieve improvements in ventilatory efficiency, considering they were classified as not being highly physically active prior to the intervention. However, no statistically significant difference in $Eq\dot{V}CO_{2VThan}$ from baseline to post-test was found between the groups. All three groups in the study by Prado et al. had lower $\dot{V}O_{2peak}$ at baseline (group one: 15.0±0.4 $mL \cdot kg^{-1} \cdot min^{-1}$, group two: 20.2±0.2 $mL \cdot kg^{-1} \cdot min^{-1}$, group three: 27.4±0.5 $mL \cdot kg^{-1} \cdot min^{-1}$) compared to the participants in the intervention (35.4±7.7 $mL \cdot kg^{-1} \cdot min^{-1}$) and control group (32.6±8 $mL \cdot kg^{-1} \cdot min^{-1}$) in the present study. Hence, the participants in the present study appear to be more physically active than initially classified. These arguments further support the speculation that lack of statistically significant difference in $Eq\dot{V}CO_{2Vthan}$ between the respective groups in the present study may be explained by relatively healthy participants with initially high aerobic fitness.

As mentioned, Guazzi et al. (16) and Gademan et al. (20) reported decreased $\dot{V}_E/\dot{V}CO_2$ slope following exercise intervention and both studies interventions did not consist of high intensity interval training, which is in contrast to Cardozo et al. (19) and the present study. In addition, both Guazzi et al. and Gademan et al. had one group who exercised, and one non-exercise control group (16, 20). In contrast, the present study´s control group performed individual exercise according to the NorEx protocol during the intervention period, which could lead to less differences in amount of exercise performed between groups. Thus, potentially explaining the discrepancies in effect of exercise on ventilatory efficiency between the present study and previous research. However, there was a statistically significant mean difference in $\dot{V}O_{2peak}$ after 12 weeks in the present study between the intervention group and control group ($p = .04$). Hence, indicating that the participants in the intervention group improved $\dot{V}O_{2peak}$ ($p = .053$), whereas the control group decreased $\dot{V}O_{2peak}$ ($p = .36$).

Age does not appear to be a factor relating to the discrepancies in findings between the three mentioned studies. Guazzi et al. had participants with a mean age of 52±5 years and 54±4 years, while Gademan et al. had participants with a mean age of 60±9 years and 63±10 years in each group (16, 20). Cardozo et al. (19) included participants with a mean age of 64±12 years, 62±12 years and 56±12 years, whereas the present study had mean age 60.9±9.1 years and 67.6±7.4 years in the intervention and control group, respectively. Nevertheless, the control group in the present study had the oldest mean age and may be an explanation for their lack of improvement in $Eq\dot{V}CO_{2Vthan}$. The present study and Cardozo et al. (19), who found no difference in ventilatory efficiency between the two groups after intervention, had similar distribution of sexes. The intervention group in the present study had 50% male participants, control group had 75% male participants, whereas Cardozo et al. three groups had 76%, 66% and 63% male participants (19). In contrast, Guazzi et al. included only male participants, while Gademan et al. included 95% and 92% male participants in the two groups, and these two studies found a significant difference in ventilatory efficiency following an exercise intervention (16, 20). Thus, one may speculate that sex might be a contributing factor in the effect of exercise on ventilatory efficiency, and potentially explain the differing findings.

The possible physiological mechanisms involved in ventilatory efficiency and its response to exercise training in participants with a history of MI are beyond the scope of the present study. However, it is suggested by previous research that ventilatory inefficiency in patients with CAD may be related to high ventilation-perfusion mismatching and high CO_2 chemosensitivity (14, 15, 35). End-tidal CO_2 pressure ($PeTCO_2$) is a non-invasive index that is considered to be a good indicator for evaluating the ventilation-perfusion relationship (36). A negative association between $PeTCO_2$ and $\dot{V}_E/\dot{V}CO_2$ at V_{Than} has been found in patients with CAD after 12 weeks of continuous exercise and interval exercise training (36), which may reflect an improvement in cardiac output in response to physical training via decreased ventilation-perfusion mismatch (37). Meanwhile, Tomita et al. found a correlation between $\dot{V}_E/\dot{V}CO_2$ attenuation after training with a reduction in CO_2 chemosensitivity in patients with CAD (35). Respiratory chemosensitivity is defined as the brain`s ability to detect changes in CO_2 and regulate its levels by altering physiological systems within tightly controlled parameters (38). This correlation suggest that exercise training may reduce elevated $\dot{V}_E/\dot{V}CO_2$ slope, at least partially, by reducing CO2 chemosensitivity (35).

