Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

Alexander Robert Gran Svenningsen

Cardiorespiratory Reference Data in Norwegian Post-Myocardial Infarction Patients

A cross-sectional substudy of the Norwegian Trial of Physical Exercise After Myocardial Infarction (NorEx)

Master's thesis in Physical Activity and Health
Supervisor: Ulrik Wisløff
Co-supervisor: Arnt Erik Tjønna & Henrik Loe
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Gran Svenningsen AR (2021)

Aim: Establish reference values and non-exercise prediction models for key cardiorespiratory variables in Norwegian non-institutionalized men and women (18-79 years), with a history of myocardial infarction (MI)

NorEx

The Norwegian Trial of Physical Exercise After Myocardial Infarction

n=18, 63.7±9.4 years

- Peak ventilation ($\dot{V}_{Epeak}$) and peak tidal volume (V_{Tpeak}) were similar below 65- and above 65 years
- Women had 10% higher ventilatory efficiency (lower $Eq\dot{V}CO_{2VThan}$) than men, irrespective of age. In fact, comparable to healthy counterparts
- 32% lower cardiorespiratory fitness (CRF), 37% lower V_{Epeak}, and 32% lower V_{Tpeak} than men

- **Attenuated CRF, $\dot{V}_{Epeak}$ and V_{Tpeak} compared to healthy Norwegians**
- **Higher CRF, $\dot{V}_{Epeak}$ and V_{Tpeak} than infarction patients and even healthy individuals in other countries**

n=52, 64.9±8.5 years

- 18% lower $\dot{V}_{Epeak}$ and V_{Tpeak} in men above 65 years of age, which can be seen as a normal consequence of ageing
- Reduced ventilatory efficiency was associated with increased age, and in general it was 8-11% lower compared to healthy peers
- Percentage of peak oxygen uptake at ventilatory anaerobic threshold was 5% higher above 65 years in men only

Non-Exercise Prediction Equations (men=0, women=1)	R^2	SEE
$\dot{V}_{Epeak}$ ($L\,min^{-1}$) = -49.627 – (1.156 x age) – (22.391 x sex) + (1.27 x height)	0.53	19.94
V_{Tpeak} (L) = 0.955 – (0.020 x age) – (0.580 x sex) + (0.014 x height)	0.51	0.39
$Eq\dot{V}CO_{2VThan}$ = 6.202 + (0.152 x age) – (1.422 x sex) + (0.91 x height)	0.24	3.41

Conclusion: First reference material of its kind, establishing normative values for-, associations between- and non-exercise prediction models for key cardiorespiratory variables in Norwegian MI patients

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My co-supervisors, Arnt Erik Tjønna and Henrik Loe, also deserve praise for all the essential feedback and support they have provided during the writing process. Furthermore, this would not have been possible without my fellow student, Daniel Leven Gjerdset. I am truly grateful for how well we cooperated and what we were able to accomplish in the lab. Lastly, we received extensive instruction and training in the lab by Thomas Fremo, and I am very thankful that he was always available and willing to lend a hand throughout our data collection.

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ABBREVIATIONS

BMI	Body mass index
CHD	Coronary heart disease
CPET	Cardiopulmonary exercise test
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
f_B	Breathing frequency
f_C	Cardiac frequency
MI	Myocardial infarction
RER	Respiratory exchange ratio
R^2	Coefficient of determination (Variance explained)
RCP	Respiratory compensation point
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SD	Standard deviation
SEE	Standard error of the estimate
$\dot{V}_E$	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)
$\dot{V}O_{2max}$	Maximal oxygen uptake
$\dot{V}O_{2peak}$	Peak oxygen uptake
V_T	Tidal volume
V_{Than}	Ventilatory anaerobic threshold

DEFINITIONS

Cardiorespiratory Fitness (CRF):
The integrated ability to transport oxygen from the atmosphere to the mitochondria to perform physical work. Evidently, CRF is directly related to the integrated functions of numerous systems, and it is thus considered a reflection of total body health (6).

Cardiopulmonary Exercise Test (CPET):
Exercise testing with the addition of ventilatory gas exchange measurements, providing a wide array of unique and clinically useful incremental information (10).

Maximal- ($\dot{V}O_{2max}$) and Peak Oxygen Uptake ($\dot{V}O_{2peak}$):
$\dot{V}O_{2max}$ is a measure of the maximal ability, or highest rate at which oxygen can be transported by the cardiovascular and respiratory system from ambient air to mitochondria, and utilized by the tissues during dynamic work with large muscle mass (17). Specific criteria should be met, such as observation of a stable plateau in $\dot{V}O_2$ despite increased workload, in combination with respiratory exchange ratio >1.05 (11). $\dot{V}O_{2peak}$ is the highest measured oxygen uptake, not necessarily fulfilling all criteria for $\dot{V}O_{2max}$. $\dot{V}O_{2peak}/\dot{V}O_{2max}$ are the most common measure(s) of CRF.

Respiratory Compensation Point (RCP):
The point where ventilation increases faster relative to $\dot{V}CO_2$, thus marking the onset of hyperventilation (35).

Ventilatory Anaerobic Threshold (V_{Than}):
Ventilatory anaerobic threshold is thought to be a reflection of anaerobic threshold, assessed by ventilatory expired gas. Anaerobic threshold represents the work load where production and elimination of lactic acid are at an equilibrium, while V_{Than} can be defined as the beginning of excess CO_2 output generated from buffering of H^+, as a consequence of transitioning from aerobic to anaerobic metabolism (36).

Ventilatory Efficiency:
Defined by the relationship of the liters of ventilation required to consume a liter of oxygen or eliminate a liter of carbon-dioxide (36).

ABSTRACT

Purpose: To establish objectively measured reference values and non-exercise prediction models for key cardiorespiratory variables in Norwegian non-institutionalized men and women (18-79 years), with a history of myocardial infarction (MI) within the time period 2013-2020.

Methods: In total, 70 (18 women) participants were randomly selected from the ongoing Norwegian Trial of Physical Exercise After Myocardial Infarction and underwent cardiopulmonary exercise testing, using an individualized graded protocol while walking or running on a treadmill. Sub-maximal and peak values for key cardiorespiratory variables were measured using the MetaLyzer II (Cortex Biophysik GmBh, Leipzig, Germany) ergospirometry system for mixing chamber gas analysis.

Results: Mean age was 64.9±8.5 and 63.7±9.4 years, body mass index 28.2±3.6 and 27.6±5.4 and $\dot{V}O_{2peak}$ ($mL \cdot kg \cdot min^{-1}$) 31.61±7.97 and 25.66±6.1 for men and women, respectively. Men aged <65 years had the highest peak minute ventilation (112.3±27.3 $L \cdot min^{-1}$) and -tidal volume (2.67±0.45 L), with 18% (p=0.004) and 17% (p<0.001) lower values, respectively, in men aged >65 years. Peak ventilation (65.1±16.2 $L \cdot min^{-1}$) and tidal volume (1.68±0.41 L) were lower compared to men, but similar in both age groups among women. Ventilatory anaerobic threshold (V_{Than}) and respiratory compensation point were observed at approximately 73% and 90% of peak oxygen uptake ($\dot{V}O_{2peak)}$ for both sexes. Men >65 years had 5% (p<0.001) higher V_{Than} ($\%\dot{V}O_{2peak}$) than men <65 years. No such difference was observed among women. The ventilatory equivalent for CO_2 at V_{Than} ($Eq\dot{V}CO_{2VThan}$) in men <65 years (30.5±2.9) was significantly lower compared to peers >65 years (34.3±3.7), indicating 11% (p<0.001) better ventilatory efficiency in the youngest age group. $Eq\dot{V}CO_{2VThan}$ in women (29.6±2.8 vs 29.4±3.4) was similar for those aged above/below 65 years. Non-exercise prediction models showed ±23.8%, ±25%, ±24.2% ±18.8%, ±11% and ±11.2% accuracy in predicting $\dot{V}_{Epeak}$, $\dot{V}CO_{2peak}$, V_{Than}, V_{Tpeak}, $Eq\dot{V}CO_{2VThan}$ and $Eq\dot{V}O_{2VThan}$, respectively.

Conclusions: This is the first reference material of its kind, establishing normative values for-, associations between- and prediction models for key cardiorespiratory variables in a specific Norwegian MI population.

ABSTRAKT

Hensikt: Etablere objektivt målte referanseverdier med tilhørende prediksjonsmodeller for kardiorespiratoriske variabler blant norske ikke-institusjonaliserte menn og kvinner (18-79 år), som gjennomgikk hjerteinfarkt i perioden 2013-2020.

