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# Moderate-to-high intensity aerobic interval training versus continuous aerobic training in real life, centre based, cardiac rehabilitation

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# MODERATE-TO-HIGH INTENSITY AEROBIC INTERVAL TRAINING VERSUS CONTINUOUS AEROBIC TRAINING IN REAL LIFE, CENTRE BASED, CARDIAC REHABILITATION

By

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Submitted in accordance with the requirements of the Degree of

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# AUTHOR'S DECLARATION

This work had not been previously accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

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# Summary

Cardiac rehabilitation (CR) programs usually consist of moderate intensity exercise sessions for the purpose of enhancing the physiological and psychosocial status of cardiac patients. It has been postulated that interval training is superior to the traditional continuous training in CR. Most of studies of interval training in cardiac patients have relatively small sample sizes, diverse training methodologies, and included heart failure patients. Furthermore, there have been relatively few comparisons of interval versus continuous exercise in a real life, center-based CR setting. This PhD thesis reports a single–site, randomized controlled trial of aerobic interval training in CR that was undertaken to address some of these concerns. Following 4 weeks of adjustment in the center, 84 coronary artery disease patients were randomly assigned to either an interval exercise group (IE) or a continuous exercise group (CE). Functional capacity, clinical outcomes and quality of life (QoL) were assessed at baseline and after 12 weeks of training. Both groups exercised twice a week under supervision at the center. The CE group exercised continuously at a moderate intensity (50-60% $VO_2$max), whereas the IE group performed 2 minutes of low intensity (40-60% $VO_2$max) followed by 2 minutes of moderate-high intensity (60-85% $VO_2$max) interchangeably. Both groups increased $VO_2$ peak significantly after training; however, IE was no better than CE at eliciting an improvement. In contrast, IE did elicit a significantly greater improvement in maximal power measured during cardiopulmonary exercise testing (CPET), as well as significant reductions in several sub-maximal variables. Some cardiac related risk factors, such as waist circumference, HbA1c% and hs-CRP were reduced in the IE group alone; however some of these changes do not seem to be clinically important. Next, measurements were repeated at 9 months to determine whether or not any of the training induced changes persisted at 6 months follow-up. Peak $VO_2$ remained significantly higher versus baseline within the IE group only. High sensitivity (hs)-CRP was increased in the former CE group, and HDL-C was improved in the former IE group from 3 to 9 months. Finally, a single-group analysis (i.e. regardless of training modality) was undertaken to identify the best predictors of improvement functional capacity in cardiac patients. It was found that the magnitude of change in peak $VO_2$ is dependent upon 6 factors: baseline body

fat percentage, baseline left ventricular ejection fraction (LVEF), baseline fitness level, maximal rate pressure product during CPET, baseline psychological state, and number of exercise sessions completed. These observations indicate that interval training in a real life CR setting does not necessarily elicit higher peak $VO_2$, but that it may have some superiority over continuous training in relation to exercise tolerance and performing daily activities. Furthermore, favorable changes may be preserved for up to 6 months following interval training. Finally, several factors that influence the magnitude of improvement in functional capacity following exercise training in CR patients have been identified. Using these factors, CR professionals may be able to identify those cardiac patients for whom the chances of improving functional capacity is low. Furthermore, it may be possible to focus on some of these factors in order to improve the prognosis for patients undergoing CR.

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# Publications

**Poster presentation at the ESC Congress, August 2015, London.**

Y. Pernick, I. Zyssman, HP. Kubis, JP. Moore, Z. Vered*. Comparison between moderate-high exercise and continuous exercise in a real-life cardiac rehabilitation setting - six months follow-up*

**Oral presentation at The 63rd Annual Conference of the Israel Heart Society, April 2016, Tel-Aviv.**

Y. Pernick, JP. Moore, HP. Kubis, I. Zyssman, Z. Vered. *Comparison between moderate-high exercise and continuous exercise in a real-life cardiac rehabilitation setting - six months follow-up*