Considering the former research on the field of ventilatory efficiency and its response to exercise, the results appear mixed and non-conclusive. The present study found no significant difference in ventilatory efficiency between the two groups, but the mean difference suggests a possible trend. Considering the small sample size, in addition to a rather short intervention period, there is a possibility that presented results under-estimate the true difference in effect. Additional information regarding all participants, as for example medical conditions such as chronic obstructive pulmonary disease, long-COVID, injuries etc., was not accounted for. Such information could have further enlightened the findings, and possibly provided explanations for the discrepancies between the present study and previous research.

Secondary Outcomes: Ventilatory Efficiency ($Eq\dot{V}O_{2VThan}$, $Eq\dot{V}CO_{2peak}$ and $Eq\dot{V}O_{2peak}$)

The present study found no difference in $Eq\dot{V}O_{2VThan}$ between the intervention group and control group after the intervention period ($p = .373$). The majority of previous research focuses on $Eq\dot{V}CO_{2VThan}$ rather than $Eq\dot{V}O_{2VThan}$ (6, 7, 11, 14-16, 19, 20). The $\dot{V}_E/\dot{V}CO_2$ relationship follows a general linear pattern which allows for a slope calculation, while the relationship between $\dot{V}_E$ and $\dot{V}O_2$ does not follow a similar pattern (39). Thus, the $\dot{V}_E/\dot{V}O_2$ relationship has historically been expressed as a peak exercise ratio (39).

No difference between the intervention group and control group was found in neither $Eq\dot{V}CO_{2peak}$ ($p = .259$) or $Eq\dot{V}O_{2peak}$ ($p = .425$). Previous research by Mejhert et al. found $Eq\dot{V}CO_{2peak}$ to be the strongest predictor of mortality in heart failure (40). In addition, Arena et al. have demonstrated that $Eq\dot{V}O_{2peak}$ is a strong univariate predictor of major adverse events in heart failure (39). However, at peak exercise participants typically hyperventilate secondarily to excessive metabolic acidosis. Thus, ventilatory efficiency at $\dot{V}O_{2peak}$ incorporates the hyperventilation response to late-exercise acidosis. Therefore, $Eq\dot{V}CO_{2peak}$ and $Eq\dot{V}O_{2peak}$ are considered a poor index of ventilatory efficiency in individuals who can exercise above the anaerobic threshold and should be used with caution (6, 7).

Ventilatory Thresholds (V_{Than}) and Cardiorespiratory Fitness ($\dot{V}O_{2peak}$)

The present study found no significant mean difference in change of V_{Than} between the intervention and control group ($p = .129$). However, previous research shows that supervised aerobic exercise initiated early after acute MI resulted in improvements shown by increased V_{Than} (37). Hence, the result of the present study is not in line with previous research. Nevertheless, the precise definitions of $\dot{V}O_2$ at V_{Than} have uncertainties, and even skilled individuals from highly experienced laboratories may provide different values (17).

The mean difference between the participants in the intervention group and control group was statistically significant for both $\dot{V}O_{2peak}$ measured in $mL \cdot kg^{-1} \cdot min^{-1}$ ($p = .04$) and l/min ($p = .029$). The participants in the intervention group improved on average their $\dot{V}O_{2peak}$ ($p = .053$) whereas the control group decreased ($p = .36$). These results are in line with previous research reporting aerobic interval training to be effective in increasing $\dot{V}O_{2peak}$ in patients with a history of MI (23). The reduction in $\dot{V}O_{2peak}$ within the control group indicate that the participants, carrying out the original NorEx intervention, were not exercising adequately in order to maintain or enhance their CRF. Further, the results from the present study could indicate that the home-based peer-supported group exercise intervention led to higher adherence to exercise.