Metode: Totalt 70 (18 kvinner) deltakere ble randomisert fra den pågående studien *Norwegian Trial of Physical Exercise After Myocardial Infarction,* til å gjennomføre en kardiopulmonal belastningstest med individualisert gradvis protokoll på tredemølle. Kardiorespiratoriske variabler av betydelighet ble målt både ved submaksimal og maksimal belastning, ved bruk av MetaLyzer II (Cortex Biophysik GmBh, Leipzig, Germany) for gassanalyse med miksekammer.

Resultater: Gjennomsnittlig alder var 64.9±8.5 og 63.7±9.4 år, kroppsmasseindeks 28.2±3.6 og 27.6±5.4 og $\dot{V}O_{2peak}$ ($mL \cdot kg \cdot min^{-1}$) 31.61±7.97 og 25.66±6.1 blant henholdsvis menn og kvinner. Høyeste minuttventilasjon (112.3±27.3 $L \cdot min^{-1}$) og tidalvolum (2.67±0.45 L) ble målt hos menn <65 år, der det ble observert henholdsvis 18% (p=0.004) og 17% (p<0.001) lavere verdier for menn >65 år. Blant kvinner var både minuttventilasjon (65.1±16.2 $L \cdot min^{-1}$) og tidalvolum (1.68±0.41 L) tilsvarende på tvers av aldersgruppene. Ventilatorisk anaerob terskel (V_{Than}) og respiratorisk kompensasjonspunkt ble observert ved 73% og 90% av høyeste målte oksygenopptak ($\dot{V}O_{2peak}$) blant begge kjønn. Menn over 65 år hadde 5% (p<0.001) høyere V_{Than} ($\%\dot{V}O_{2peak}$) enn den yngre gruppen, mens det ikke ble observert en forskjell mellom kvinnelige aldersgrupper. Ventilatorisk ekvivalent for CO_2 ved V_{Than} ($Eq\dot{V}CO_{2VThan}$) blant menn <65 år (30.5±2.9) var signifikant lavere enn menn >65 år (34.3±3.7), hvilket indikerer 11% (p<0.001) bedre ventilatorisk effektivitet hos den yngste gruppen. Derimot var $Eq\dot{V}CO_{2VThan}$ forholdsvis likt for kvinner over- og under 65 år (29.6±2.8 vs 29.4±3.4). Prediksjonsmodellene viste ±23.8%, ±25%, ±24.2% ±18.8%, ±11% og ±11.2% presisjon for prediksjon av henholdsvis $\dot{V}_{Epeak}$, $\dot{V}CO_{2peak}$, V_{Than}, V_{Tpeak}, $Eq\dot{V}CO_{2VThan}$ og $Eq\dot{V}O_{2VThan}$.

Konklusjoner: Dette er det første referansematerialet som presenterer normalverdier for-, assosiasjoner mellom- og prediksjonsmodeller for kardiorespiratoriske variabler blant norske infarktpasienter.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, exceeding 17 million deaths annually (1), with coronary heart disease (CHD) being the most common form. CHD can lead to acute myocardial infarction (MI), accounting for nearly half of the total annual deaths from CVDs. Inevitably, CVDs impose a massive societal and economic burden, with annual treatment costs of €210 billion in the EU (2) and $219.6 billion in the US (3). Cardiorespiratory fitness (CRF) predicts survival in CHD patients (4), and direct measurement of CRF in terms of peak oxygen uptake ($\dot{V}O_{2peak}$) has considerable influence on prognosis after MI (5,6). Recently, ventilatory efficiency ($\dot{V}_E/\dot{V}CO_2$) has also been suggested as an even more powerful predictor of mortality and hospitalization than CRF in heart failure patients and likely other CVD populations (7). Given the attenuated CRF often associated with CVD, exercise after MI is of great importance and each 1 MET (equivalent to 3.5 mL·kg·min^{-1} $\dot{V}O_2$) increase in CRF is associated with an 8-10% reduction in risk of early mortality (8). Since individuals with CVD are typically excluded in studies aiming to present normative values for CRF (9–13), the available data on cardiorespiratory variables in MI patients is insufficient. Thus, there does not exist reference values for key cardiorespiratory variables in MI patients, which can serve an important purpose of predicting prognosis and in designing individualized rehabilitation and secondary prevention programs required to improve CRF (5).

Traditional Cardiopulmonary Exercise Testing of MI Patients

The gold standard for measuring CRF is to test $\dot{V}O_{2peak}$ using cardiopulmonary exercise testing (CPET) (14,15). Measuring exercise capacity has undergone a paradigm shift from expressing CRF as an estimated value based on submaximal or maximal work rate achieved on primarily a cycle ergometer, to direct measurement of maximal or peak CRF preferably conducting CPET on a treadmill (14). Estimation of $\dot{V}O_{2peak}$ has proven to be an inaccurate method (16,17). Therefore, direct measurement of CRF before initiating an exercise program is important to provide optimal exercise prescription. Direct measurement is not only more precise compared to estimation, it offers additional information important for assessing CVD diagnosis, prognosis and risk stratification, made possible by comparing results to established reference values (5,18).The change of preferred mode of exercise is mainly justified by the argument that measurements on a cycle ergometer consistently display $\dot{V}O_{2peak}$ values 6-15% lower than on a treadmill (19,20). Regardless of a recent AHA statement recommending routinely assessment of CRF as a clinical vital sign, it still remains an underutilized clinical tool (6,21).

Exercise Testing of MI Patients Beyond $\dot{V}O_{2peak}$

By evolving from measuring only $\dot{V}O_{2peak}$, to incorporating the full extent of CPET, conventional exercise testing is combined with ventilatory expired gas analysis which allows assessment of cardiorespiratory function through additional prognostic parameters, such as exhaled carbon dioxide ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) (6). Additionally, CPET determines $\dot{V}_E/\dot{V}CO_2$ slope, a key indicator of ventilatory efficiency, which is abnormally elevated in most patients with CVD (6,7). Several randomized controlled trials (RCTs) have conducted CPET and presented $\dot{V}O_{2peak}$ and ventilatory anaerobic threshold (V_{Than}) values for MI patients (22–30); however, many of them have tested on cycle ergometers (28–31) and other key cardiorespiratory variables such as $\dot{V}_E/\dot{V}CO_2$, $\dot{V}_E$, tidal volume (V_T) and breathing frequency (f_B), have seldomly been paid any attention. Aforementioned studies observed $\dot{V}_{Epeak}$ ranging from 42.3-60.5 L·min^{-1}

(27,30), $\dot{V}_E/\dot{V}CO_2$ of 27-29 (22,24,27) and V_{Than} at 57-75% of $\dot{V}O_{2peak}$ (22,25,27,28,30) in MI patients. Although the Generation 100 Study (32) previously published comprehensive cardiorespiratory reference data from a general CVD population, only 19 included subjects had a history of MI.

There is a need for establishing reference values and future studies to evaluate the utility of the many key cardiorespiratory variables obtained from CPET in MI patients. Therefore, the aim of this study was to establish objectively measured cardiorespiratory reference values and non-exercise prediction models with focus upon CPET-parameters beyond $\dot{V}O_{2peak}$ for Norwegian non-institutionalized men and women (18-79 years), who suffered a MI within the time period 2013-2020.

METHODS

The Norwegian Trial of Physical Exercise After Myocardial Infarction (NorEx)
So far, no RCT has convincingly shown that physical exercise reduces the risk of MI, and secondary prevention trials in MI patients have often been of insufficient size or quality to provide conclusive evidence on morbidity and mortality. Therefore, the primary objective of NorEx is to provide causative evidence on long-term effects of physical activity, by determining the efficacy of 3.5 years of supervised physical exercise on mortality and cardiovascular morbidity in patients with MI. Within the planned study period from 2020-2025, substudies will examine numerous parameters, one of them being the effects of supervised physical exercise on objectively measured CRF by CPET, and the recruitment process is displayed in Figure 1.

Participants
The current study is a descriptive cross-sectional substudy as a part of NorEx. Due to the ongoing pandemic, initiation of data collection was postponed at the other test centers, which reduced the total sample size from n=300 to n=70. Included participants consist of non-institutionalized Norwegian men (n=52, 64.9±8.5 years) and women (n=18, 63.7±9.4 years), registered as inhabitants of Trøndelag county, whom have been recruited to NorEx and have a history of index myocardial infarction within the time frame 2013-2020.