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# List of Abbreviations

| | |
|---|---|
| ACCP | American College of Chest Physicians |
| ACE | angiotensin converting enzyme |
| ACSM | American College of Sports Medicine |
| ADL | Activities of daily living |
| AHA | American Heart Association |
| ARB | angiotensin II receptor blockers |
| ASE | American Association of Echocardiography |
| ATS | American Thoracic Society |
| BF | body fat |
| BIA | bioelectrical impedence analysis |
| BMI | body mass index |
| BP | blood pressure |
| BPM | beat per minute |
| CABG | coronary artery bypass graft |
| CAD | coronary artery disease |
| CCB | calcium channel blockers |
| CE | continuous exercise |
| cm | centimeter |
| CPET | cardiopulmonary exercise test |
| CR | cardiac rehabilitation |
| CRP | c-reactive protein |
| cTnT | Troponin - T |

| | |
|---|---|
| CVD | coronary vascular disease |
| DBP | diastolic blood pressure |
| DM | diabetes mellitus |
| DT | deceleration time |
| ECG | electrocardiogram |
| EDV | end diastolic volume |
| ESC | European Society of Cardiology |
| ESV | end systolic volume |
| FPS | frames per second |
| HbA1c | glycosilated hemoglobin |
| HDL-C | high density lipoprotein cholesterol |
| HF | heart failure |
| HIIT | high intensity interval training |
| HR | heart rate |
| HRR | heart rate reserve |
| hs-CRP | high sensitive C-reactive protein |
| ICD | implantable cardioversion device |
| IE | interval exercise |
| kcal | kilo calorie |
| Kg | kilogram |
| LA | left atria |
| LDL-C | low density lipoprotein cholesterol |
| LV | left ventricular |
| LVEF | left ventricular ejection fraction |

| | |
|---|---|
| m | meter |
| MACE | major acute cardiac event |
| MAP | mean arterial pressure |
| METS | metabolic equivalents |
| mg | milligram |
| MH | mental health |
| MHR | maximal heart rate |
| MI | myocardial infarction |
| min | minute |
| ml | milliliter |
| MOS | Medical Outcomes Study |
| MV | mitral valve |
| NO | nitric oxide |
| NWORTH | North Wales Organisation for Randomised Trials in Health |
| NYHA | New-York Heart Association |
| PCI | percutaneous coronary intervention |
| PH | physical health |
| PPO | peak power output |
| PW | pulse wave |
| Q | cardiac output |
| QOL | quality of life |
| RCT | randomized controlled tria |
| RER | respiratory exchange ratio |
| RHR | resting heart rate |

| | |
|---|---|
| RPE | rating of perceived exertion |
| RPP | rate peressure product |
| SBP | systolic blood pressure |
| SD | Standard deviation |
| SF | short form |
| SPSS | statistical package for the social sciences |
| SV | stroke volume |
| TC | total cholesterol |
| TDI | tissue doppler imaging |
| TG | triglycerides |
| $VO_2$ | oxygen consumption |
| VT | ventilatory threshold |
| WC | waist circumference |

# Chapter 1
# General Introduction

According to the European Society of Cardiology (ESC), cardiovascular diseases (CVD) causes over 4 million deaths in Europe and is considered to be the cause of 47% of all deaths (Nichols *et al.*, 2012). In Israel there are 25,000 cardiac events each year, with 7,000 cardiac-related deaths annually, thus making CVD the second leading cause of death after cancer (17%) (Goldshmidt, 2007). Therefore, secondary prevention of CVD is very important and offered via cardiac rehabilitation (CR) programs in many countries. CR has been defined as the "co-ordinated sum of interventions required to ensure the best physical, psychological and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume optimal functioning in society and, through improved health behaviors, slow or reverse progression of disease" (Fletcher *et al.*, 2001). These programs usually involve various interventions in addition to the exercise component including nutritional guidance, risk factor education, psychological assistance, and drug therapy. Nonetheless, international guidelines constantly refer to the exercise element as the central component of CR programs (Fletcher *et al.*, 2001).

The benefits of exercise-based CR programs have been clearly documented before and include: significant enhancement in exercise capacity (Dugmore *et al.*, 1999; Feuerstadt, Chai & Kligfield, 2007; Lavie, Thomas, Squires, Allison & Milani 2009; Onishi *et al.*, 2010), decreased major adverse cardiac events (MACE) (Jolliffe *et al.*, 2001; Lawler, Filion & Eisenberg, 2011), decreased risk of cardiac (Kavanagh *et al.*, 2002) and all-cause death (Goel, Lennon, Tilbury, Squires & Thomas, 2011), reduction in cardiac risk factors (Franklin *et al*., 2002; Onishi *et al.,* 2010), decreased cardiac symptoms (Dugmore *et al.,* 1999 ), improved left ventricular (LV) function (Giallauria *et al.*, 2009; Yu *et al*., 2004), reduced hospital re-admissions and length of hospital stay, and induced noticeable improvement in psychosocial status (Dugmore *et al.,*1999; Lavie *et al.,* 2009). These positive changes were summarized by Lavie *et al*. (2009) and presented in Table 1. A meta-analysis of 63 randomized trials consisting of over 20,000 patients undergoing cardiac rehabilitation programs, revealed long term beneficial effects