Exercise Adherence: Pros and Cons of Home-Based Peer-Supported Group Exercise

The present study found high adherence rate among participants with complete data in the intervention group, with an average attendance of 79% for each participant. Hence, indicating that home-based peer-instructed group exercise are feasible. Home-based cardiac rehabilitation programs have been increasingly introduced to widen access and participation to cardiac rehabilitation in patients with CAD (41). A review by Anderson et al. found no definite evidence of an important difference in the cost of providing home-based programs in comparison to center-based programs in patients with heart disease, with a possible reason being that healthcare personnel can be a major cost driver (26). On the other hand, the home-based peer-supported group exercise intervention in the present study does not require major resources with regard to healthcare personnel. Therefore, it might be more cost-effective in comparison to center-based programs.

The present study suggests that the presence of healthcare personnel is not necessary for each session, since results indicate that adherence rate is high regardless. Considering solely the sessions study leaders were present, the average number of participants per session was 8.5±2.0, whereas it was 5.9±1.2 participants at sessions without study leaders present. The presented attendance rates might indicate that the presence of study leaders led to higher attendance. However, study leaders were present for the first four sessions which had quite high attendance (9.8±1.1 participants), whereas the attendance for the remaining 20 sessions which study leaders sporadically attended were lower (6.7±1.8 participants). Thus, one may speculate that attendance was high initially due to onset motivation while only those adequately motivated continued to attend, regardless of study leaders' presence. Research indicates that the lowest rates of adherence among patients with ischemic heart disease in cardiac rehabilitation were observed in the last stage of the exercise program (42), which is in line with the present study´s finding of lower attendance after the initial four sessions.

Social influences have been shown as one of the major motivators for both making and maintaining PA, and social support and companionship are identified as powerful facilitators, following a MI (27, 28). Being able to share PA stories and seek reassurance from other survivors of MI were also highly praised (27). Therefore, the intervention in the present study aimed to create an arena where the participants could experience social support, build companionship, and share experiences. However, despite research stating social influences and companionship as key facilitators, there is also research reporting conflicting results. Beswick et al. found that one explanation patients with CVD provide for not accepting invitation to cardiac rehabilitation are reluctance to take part in group-based classes (43). This discrepancy probably reflects each individuals' preferences in regard to performing exercise (44). Thus, the intervention in the present study will not fit the preferences for all survivors of MI and might explain the high number of drop-outs in the intervention group (50%).

Research has shown that a common reason for patients with ischemic heart disease dropping out partially or completely from cardiac rehabilitation is inadequate physical training programs (too low/high intensity) given the patient´s physical condition (42). The six drop-outs from the intervention group in the present study had higher $\dot{V}O_{2peak}$ at baseline compared to the six participants completing the intervention (38.1±3.9 $mL \cdot kg^{-1} \cdot min^{-1}$ vs. 35.44±7.7 $mL \cdot kg^{-1} \cdot min^{-1}$). One might speculate that the participants who dropped out of the intervention had higher aerobic fitness compared to those with complete data, thus not considering participation in peer-supported group exercise training necessary. However, all drop-outs communicated medical conditions as their explanation for dropping out which discard previous arguments, assuming true explanations were communicated.

Difficulty with regularly attending sessions at their local hospital, inconvenient transportation, and parking problems, are frequently cited as barriers to attending center-based cardiac rehabilitation in survivors of MI (43, 45). The participants in the present study decided which days, time, and location for the sessions in the intervention, which can reduce the experience of the barriers mentioned above. In addition, this level of co-determination can strengthen their sense of self-determination, autonomy and ownership to the exercise intervention (46).

Goal setting is found to be motivating and helpful in survivors of MI (27), which is why the present study´s participants in the intervention group were asked to write down individual goals. Considering an average attendance of 79% for each participant over the three months with exercise sessions twice a week, despite study leaders not being present each session, it could appear that the participants perceived the exercise program and goal setting as valuable.

Figure 4 displays attendance and change in $Eq\dot{V}CO_{2VThan}$ for each participant in the intervention group with complete data. There is no apparent trend that those with highest attendance had larger enhancement in $Eq\dot{V}CO_{2VThan}$. Objective measurement of exercise intensity during the exercise sessions are lacking in the present study. Therefore, it is not possible to document the participants' exercise efforts which limits further investigation of the relationship between exercise intensity and change in $Eq\dot{V}CO_{2VThan}$.