Other inclusion criteria were: age 18-79 years, minimum three months since MI related hospitalization, having a Norwegian national identification number, ability to communicate in Norwegian and providing signed informed consent. Exclusion criteria were: participation in regular physical activity of more than moderate intensity, known CVD contraindicative of moderate-high intensity physical exercise, inability to exercise owing to non-cardiovascular limitations, life expectancy less than 3.5 years for non-coronary conditions, cognitive impairment compromising compliance with study protocol, alcohol/drug abuse or severe psychiatric disorders.

From September 2020- March 2021, a random independent sample was drawn weekly from the pool of participants who had passed the screening process and were included in NorEx. Subsequently they were contacted and informed that they had been randomly selected to undergo CPET as a part of this substudy. The plan according to the NorEx protocol was to recruit n=70 participants.

Nine individuals declined participation as a consequence of the Covid-19 pandemic, resulting in the randomization of additional participants to achieve the predetermined sample size (Figure 1). Data collection was carried out in Trondheim from November 2020-March 2021, during which all subjects underwent CPET at St. Olav's Hospital, with no further follow up related to the current substudy.

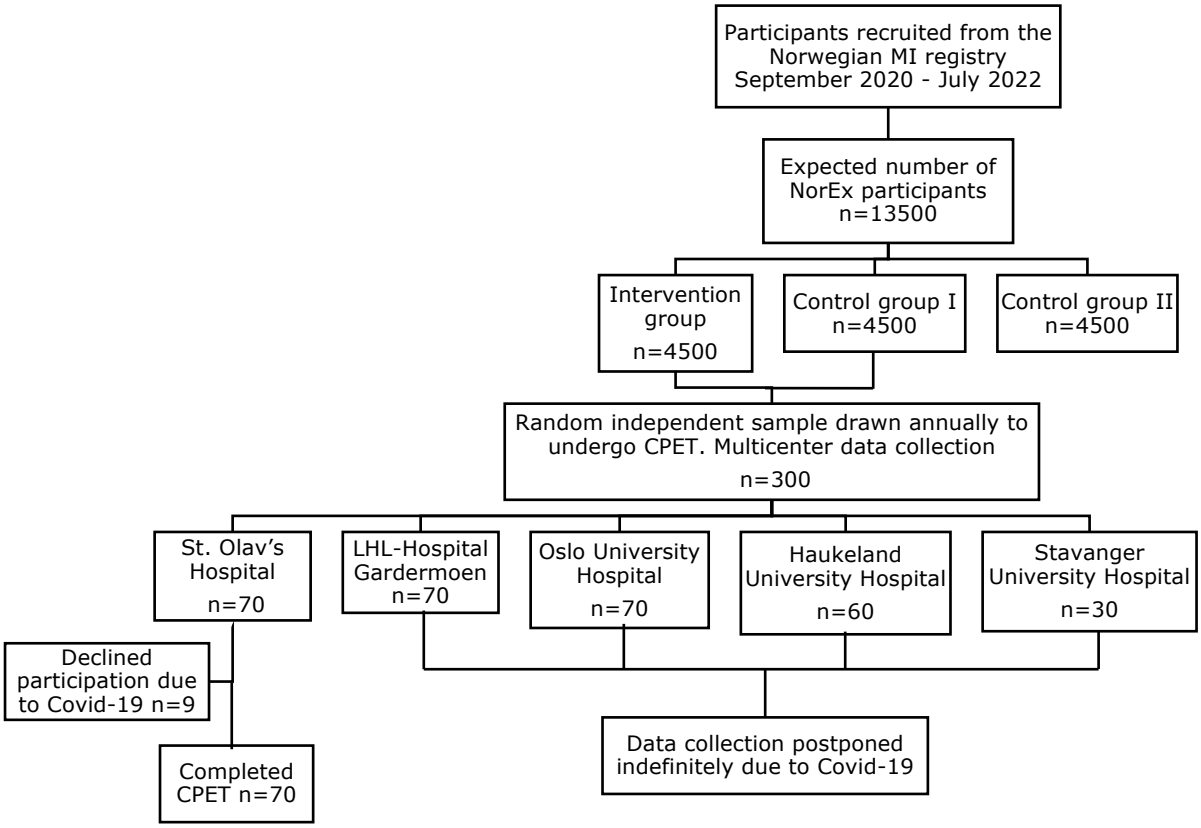

Figure 1: Flow chart describing the recruitment process to NorEx and the current substudy

Measurement of Descriptive Variables

All measurements and tests were performed by two exercise physiology master's students, after completing sufficient supervised training in the lab. Cognitive function was measured using the Montreal Cognitive Assessment test (MoCA); however, the data was mainly collected to be analyzed in a separate substudy and only serves a purpose as descriptive statistics in this study. Height (cm) measurements were completed on a standard medical stadiometer, and body mass (kg) by using a mobile personal weighing scale (Soehnle, Backnang, Germany). Immediately prior to initiating the warm-up protocol, standing blood pressure was measured with a Tango M2 Stress Test Monitor (SunTech Medical, Morrisville, NC, USA), followed by repeated measurement immediately post CPET completion.

Cardiopulmonary Exercise Testing (CPET)
Subjects completed an individualized graded protocol walking/running on a treadmill (Woodway PPS Med, Waukesha, WI, USA) as described in Loe et al. (9), with the exception of one woman who was unable to use the treadmill due to benign paroxysmal positional vertigo and had to be tested on a cycle ergometer instead (Lode B.V. Medical Technology, Groningen, The Netherlands). The treadmill was calibrated prior to the first test to ensure correct speed and inclination, while the ergospirometry systems at the Next Move Core Facility at St. Olav's Hospital have previously been validated against Douglas-bag method and a Metabolic Calibration System (VacuMed, Ventura, CA, USA).

Participants were fitted with a face mask of appropriate size (Hans Rudolph, Germany), linked to the MetaLyzer II (Cortex Biophysik GmBh, Leipzig, Germany) for mixing chamber gas analysis. CPETs were conducted in accordance with AHA's guidelines for exercise testing CVD patients (33), with regards to contraindications and indications for test termination. Concurrent 12-lead electrocardiography (Custo Med GmbH, Ottobrunn, Germany) was applied to monitor cardiac response for indications of test termination, and additional heart rate measurements were made by radio telemetry (Polar S610i, Polar Electro Oy, Kempele, Finland). The MetaLyzer II was calibrated prior to the first test each day, using a standard two-point gas calibration procedure. The calibration included measurements of ambient air and a gas mix of known content (15.03% O_2 and 4.98% CO_2 in N_2, 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. Before each test the ambient room air was measured accompanied by volume calibration, while two-point gas calibration took place every fifth.

Participants had a 10-minute treadmill familiarization phase during warm-up before test commencement, where they received instructions to maintain an intensity corresponding to 11-13 on the Borg Scale for subjective rating of perceived exertion, which ranges from 6-20 (34). Additionally, they were instructed to avoid grabbing the handrails if not absolutely necessary during the entire test. Individualized warm-up workload determined initial speed/angle for the subsequent CPET. Approximately every minute, velocity (1.0 kmh^{-1}) or inclination (2%) was increased (or 10W every 30-s if cycling), based on the participant's physiological response ie. workload was increased if the participant maintained a stable oxygen uptake >30-s. Increased workload was preferably obtained with increased speed and keeping a fixed inclination. If a participant seemed unable to increase speed, the angle was increased instead. Tests were terminated when candidates reached volitional exhaustion (shortness of breath and leg fatigue) or if any of AHA's indications for test termination were observed (33).

$\dot{V}O_{2max}$ was considered achieved if subjects reached a $\dot{V}O_2$ plateau that remained stable despite increased work load (19), i.e. $\dot{V}O_2$ did not increase more than 2 $mL \cdot kg^{-1} \cdot min^{-1}$ and respiratory exchange ratio (RER) ≥1.05. Measurements were done at three different workloads, two submaximal and peak. Level 1: The individual initial workload determined during warm-up, where participants' $\dot{V}O_2$ and heart rate stabilized after 3 minutes. Level 2: Increased treadmill gradient by 2% or speed by 1.0 $km \cdot h^{-1}$, with steady state obtained after 2–3 minutes. Level 3: peak workload, which was reached with volitional exhaustion.