on cardiac risk factors, functional status, quality of life (QoL), re-current myocardial infarctions (MI's), and mortality (Clark, Hartling, Vandermeer & McAlister, 2005). It is notable that for cardiac patients who participate in formal exercise rehabilitation programs, death rate can be lowered by 20-30% (Jolliffe *et al.,* 2001; Myers *et al.*, 2002; O'Connor *et al*., 1989). These beneficial effects were mostly attributed to the exercise component in the cardiac rehabilitation program (Jolliffe *et al.,* 2001; Taylor *et al.*, 2004). Therefore, it is widely acknowledged that CR exercise-based programs can improve cardiorespiratory fitness and maximal exercise capacity.

**Table 1. Benefits of cardiac rehabilitation and exercise training programs**

| |
|---|
| Improvement in exercise capacity |
| Increases METS by 35% |
| Increases peak $VO_2$ by 15% |
| Increases peak anaerobic threshold by 11% |
| Improvements in lipid profile |
| Decreases total cholesterol by 5% |
| Decreases triglycerides by 15% |
| Increases serum high-density lipoprotein cholesterol levels by 6% |
| Reduces low-density lipoprotein cholesterol levels by 2% |
| Reductions in obesity indices |
| Decreases body mass index by 1.5% |
| Decreases body fat by 5% |
| Lowers metabolic syndrome by 37% |
| Reduction in inflammation (high-sensitive C-Reactive Protein) by 40% |
| Improvements in quality of life |
| Reductions in overall morbidity and mortality |

*Adapted from Lavie et al. 2009*

Maximal exercise capacity is considered to be the most important predictor of cardiac and all cause deaths (Feuerstadt *et al.,* 2007; Kavanagh *et al.,* 2002; Myers *et al.*, 2008), even more than clinical variables or existing cardiac risk factors (Myers *et al.,* 2002). Maximal oxygen consumption ($VO_2$ max) is the best objective measure of fitness and is a widely used index of cardiovascular function (Fletcher *et al.*, 2013). Exercise capacity can also be assessed by the metabolic equivalents (METS); One MET is a unit of resting oxygen uptake, which is approximately 3.5 ml

of $O_2$ per kilogram of body weight per minute ($ml \cdot kg^{-1} \cdot min^{-1}$) (Fletcher *et al.*, 2001). Apparently, there is some inconsistency between estimated exercise capacity, as assessed with METS, and directly measured exercise capacity, as measured by gas exchange (oxygen consumption) (Fletcher *et al.*, 2013). Consequently, measuring $VO_2$ max using the cardiopulmonary exercise testing (CPET) provides the most accurate, noninvasive quantification of maximal exercise capacity (Fletcher *et al.*, 2013). It is repeatedly demonstrated that cardiac patients with lower values of $VO_2$ peak have greater risk of mortality (Feuerstadt *et al.,* 2007; Kavanagh *et al.,* 2002; Myers *et al.,* 2002). In fact, any given increase in exercise capacity, as measured with $VO_2$ max, was found to be meaningful in reducing mortality (Dorn, Naughton, Imamura & Trevisan, 1999; Feuerstadt *et al.,* 2007). For example, it was found that even a 1-ml/kg/min increase in peak $VO_2$ was correlated with an approximately 10% lower rate of cardiovascular mortality in studies including over 12,000 men and women (Kavanagh *et al.,* 2002).

According to the Fick principle, maximal $VO_2$ is the product of cardiac output (Q) multiplied by the arteriovenous difference across the body. Thus, there are both central (oxygen delivery) and peripheral (oxygen extraction) factors that determine the maximal $VO_2$ (Balady, Williams & Ades, 2007). The Fick equation is presented as follows:

$$\mathbf{VO_2 = (HR\ X\ SV)\ X\ [C(a\text{-}v)O2]}$$

where (HR X SV) represents the product of heart rate multiplied by stroke volume, which is the cardiac output; and $C(a - v)O_2$ is the arteriovenous $O_2$ content difference. While it is still controversial whether cardiac patients can increase their heart's pumping ability, it is more than clear that these patients can enhance their ability to take in and use oxygen in the muscles. Consequently, daily activities can be completed more easily with less fatigue. Cardiac patients often experience lower functional capacities; hence these muscle adaptations are even more important for them (Myers *et al.,* 2002).