The exercise sessions in the present study´s intervention consisted of 4x4 high intensity intervals, which is found more efficient than continuous training at low- to moderate intensity in improving cardiac output, aerobic capacity, and cardiovascular risk profile in patients with CAD (25). A study reported that high intensity decreased adherence and resulted in the completion of less exercise compared to moderate intensity in healthy but sedentary people (47). However, Aamot et al. found that exercise performance was per protocol and exercise attendance was high in the group which completed 4x4 high intensity interval training in patients with CAD (25). These results are in line with the present study´s findings of a high attendance rate in the intervention group performing 4x4 high intensity intervals. The feasibility of high intensity interval training is further supported by the collective choice made by the participants of only performing 4x4 high intensity interval training for the entire intervention.

Strengths and Limitations

The present study is a randomized controlled trial, which is the gold standard for studying causal relationships. Randomization has major advantages, as it eliminates selection bias and allows the use of probability theory to express the probability that any difference in outcome between the groups merely reflects chance. The outcomes are objectively measured, with the use of the cardiopulmonary exercise testing.

The present study should be interpreted within the context of its limitations. Firstly, as an attempt to avoid the Hawthorne effect, the participants were randomized to each group before receiving invitation to baseline testing. Thus, the control group was not informed about post-testing until the end of the 12 weeks. The chosen form of randomization could account for differences identified between the two groups. At baseline, participants in the intervention group were on average younger (60.8±9.1 years vs. 67.6±7.4 years), had lower body mass (74.8±9.3 kg vs. 82.4±14.3 kg), and a higher $\dot{V}O_{2peak}$ (35.4±7.7 $mL \cdot kg^{-1} \cdot min^{-1}$ vs. 32.6±8 $mL \cdot kg^{-1} \cdot min^{-1}$) compared to the control group. Thus, possibly indicating that the intervention group on average had higher CRF and PA-level than the control group. The differences between groups might be explained by the phenomenon that the most exercise-motivated participants tend to sign up for participation in exercise trials (25). However, the present study targeted participants with initially lower levels of PA, meaning highly physically active participants were excluded. One may speculate that a misclassification bias occurred.

Second, due to issues with losing participants to follow-up, the present study was under-powered for the primary and secondary outcomes, which makes it difficult to distinguish between a real effect and random variation. In addition, there are almost twice as many participants in the control group as in the intervention group, and uneven distribution of sexes. There are only two female participants in each group. Therefore, results have to be carefully interpreted in order to not make undue claims about an effect (48). Since the present study was not adequately powered, it should serve to stimulate a larger randomized controlled trial.

Third, the study leaders were not blinded, resulting in another possible limitation and bias. The study leaders conducted all testing, contact and follow-up throughout the intervention period. Not blinding the study leaders could influence how the testing occurred. For example, the participants in the intervention group could unconsciously receive extra cheering on during testing, to achieve larger increase in CRF. The intervention group had higher RER at $\dot{V}O_{2peak}$ at both baseline testing (1.14±0.67 vs. 1.06±0.07) and post-testing (1.13±0.04 vs. 1.06±0.05) compared to the control group, indicating higher effort among the intervention group. However, the main outcome measure was $Eq\dot{V}CO_{2VThan}$ which is measured at submaximal effort. Further, it was not feasible to have blinded test-personnel due to the capacity and restrictions of the study. Lastly, there were some differences in familiarization with testing, since some participants included in both groups in the present study had conducted cardiopulmonary exercise testing prior during their participation in NorEx.

Conclusion

The intervention group did not improve ventilatory efficiency at V_{Than} and RCP as hypothesized. However, results supported the hypothesis regarding $\dot{V}O_{2peak}$, which was significantly higher among the intervention group after 12 weeks. The present randomized controlled trial has shown a possible trend, though not statistically significant, that home-based peer-supported group exercise might enhance ventilatory efficiency among post-MI patients, in comparison to individually performed exercise. In the future, larger confirmatory studies should investigate this further.

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