Gas exchange variables were reported as 10s averages. $\dot{V}O_{2peak}$ was calculated as the mean of the three highest consecutive 10-s measurements, then $\dot{V}CO_{2peak}$, $\dot{V}_{Epeak}$, V_{Tpeak} and f_{Bpeak} were determined as the mean of the three corresponding values. Peak ventilatory efficiency was calculated as Eq$\dot{V}O_2$ ($\dot{V}_{Epeak}/\dot{V}O_{2peak}$) and Eq$\dot{V}CO_2$ ($\dot{V}_{Epeak}/\dot{V}CO_{2peak}$). In addition, ventilatory efficiency was calculated at V_{Than} as suggested by Wasserman et al. (35), since ventilation varies least in the range between V_{Than} and RCP. Special emphasis was placed on Eq$\dot{V}CO_{2VThan}$, considering that ventilation is more closely related to expired CO_2 than inspired O_2 and therefore a better measure for ventilatory efficiency (35). Total vertical distance was calculated by multiplying treadmill velocity ($m{\cdot}s^{-1}$) with inclination (%) and time (s), in order to determine total work, which was then divided by time to provide the treadmill workload (Watts) at the three described workloads (Level 1-3) (36).

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

V-slope method was utilized to determine ventilatory anaerobic threshold (V_{Than}: $L{\cdot}min^{-1}$, $\%\dot{V}O_{2peak}$) and respiratory compensation point (RCP: $L{\cdot}min^{-1}$, $\%\dot{V}O_{2peak}$) (37). V_{Than} is the beginning of excess CO_2 output generated from buffering of H^+, as a consequence of transitioning from aerobic to anaerobic metabolism. Detecting V_{Than} involved computerized regression analysis of the slopes of $\dot{V}CO_2$ and $\dot{V}O_2$ plots, the breakpoint where the slopes coincided being the ventilatory anaerobic or lactic acidosis threshold (35). RCP was detected by examining $\dot{V}_E$ vs $\dot{V}CO_2$ plots, since RCP is regarded as the point where $\dot{V}_E$ increases faster relative to $\dot{V}CO_2$, thus marking the onset of hyperventilation (37).

Statistical Analysis

To reduce confounding factors, data were stratified by sex, age and height and presented as arithmetic mean ± standard deviation. Age groups <65 and >65 years were chosen, because 65 was the mean age in the study sample and both sexes were evenly distributed between the two age groups. Additional analysis of data stratified by height (groups per 10cm) was regarded as necessary due to the known influence of stature and weight on respiratory parameters, since lung dimensions and -capacity increase proportionally with height (35). Statistical analyses were performed in SPSS (Statistical Package for Social Science v27, Chicago, IL, USA). QQ-plots and histograms confirmed normally distributed data, resulting in the use of parametric analysis. All tests were two-sided with a significance level of $p<0.05$. Independent-Samples T-tests were used to compare means between sexes, while analysis of variance (Anova) was used to determine differences between age- and height groups. If a significant F-ratio was achieved with Anova, post hoc evaluations were completed using Bonferroni tests. Associations between cardiorespiratory parameters were tested by linear regression and curve linear regression with 95% confidence intervals. To generate non-exercise prediction models, multiple linear regression was used and variables were entered stepwise to evaluate each variable's effect on the outcome, whereby variables that did not considerably improve variance explained (R^2) were removed from the model.

Ethical Statement
NorEx will be carried out according to the Declaration of Helsinki, Vancouver rules for authorship and has been approved by the Regional Committee for Medical Research Ethics (REK 2019/797). Additionally, NorEx is registered in the ClinicalTrials.gov registry (NCT04617639).

RESULTS

Descriptive characteristics of study participants are given in Table 1. In subsequent tables, since 27% of the participants were unable to fulfill the predetermined criteria for $\dot{V}O_{2max}$, the term $\dot{V}O_{2peak}$ has been used instead and corresponding cardiorespiratory variables are referred to as peak values as well.

Table 1. Descriptive Data for Men and Women

	Women (n=18)	Men (n=52)
Age (years)	63.7±9.4	64.9±8.5
Height (cm)	165.9±5.2	179.2±5.7
Body mass (kg)	75.8±14.5	90.5 ± 12.4
BMI ($kg \cdot m^{-2}$)	27.6±5.4	28.2±3.6
SBP (mmHg)	156.5±29.1	150.9±18.4
DBP (mmHg)	91.6±14.7	92.1±10.9
Never smoked/Quit smoking (%)	27.8/55.6	36.5/55.8
Daily smoker/Occasional smoker (%)	11.1/5.6	5.8/1.9
MoCA score	24.8±3.7	25.5±2.8

Data presented as arithmetic mean ± SD. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, MoCA: Montreal Cognitive Assessment. Scoring range MoCA: >25= normal cognitive function, 18-25= mild cognitive impairment, 10-17= moderate cognitive impairment and <10= severe cognitive impairment

Peak Ventilation ($\dot{V}_{Epeak}$), Tidal Volume (V_{Tpeak}) and Breathing Frequency (f_B)
Overall, women had 37% (p<0.001) lower $\dot{V}_{Epeak}$ and 32% (p<0.001) lower V_{Tpeak} compared to men, while there was no significant difference in f_B at submaximal levels or peak workload. The highest overall $\dot{V}_{Epeak}$ (18% higher than men >65 years, p=0.004) and V_{Tpeak} (17% higher than men >65 years, p<0.001) were measured in men <65 years. No significant differences were observed for these parameters between the age groups among women. f_B was similar for both sexes and age groups (Table 2). Stratified by height, $\dot{V}_{Epeak}$, V_{Tpeak} and f_B were not significantly higher for each subsequent 10cm increase in height for neither sex (Table 3).

Table 2. Physiological Cardio-respiratory Variables Stratified by Intensity Levels, Sex and Age Groups

	Level 1 (<V_{Than})		Level 2 (<RCP)		Peak	
	Men	Women	Men	Women	Men	Women
All	(n=52)	(n=18)	(n=52)	(n=18)	(n=52)	(n=18)
Workload (Watts)	39.1±18.4	27.5±12.7	63.1±22.5	41.7±15.7	177.8±52.1	111.9±32.1
f_c (beats·min^{-1})	115±21	115±18	126±22	128±21	158±17	156±20
%$f_c$peak	72.9±10.2	74.1±8.7	79.7 ± 10.6	81.7±8.2	100	100
%$\dot{V}O_{2peak}$	58.4±12.1	62.3±10.5	67.3±13.7	69.5±12.2	100	100
f_B (breaths·min^{-1})	27±6	26±5	29±7	29±5	42±7	39±5
$\dot{V}_E$ (L·min^{-1})	50.3±16.7	32.8±7.1	59.8±20.3	40.6±10.1	102.8±25.2	65.1±16.2
V_T ($\dot{V}_E$·f_B^{-1})	1.86±0.38	1.33±0.33	2.05±0.43	1.42±0.35	2.46±0.45	1.68±0.41
$\dot{V}CO_2$ (L·min^{-1})	1.43±0.49	1.01±0.25	1.73±0.61	1.26±0.35	3.02±0.79	1.94±0.51
$\dot{V}O_2$ (L·min^{-1})	1.64±0.52	1.18±0.29	1.89±0.59	1.32±0.35	2.83±0.71	1.94±0.51
RER (CO_2·$\dot{V}O_2^{-1}$)	0.86±0.04	0.86±0.04	0.90±0.05	0.92±0.05	1.07±0.06	1.08±0.07
BMI (kg·m^{-2})	28.2±3.6	27.6±5.4				
<65 years	(n=27)	(n=10)	(n=27)	(n=10)	(n=27)	(n=10)
Workload (Watts)	45±20.6	27.5±11.3	71.2±25.2	42.2±15.2	198.9±55	109.5±41.9
f_c (beats·min^{-1})	114±22	116±21	125±24	127±26	162±15	156±25
%$f_c$peak	70.5±10.9	74.5±11.3	77.2±11.4	81.5±10.6	100	100
%$\dot{V}O_{2peak}$	57.2±12.5	64.5±12.9	65.5±13.1	68.2±14.8	100	100
f_B (breaths·min^{-1})	27±6	26±5	29±7	29±6	42±7	39±5
$\dot{V}_E$ (L·min^{-1})	52.5±18.6	33.5±8.4	62.3±21.8	40.9±12.1	112.3±27.3	64.8±19.7
V_T ($\dot{V}_E$·f_B^{-1})	1.96±0.42	1.35±0.38	2.18±0.44	1.43±0.44	2.67±0.45	1.69±0.52
$\dot{V}CO_2$ (L·min^{-1})	1.57±0.54	1.06±0.32	1.90±0.65	1.30±0.47	3.44±0.78	2.12±0.76
$\dot{V}O_2$ (L·min^{-1})	1.81±0.57	1.21±0.38	2.08±0.63	1.32±0.47	3.19±0.71	1.99±0.67
RER (CO_2·$\dot{V}O_2^{-1}$)	0.85±0.04	0.87±0.03	0.91±0.05	0.91±0.03	1.08±0.06	1.06±0.07
BMI (kg·m^{-2})	29.1±3.5	28.4±6.9				

Table 2. Cont.