For the purpose of increasing functional capacity, recommendations for secondary prevention programs include aerobic training for 3-5 days a week, with duration of at least 30 min, and intensity of 40-85% $VO_2$ max (depending on risk stratification and aerobic capacity) (Fletcher *et al.,* 2001; Thompson, 2005). However, most

recommendations do not include specific guidelines for the type of aerobic exercise intervention and the range of intensity is very wide (Kavanagh *et al.,* 2002; Moholdt, Amundsen & Rustad*,* 2009). It has been established repeatedly that moderate exercise is adequate to reduce cardiovascular risk and mortality (Fletcher *et al.,* 2001; Myers *et al.,* 2002). Yet, there are reports in the literature showing that performing the same amount of exercise at a higher intensity, is associated with further risk reduction and greater cardiovascular benefits over moderate intensity exercise (Marrugat *et al.,* 1996; Siscovick *et al.,* 1997; Swain & Franklin, 2006; Tanasescu *et al.,* 2002).

For that reason some studies have examined the use of interval training in cardiac rehabilitation programs, thus testing the assumption that resting periods (usually active recovery bouts) in-between high intensity exercise bouts, will allow the patients to fully complete the exercise session, while enabling them to induce the favorable changes that take place following vigorous exercise training. However, it seems that there is a lack of studies looking at interval training in real-life CR programs, examining the effectiveness of this modality compared to the standard exercise modality on coronary artery disease (CAD) non-heart failure (HF) patients. Moreover, there is even less information concerning long-term effects of interval exercise on cardiac outcomes.

The current PhD thesis addresses these questions through a prospective randomized controlled trial (RCT). Participants were recruited from CAD patients eligible for a CR program in a single center, the Assaf Harofeh Medical Center in Zerifin, Israel. After 4 weeks of standardized care, patients underwent baseline testing and allocation (randomized) to either standard continuous exercise group or interval exercise group. The subjects continued to attend their exercise sessions for additional 12 weeks. These subjects were subsequently followed for 6 months. Real-life conditions were preserved throughout the study including training in groups with other patients who were not participating in this trial, being supervised by one exercise trainer, receiving the same instructions for additional physical activity at home as usually recommended, and being offered the standard professional guidance of the dietitian and psychologist of the CR center. Moreover, during the follow-up term, real-life environment was still maintained and therefore

no interference was made when subjects have decided to either leave the CR program or continue to attend the facility.

There is little and equivocal evidence regarding the superiority of interval training over continuous training in CAD patients in previous research. However, research involving healthy individuals and even heart failure patients, usually resulted in beneficial effects of interval exercise compared to continuous exercise. Therefore, we hypothesized that interval training would yield greater $VO_2$ peak improvements compared to continuous aerobic exercise. Also, since CR programs are designed to improve cardiac risk factors, cardiac function and QoL, it was important for us to examine the effects of interval training on these parameters as well.

There is, however, conclusive evidence showing that maximal exercise capacity, as represented by maximal oxygen consumption, is the single most prognostic value of cardiac morbidity and mortality (Dorn *et al.,* 1999; Feuerstadt *et al.,* 2007; Kavanagh *et al.,* 2002). It seems that exercise practitioners that work in CR programs could benefit from a better understanding of which parameters can affect $VO_2$ max and its change with training. Since this study included wide-ranging cardiac-related data, it was possible to explore the contribution of each of the relevant variables to the change in maximal functional capacity. It was suggested before that improvements in peak $VO_2$ are influenced mainly by uncontrolled factors such as age (Marchionni *et al.,* 2003; Sandercock, Hurtado & Cardoso*.,* 2013), gender (Sandercock, Hurtado & Cardoso*.,* 2013), and other genomic features (Bouchard *et al.,* 2011), while others demonstrated the influence of exercise intensity on enhanced maximal exercise capacity (O'Donovan *et al.,* 2005*;* Tanasescu *et al.,* 2002; Uddin *et al.,* 2015). Using a multiple regression analysis in this present research, enabled us to examine the possible contribution of certain parameters on the change in maximal functional capacity and perhaps find the predictors of better prognosis for cardiac patients who participate in CR programs.