>65 years	(n=25)	(n=8)	(n=25)	(n=8)	(n=25)	(n=8)
Workload (Watts)	32.7±13.2	27.5±15	54.3±15.2	41.1±17.4	155.1±37.9	114.8±14.8
f_c (beats·min^{-1})	116±20	115±15	126±21	129±17	154±18	156±14
%$f_c$peak	75.7±8.7	73.6±4.6	82.3±9.2	82±4.5	100	100
%$\dot{V}O_{2peak}$	59.7±11.8	59.5±5.7	69.3±14.4	71.1±8.6	100	100
f_B (breaths·min^{-1})	27±6	26±6	30±7	29±4	42±6	39±5
$\dot{V}_E$ (L·min^{-1})	47.9±14.4	32±5.4	57.1±18.7	40.4±7.6	92.6±18.1	65.6±11.6
V_T ($\dot{V}_E \cdot f_B^{-1}$)	1.75±0.32	1.29±0.28	1.90±0.39	1.20±0.24	2.23±0.34	1.66±0.24
$\dot{V}CO_2$ (L·min^{-1})	1.25±0.37	0.94±0.11	1.54±0.52	1.22±0.14	2.44±0.47	2.04±0.31
$\dot{V}O_2$ (L·min^{-1})	1.45±0.38	1.11±0.12	1.69±0.50	1.32±0.11	2.44±0.47	1.87±0.21
RER ($CO_2 \cdot \dot{V}O_2^{-1}$)	0.85±0.04	0.85±0.05	0.89±0.05	0.92±0.07	1.05±0.06	1.10±0.06
BMI (kg·m^{-2})	27.2±3.6	26.5±2.8				

Data presented as arithmetic mean ± SD. Level 1: submaximal workload at 11-13 on BORG-scale, Level 2: submaximal workload increased by 2% treadmill gradient or 1 km·h^{-1}, Workload: treadmill exercise load, f_c: cardiac frequency, f_B: breathing frequency, $\dot{V}_E$: minute ventilation, V_T: tidal volume, $\dot{V}CO_2$: expired carbon dioxide, $\dot{V}O_2$: oxygen uptake, RER: respiratory exchange ratio, BMI: body mass index, V_{Than}: ventilatory anaerobic threshold, RCP: respiratory compensation point.

Table 3. Peak Respiratory Variables Stratified by Sex and Height

	Men	Women
150-159 cm		(n=2)
$\dot{V}_E$ (L·min^{-1})		61.6±24.3
V_T ($\dot{V}_E \cdot f_B^{-1}$)		1.43±0.64
f_B (breaths·min^{-1})		44±3
160-169 cm	(n=3)	(n=10)
$\dot{V}_E$ (L·min^{-1})	84.4±10.9	69.1±18.6
V_T ($\dot{V}_E \cdot f_B^{-1}$)	2.21±0.2	1.76±0.45
f_B (1·min^{-1})	38±8	39±5
170-179 cm	(n=22)	(n=6)
$\dot{V}_E$ (L·min^{-1})	99.9±21.5	59.8±9
V_T ($\dot{V}_E \cdot f_B^{-1}$)	2.4±0.47	1.64±0.29
f_B (breaths·min^{-1})	42±7	37±5
180-190 cm	(n=27)	
$\dot{V}_E$ (L·min^{-1})	107.3±28.2	
V_T ($\dot{V}_E \cdot f_B^{-1}$)	2.53±0.45	
f_B (breaths·min^{-1})	42±7	

Data presented as arithmetic mean ± SD. $\dot{V}_E$: ventilation, V_T: tidal volume, fB: breathing frequency.

Carbon Dioxide ($\dot{V}CO_2$) Elimination

As seen in Table 2, women had 31% ($p<0.001$) lower $\dot{V}CO_{2peak}$ compared to men. Men <65 years had 26% ($p<0.001$) higher $\dot{V}CO_{2peak}$ compared to >65 years, while there was a slight but non-significant difference between age groups among women.

Ventilatory Anaerobic Threshold (V_{Than})

In absolute terms V_{Than} was significantly higher in men, but occured at the same percentage of $\dot{V}O_{2peak}$ in men and women (Table 4). We observed 17% ($p=0.002$) higher absolute V_{Than} among the youngest men, although V_{Than} was obtained at a 5% ($p<0.001$) higher percentage of $\dot{V}O_{2peak}$ in men aged >65 years, at 71.9±4.6% and 76.5±4.2%, respectively. No difference was observed between age groups in women.

Respiratory Compensation Point (RCP)

No statistical difference was found in $\%\dot{V}O_{2peak}$ at RCP between sexes or across age groups, appearing at approximately 90% of $\dot{V}O_{2peak}$. The highest RCP ($L \cdot min^{-1}$) was observed in men <65 years, which was 22% ($p<0.001$) lower in men >65 years. No such difference was observed in women (Table 4).

Table 4. Cardiorespiratory Variables Stratified by Sex and Age Groups

	N	$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	$\dot{V}O_{2peak}$ ($mL \cdot kg \cdot min^{-1}$)	V_{Than} ($L \cdot min^{-1}$)	V_{Than} ($\%\dot{V}O_{2peak}$)	RCP ($L \cdot min^{-1}$)	RCP ($\%\dot{V}O_{2peak}$)
All							
Men	52	2.83±0.71	31.61±7.97	2.09±0.49	74.2±4.9	2.55±0.66	90.3±5.3
Women	18	1.94±0.51	25.66±6.1	1.39±0.38	72.1±6.6	1.71±0.44	88.6±6.8
<65 years							
Men	27	3.19±0.71	34.18±8.07	2.29±0.52	71.9±4.6	2.86±0.66	89.7±5.3
Women	10	1.99±0.67	25.61±7.88	1.41±0.49	71.1±6.8	1.73±0.56	87.9±8.4
>65 years							
Men	25	2.44±0.47	28.84±6.99	1.87±0.38	76.5±4.2	2.22±0.47	90.9±5.4
Women	8	1.88±0.21	25.73±3.27	1.38±0.19	73.4±6.4	1.68±0.23	89.5±4.6

Data presented as arithmetic mean ± SD. $\dot{V}O_{2peak}$: peak oxygen uptake, V_{Than}: Ventilatory anaerobic threshold, RCP: respiratory compensation point.

Ventilatory Efficiency at $\dot{V}O_{2peak}$ and at V_{Than}

Higher equivalents were observed in men for all variables ($p<0.001$)(Table 5). Equivalents for oxygen and carbon-dioxide were higher in the >65 years age group for both sexes, but the difference was non-significant in women. $Eq\dot{V}O_{2peak}$ proved similar between age groups of the respective sexes, although 9% ($p=0.010$) higher in men when comparing sexes. $Eq\dot{V}CO_{2peak}$ was on average 11% higher in men than women and was 9% ($p=0.002$) higher for men >65 years. $Eq\dot{V}O_{2VThan}$ and $Eq\dot{V}CO_{2VThan}$ was 8% higher in men, with a respective 10% ($p=0.001$) and 11% ($p<0.001$) higher observed value for men aged >65 years compared to those <65 years of age.

Table 5. Ventilatory Equivalents at Peak Exercise and at Ventilatory Anaerobic Threshold

	Men	Women
<65 years	(n=27)	(n=10)
$Eq\dot{V}O_{2peak}$ ($\dot{V}_{Epeak}\cdot\dot{V}O_{2peak}^{-1}$)	33.4±4.2	30.4±3.9
$Eq\dot{V}CO_{2peak}$ ($\dot{V}_{Epeak}\cdot\dot{V}CO_{2peak}^{-1}$)	30.9±3.2	28.8±3.4
$Eq\dot{V}O_{2VThan}$ ($\dot{V}_{EVThan}\cdot\dot{V}O_{2VThan}^{-1}$)	27.9±2.7	26.5±3.3
$Eq\dot{V}CO_{2VThan}$ ($\dot{V}_{EVThan}\cdot\dot{V}CO_{2VThan}^{-1}$)	30.5±2.9	29.4±3.4
>65 years	(n=25)	(n=8)
$Eq\dot{V}O_{2peak}$ ($\dot{V}_{Epeak}\cdot\dot{V}O_{2peak}^{-1}$)	35.7±4.5	32.2±5.7
$Eq\dot{V}CO_{2peak}$ ($\dot{V}_{Epeak}\cdot\dot{V}CO_{2peak}^{-1}$)	34.1±3.9	29.1±4.2
$Eq\dot{V}O_{2VThan}$ ($\dot{V}_{EVThan}\cdot\dot{V}O_{2VThan}^{-1}$)	30.9±3.2	27.6±3.3
$Eq\dot{V}CO_{2VThan}$ ($\dot{V}_{EVThan}\cdot\dot{V}CO_{2VThan}^{-1}$)	34.3±3.7	29.6±2.8

Data presented as arithmetic mean ± SD. $Eq\dot{V}O_2$ and $Eq\dot{V}CO_2$: ventilatory efficiency

Association Between $Eq\dot{V}CO_{2VThan}$ and Age

Analysis showed a rather weak but significant correlation between age and $Eq\dot{V}CO_{2VThan}$ in men r=0.388 (p=0.004), implying decreased ventilatory efficiency with age (Figure 2). The same association was not observed in women.

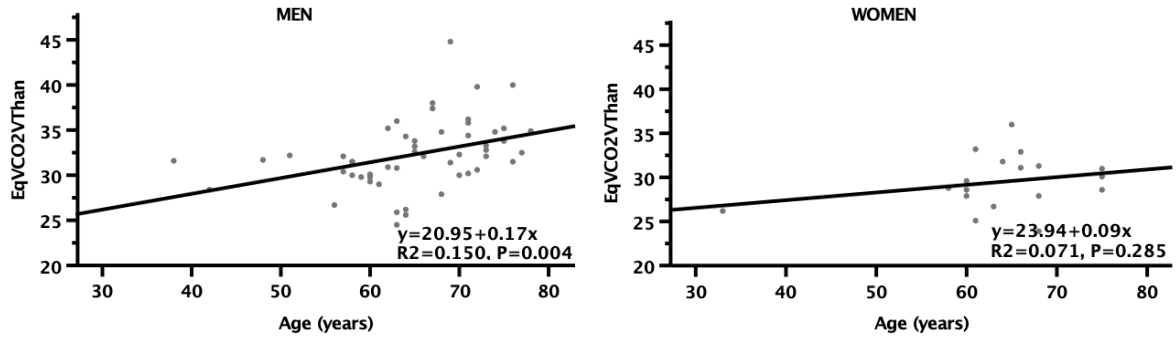

Figure 2: Correlations between $Eq\dot{V}CO_{2VThan}$ (ventilatory efficiency at ventilatory anaerobic threshold) and age groups.

Estimating Key Cardio-Respiratory Variables From Non-Exercise Prediction Models

Non-exercise variables, including age, sex, height and weight were used as independent variables in multiple linear regressions to establish prediction equations for $\dot{V}_{Epeak}$, $\dot{V}CO_{2peak}$, V_T peak, V_{Than}, $Eq\dot{V}CO_{2VThan}$ and $Eq\dot{V}O_{2VThan}$. Weight proved negligible in predicting all of the included key cardiorespiratory variables, resulting in exclusion form the final regression models presented in Table 6. For all models, enter 0 for men and 1 for women with regards to sex.

Table 6. Multiple Linear Regression Models for Predicting Key Cardio-Respiratory Variables From Non-Exercise Variables

Equations	R^2	SEE
$\dot{V}_{Epeak}$ ($L{\cdot}min^{-1}$) = -49.627 – (1.156 x age) – (22.391 x sex) + (1.27 x height)	0.53	19.94
$\dot{V}CO_{2peak}$ ($L{\cdot}min^{-1}$) = 0.207 – (0.045 x age) – (0.565 x sex) + (0.032 x height)	0.49	0.62
V_{Than} ($L{\cdot}min^{-1}$ of $\dot{V}O_2$) = -1.229 – (0.018 x age) – (0.355 x sex) + (0.023 x height)	0.45	0.42
V_{Tpeak} (L) = 0.955 – (0.020 x age) – (0.580 x sex) + (0.014 x height)	0.51	0.39
$Eq\dot{V}CO_{2VThan}$ = 6.202 + (0.152 x age) – (1.422 x sex) + (0.91 x height)	0.24	3.41
$Eq\dot{V}O_{2VThan}$ = 12.24 + (0.113 x age) – (1.575 x sex) + (0.055 x height)	0.19	3.17

$\dot{V}_{Epeak}$: peak ventilation, $\dot{V}CO_2$: peak expiration of carbon dioxide, V_{Than}: ventilatory anaerobic threshold, V_{Tpeak}: peak tidal volume, $Eq\dot{V}CO_{2VThan}$ and $Eq\dot{V}O_{2VThan}$: ventilatory efficiency at ventilatory anaerobic threshold, R^2: coefficient of variation, SEE: standard error of the estimate, Sex: Enter 0 for men and 1 for women

DISCUSSION

This is the first and largest cardiorespiratory reference material on MI patients up to date. The main findings of the present study were 1) Men <65 years had the highest $\dot{V}_{Epeak}$ and V_{Tpeak}, 2) $\dot{V}_{Epeak}$ and V_{Tpeak} were lower compared to men, but similar in both age groups among women, 3) V_{Than} and RCP were observed at approximately 73% and 90% of $\dot{V}O_{2peak}$ for both sexes, 4) Men >65 years had higher V_{Than} (%$\dot{V}O_{2peak}$) than men <65 years, while there was no such difference among women, 5) $Eq\dot{V}CO_{2VThan}$ in men <65 years was lower compared to peers >65 years, indicating better ventilatory efficiency in the younger group, and 6) $Eq\dot{V}CO_{2VThan}$ in women was similar for those aged above/below 65 years.

Sex and Age Group Differences in Peak Ventilation ($\dot{V}_{Epeak}$), Tidal Volume (V_{Tpeak}) and Breathing Frequency (f_B)

Women had lower $\dot{V}_{Epeak}$ and V_{Tpeak} than men, as expected since there are known sex differences related to lung size and dynamic lung function, even after taking stature into account (38). The findings were also in agreement with other reference materials on cardiorespiratory function among healthy Norwegian men and women (9,32). Whereas previous studies have shown higher fB in men, there was not a statistically significant difference in this study. This could be a consequence of the low sample size in our study, impacting statistical strength. Findings will be conclusive when the reference material includes the planned 300 participants.

Furthermore, results indicate a tendency of deteriorated respiratory function among MI patients, as an expected increase in V_{Tpeak} and $\dot{V}_{Epeak}$ with height (35), as observed by Loe et al. (9) in healthy Norwegian adults, was not observed in our study and values remained low irrespective of height (Table 3). There was indeed an observable 11% and 4% increase in $\dot{V}_{Epeak}$ and V_{Tpeak} per 10 cm in men; however, analysis failed to prove statistical significance, likely as a consequence of small sample size per stratified height group and large spread among participants. Surprisingly, $\dot{V}_E$ and V_T seemed to decline from 160-169cm to 170-179cm among women, a plausible explanation being inability to exert maximal effort among the tallest women, considering achieved RER values of 1.11 and 1.03 (p=0.034), respectively.

Substantially higher $\dot{V}_{Epeak}$ was observed in men and women in this study compared to RCTs conducting CPET on MI patients in Poland (30) and Brazil (27), but comparison of results proved difficult in terms of lack of stratification by sex or only inclusion of men in these studies. Men in the current study had 50% higher $\dot{V}_{Epeak}$ compared to reported values in Polish and Brazilian MI patients, which could largely be explained by differences in stature and weight, highlighting the importance of having reference values for MI patients in different countries, as there are inevitable genetical differences between ethnicities. Other than differing body dimensions from Brazilians, the higher $\dot{V}_{Epeak}$ among Norwegian MI patients can be seen in relation to higher measured $\dot{V}O_{2peak}$ as well.

When comparing to a sample drawn from a similar population, $\dot{V}_{Epeak}$, V_{Tpeak} and fB proved fairly consistent with men and women in Generation 100's general CVD group (93 women aged 73.0±2.2 years, 205 men aged 72.9±2.1 years) (32), although only 19 participants had a history of MI. Ventilation is normally not the limiting factor of $\dot{V}O_{2peak}$ in healthy individuals (38), seemingly this appears to be the case for people with a history of MI as well. However, resting spirometry values were not measured, thus it was not possible to calculate breathing reserve, which would have provided conclusive evidence to whether or not participants' exercise capacity was limited by ventilation (35). $\dot{V}_{Epeak}$ and V_{Tpeak} were in general 5-20% lower in our participants compared to healthy men and women from the same region presented in the HUNT Fitness study (9), with the exception of women >65 years who had a 2% higher $\dot{V}_{Epeak}$ in this study. The observed difference was undoubtedly linked to measured $\dot{V}O_{2peak}$, which was 5-19% lower in MI patients. Interestingly, the >65 years group for both sexes in this study had similar $\dot{V}_{Epeak}$ as healthy subjects from a different region in Norway (10), presumably attributed to their comparable $\dot{V}O_{2peak}$ values. Indicating inclusion of fairly physically active MI patients to NorEx so far.

Across all studies, $\dot{V}_{Epeak}$ and V_{Tpeak} was significantly lower with higher age, except women in this study, where values were similar between <65 and >65 years. $\dot{V}_{Epeak}$ was 20-25% lower in the >65 years age group among healthy Norwegians (9,10), compared to 17% in our study, while V_{Tpeak} was 10% and 17% lower >65 years, in the HUNT Fitness study (9) and men in this study, respectively. Ventilation is in fact expected to decrease with age, due to deteriorated dynamic lung function as a result of decreased elastic recoil and age related attenuated peak f_B (39). There was not observed lower peak f_B among the oldest age group of MI patients, contrary to previous findings showing an average 5% decrease per decade in healthy men and women (9). A similar decrease would likely have been observed in this study with a larger sample size and age stratification per decade and continuation of the present study will conclude this matter.

Although MI patients show lower values compared to healthy individuals in the same population, when looking at $\dot{V}_{Epeak}$, men >65 years with a history of MI were in fact comparable to healthy sedentary Brazilian men <65 years (13) and have 16% higher $\dot{V}_{Epeak}$ than healthy Israeli men >65 years (11). Whereas men <65 years had 9% higher $\dot{V}_{Epeak}$ compared to active healthy Brazilian men <65 years. This may be partially due to cultural physical activity differences resulting in lower $\dot{V}O_{2peak}$, in addition to differences in anthropometrics, since our MI population was substantially taller and heavier than Brazilian and Israeli men. In comparison, healthy Canadian men >65 years (12) had 16% higher $\dot{V}_{Epeak}$ and 13% higher $\dot{V}O_{2peak}$, which is a more comparable population in terms of height and weight, emphasizing that lower $\dot{V}_{Epeak}$ seen in Norwegian MI patients is likely mainly attributed to attenuated CRF compared to healthy men and women of similar body dimensions. In women with MI, we observed $\dot{V}_{Epeak}$ values consistent with healthy active Brazilian women (13), in fact 14-31% higher than sedentary healthy women from the same study.

Sex and Age Group Differences in V_{Than} and RCP

V_{Than} and RCP occurred at a similar percentage of $\dot{V}O_{2peak}$ among both sexes, with an average of 73% and 90% of $\dot{V}O_{2peak}$, respectively (Table 4). This is in fair agreement with previous research on V_{Than} in healthy subjects from Canada (75%) (12), Israel (66.8%) (11), Brazil (63-70%) (13), as well as healthy subjects from the same Norwegian population, whom reported V_{Than} at 75-79% and RCP at 86-90% of $\dot{V}O_{2peak}$ in men and women (9,32). Although results were quite similar, V_{Than} (%$\dot{V}O_{2peak}$) was in fact 5% lower compared to healthy counterparts in the HUNT Fitness study (9), as expected in light of them achieving higher $\dot{V}O_{2peak}$ values. Among cardiac patients with low $\dot{V}O_{2peak}$, lactate is expected to increase at exceedingly low exercise levels (35). In contrast, MI patients in the current study did not seem to accumulate lactate at a notably earlier stage than healthy counterparts in the HUNT Fitness study (9) and the Generation 100 study (32).

V_{Than} was observed at 57-67% of $\dot{V}O_{2peak}$ in previous RCTs on MI patients (22,25,28,30), which is in general lower compared to this study, with the exception of 75% presented by Kunz et al. (27). This may be attributed to considerably higher $\dot{V}O_{2peak}$ in our study, since V_{Than} is normally observed at a higher % of $\dot{V}O_{2peak}$ in an aerobically fit person (20). Another contributing factor is likely differing methods of establishing V_{Than}, although some studies utilized computerized regression analysis similar to the current study (22,27,28), others relied on visual graphical interpretation by experienced personnel (25,30), consistently displaying lower V_{Than} in comparison.

All aforementioned studies assessed V_{Than} by non-invasive methods of gas analysis, which entails certain methodological limitations and has previously shown moderately lower values for lactic threshold than the gold standard analysis of blood lactate concentrations (9). None of the RCTs on MI patients reported RCP.

Participants >65 years in the current study had higher V_{Than} displayed as percentage of $\dot{V}O_{2peak}$. However, the only significant difference was 5% lower V_{Than} (% $\dot{V}O_{2peak)}$ observed among men <65 years ($p<0.001$). The findings are supported by Inbar et al. (11), also showing a continuous rise in percentage of $\dot{V}O_{2peak}$ among healthy Israeli men with increasing age. In comparison, previously published reference data on healthy populations have shown the same trend for both men and women (9,13,32), also supported by Wasserman et al. (35), stating an inverse relationship between the decrease in absolute V_{Than} and subsequent increase in percentage with age. Possible explanations for these findings is the age-related reduced anaerobic capacity, resulting from selective loss of type II fibers and relative increase in type I fibers (9,12), though the mechanisms responsible for the decline in glycolytic ATP production are uncertain.

Ventilatory Efficiency at $\dot{V}O_{2peak}$ and V_{Than}

Results showed higher ventilatory equivalents in men at V_{Than}, indicating reduced ventilatory efficiency compared to women, consistent with findings in CVD patients from the Generation 100 study (32), while differing from the HUNT Fitness study (9) where ventilatory efficiency seemed to be reduced in women. Compared to healthy subjects in the HUNT Fitness study (9), men had 8% and 11% lower ventilatory efficiency <65 and >65 years, respectively. While women <65 years in this study showed consistent results and the >65 years age group, in fact, had slightly higher efficiency. Generation 100 (32) reported a similar increased ventilatory cost when comparing their CVD subjects to healthy counterparts. One possible explanation being that many risk factors associated with CVD, such as smoking and dyslipidemia, also affect the pulmonary system (40).

The reason higher ventilatory equivalents were observed in men is uncertain, though it should be mentioned that there was not a significant mean age difference between sexes in the respective age groups, meaning that attenuated ventilatory efficiency in men compared to women cannot be explained by differing age. Research has shown that in order to adapt ventilation to incremental exercise, men tend to increase V_T, while women increase f_B (41). Hence, reduced ventilatory efficiency in men with a history of MI could possibly be attributed to the 10% lower V_{Tpeak} observed compared to healthy men, and not necessarily in women, since f_B was consistent with findings in healthy men and women. When Eq$\dot{V}CO_2$ is high and there is no evidence of acute hyperventilation, it is likely caused by increased physiological dead space (35). Therefore, another argument for attenuated ventilatory efficiency seen in men could be elevated physiological dead space, characterized by observable ventilation-perfusion mismatching indicative of possible underlying pulmonary disease or undiagnosed heart failure, contrary to women in the study sample.

$Eq\dot{V}O_{2peak}$ was similar among age groups in men and women, while $Eq\dot{V}CO_{2peak}$ was higher in men >65 years. Additionally, older men had higher $Eq\dot{V}O_{2VThan}$ and $Eq\dot{V}CO_{2VThan}$ compared to the younger age group. The significant correlation between $Eq\dot{V}CO_{2VThan}$ and age in men was shown in Figure 2, indicating deteriorated ventilatory efficiency with age, which is in agreement with Loe et al. (9) and Nelson et al. (12), Inbar et al. (11) on the other hand, reported that ventilatory efficiency in men was not significantly influenced by age. Although there was not observed a similar significant correlation in women, this must be interpreted with caution as the female study sample was quite small compared to men in our study, greatly reducing statistical strength. Loe et al. (9) argued that increased dead space and attenuated airflow from reduced elastic recoil in lung tissue might be contributing factors to age-related reduced ventilatory efficiency. Nevertheless, it is still uncertain which factors are responsible and it should be investigated further in future research.

Studies on MI patients have previously reported $Eq\dot{V}CO_{2peak}$ of 27-29 in men and women combined (22,24,27), substantially lower than findings in the current study with a mean value of 31, indicating lower ventilatory efficiency in comparison. $Eq\dot{V}CO_2$ >30 is known to be associated with increased risk of adverse events in cardiovascular- and lung disease (6,7). However, Stensvold et al. (32) argued that the normal value for older adults should be higher than previously suggested, thus heightened $Eq\dot{V}CO_2$ observed in this study could also be a result of age-related factors as opposed to effects of CVD alone. In patients with heart failure, elevated $\dot{V}_E/\dot{V}CO_2$ slope has been linked to mechanisms such as increased ventilation-perfusion mismatching and an abnormally heightened chemosensitivity and ergoreflex response (7), whether or not this is the case for MI patients is uncertain.

Non-Exercise Prediction Models for Key Cardiorespiratory Variables

The presented prediction models (Table 6) may offer clinicians and researchers a useful tool to roughly predict several key cardiorespiratory variables in MI patients, as a surrogate measure when CPET is contraindicated or otherwise not possible to administer. Due to low variance explained and high SEE in general, application of these prediction models should be done with caution. Variables such as $Eq\dot{V}CO_{2VThan}$ and V_{Than} have been shown to be applicable in assessing prognosis with regards to several lifestyle related diseases and mortality (21,42). To date there has not been established non-exercise prediction models for key cardiorespiratory variables in MI patients, derived from CPET data. This study showed a ±23.8%, ±25%, ±24.2% ±18.8%, ±11% and ±11.2% accuracy in predicting $\dot{V}_{Epeak}$, $\dot{V}CO_{2peak}$, V_{Than}, V_{Tpeak}, $Eq\dot{V}CO_{2VThan}$ and $Eq\dot{V}O_{2VThan}$, respectively. Considering $\dot{V}_{Epeak}$ and V_{Than}, our study presented lower accuracies than previous large sample studies (9,11), while V_{Tpeak} and $Eq\dot{V}CO_{2peak}$ accuracies were approximately the same.

In existing literature, studies with small samples of homogenous fitness levels have normally provided the best accuracy for prediction. Therefore, one might argue that there is a need for reference values for specific groups, such as MI patients. Although the sample size in this study might be sufficient to provide moderate to high predictive power in a similar population, it does not provide generalizable results with wide applicability to the same extent as large population samples with greater diversity.

Whether prediction equations indeed are useful as a clinical tool or not can be debated, with a recent study showing limited prognostic utility of estimating CRF within a clinical setting, due to significant error associated with using non-exercise prediction equations to estimate CRF acutely or monitoring longitudinal changes to CRF (43).

Strengths and Limitations

Among the present study's strengths is the fairly high percentage of participants that were able to reach their true $\dot{V}O_{2max}$ (73%), and all tests were performed by the same test personnel, on the same ergospirometry system and treadmill for every single test. Use of the Norwegian Myocardial Infraction registry to recruit participants to NorEx ensured that the entire MI population received an invitation to participate, likely increasing the internal validity of the results and reducing the risk of recruitment bias often present in physical exercise related research. A second randomization from the respective intervention groups ensured a fairly representable sample of the main study sample. However, the majority whom accepted the invitation to NorEx are likely not the least inclined to participate in regular physical activity in their daily lives, thus presented reference values may represent a more active proportion of the MI population.

Unfortunately, the sample size of the study was reduced due to Covid-19 restrictions, which likely contributed to exacerbate the imbalance in number of men and women recruited. The small sample of women, in addition to large spread in measurements among them, likely affected p-values and subsequent interpretation of results as well. The small sample size made it impossible to stratify into age groups by decades as intended and as previous studies have done (9–13), since robust statistical analysis would not have been possible with such a limited sample size. This has inevitably impacted the comparability to previously published reference values in healthy populations.

Adding data from multiple centers would have been beneficial in terms of increased statistical power. Additionally, the external validity of the results would have been improved and likely proven representable for the entire Norwegian MI population.
A larger sample size would also have allowed more extensive analysis, by for example dividing participants into fitness quartiles as seen in Loe et al. (9), which can be applicable to interpretation of CPET results. Although we were eventually able to proceed with data collection at St. Olav's Hospital, it was delayed for several months, resulting in significantly reduced time for data processing, interpretation of results and writing of the master's thesis in its entirety.

Due to the fact that resting spirometry was not performed, the overall assessment of ventilatory function in study participants was restricted. Future research could benefit from including resting spirometry for further evaluation of respiratory parameters in MI patients. Although not discussed in detail in this article, there was also collected data on cognitive function and ECG recordings, providing substantial amounts of data that can be used for further research on the same population.

CONCLUSIONS

To the author's knowledge, this is the first reference material of its kind. Inconsistent findings with research on healthy adults highlight the importance of publishing cardiorespiratory reference values for specified patient groups. This material establishes normative values for-, associations between- and non-exercise prediction models for key cardiorespiratory variables in a specific Norwegian MI population. Data provided in the current study provides important information for researchers and clinicians in terms of interpreting CPET results for MI patients. The continued collection of CPET data throughout the study period of NorEx will add to and improve the current reference values and prediction equations.

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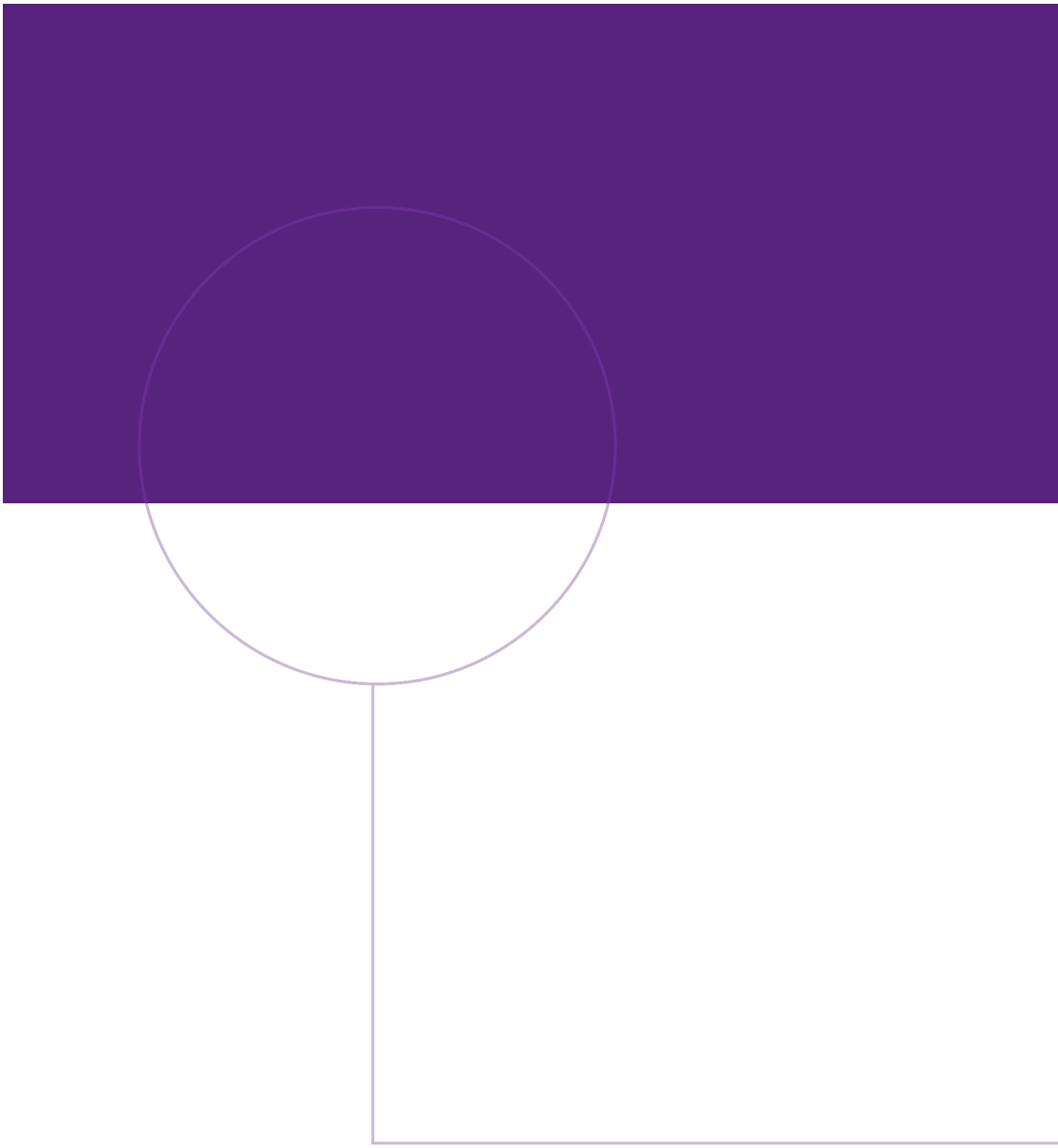

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