Current evidence relating to interval training in cardiac populations is reviewed in the following chapter (Chapter 2), followed by a chapter describing all methodologies used in this study (Chapter 3). Chapter 4 presents the data of all outcome measurements including cardiorespiratory, cardiac function, hemodynamic, blood chemistry, and QoL. The same outcomes were further measured after 6 months follow-up and are presented in Chapter 5. Since this

study was unique in including most of the cardiac-related parameters in CR setting and in following the subjects after the intervention, it seemed important to examine the data as one sample for a broader observation and for finding the parameters that will best predict improvements in maximal functional capacity (Chapter 6). The last chapter (Chapter 7) is the general discussion that summarizes all chapters and presents practical implications of the study.

# Chapter 2

# Literature Review

CR centers usually follow the general guidelines of continuous aerobic exercise at moderate intensity levels. There are reports in the literature that high intensity exercise has greater cardiovascular benefits over moderate intensity exercise when energy expenditure is equalized (Marrugat *et al.,* 1996; Siscovick *et al.,* 1997; Tanasescu *et al.,* 2002). It is suggested that high intensity exercise might result in greater autonomic adaptations compared to moderate intensity which can contribute to favorable changes in blood pressure, thrombosis, and coronary risk factors. However, high intensity exercise is usually difficult to sustain for long durations (Pattyn, Coeckelberghs, Buys, Cornelissen & Vanhees*,* 2014), especially for coronary artery disease (CAD) patients who usually suffer from reduced functional capacity due to limited cardiac function (Tjønna *et al.,* 2008). There is only a small number of studies that have investigated interval training in CR facilities. These studies compared high levels of intensities during the interval bouts (HIIT = high intensity interval training) ranging between 80-90% heart rate reserve (HRR). Even though it was demonstrated in these studies that high intensity exercise seems to be safe for cardiac patients (Guiraud *et al.,* 2011), a total of 10 studies was performed with relatively small numbers of participants, with samples ranging from 14 to 174 patients (a total of 523 subjects).

There is an increasing popularity of the interval training among healthy and cardiac populations in recent years. Consequently, it has been recommended that professionals should bear in mind that not many CAD patients have been examined and that most of them were male with high exercise capacity, thus cautious should be taken before prescribing it widely (Guiraud *et al.,* 2011). Prior trials have shown that the risk of myocardial infarction and sudden death during an episode of vigorous exertion is extremely low even among patients who have had a known coronary disease. Nonetheless, it was also claimed that, while habitual vigorous physical activity is safe, the risk for MI or sudden death increases drastically when the exerciser have been sedentary and engaged in high intensity

exercise (Albert, Mittleman & Chae, 2000; Mittleman *et al.,* 1993). From our experience the majority of the patients who enter a CR program are often characterized as sedentary, and this needs to be taken into consideration when prescribing their exercise plan and specifically levels of intensity. For these patients who have experienced a recent cardiac event it has been recommended that they return to regular activity gradually (Fletcher *et al.,* 2001). Even though interval training in CAD patients appears to pose a low risk, the risk is still higher than that seen with standard continuous training (Elliott, Rajopadhyaya, Bentley, Beltrame & Aromataris, 2015). Therefore, if interval training is involved, the patients should engage in more modest intensity training than was published in recent research (Guiraud *et al.,* 2011).

Traditionally interval training has been used to train athletes (Cornish, Broadbent & Cheema, 2011) as it is believed to force them to use very high levels of both aerobic and anaerobic exercise. Among CAD patients, interval training involves changing intensities from high intensity (> 75% $VO_2$ peak or RPE > 15) to moderate intensity for relatively short durations (between 2-5 minutes) (Cornish *et al.,* 2011). Studies have found that moderate to high intensity interval training may be superior to moderate continuous training for healthy adults (Daussin *et al.,* 2008; Nemoto, Gen-no, Masuki, Okazaki & Nose, 2007; Tjønna *et al.,* 2008) and cardiac patients (Moholdt *et al.,* 2009; Nillson, Westheim & Risberg, 2008; Wisloff, Stoylen & Loennechen, 2007). These advantages of interval exercise over continuous exercise included improvements in peak $VO_2$ (Moholdt *et al.,* 2009; Rognmo, Hetland, Helgerud, Hoff & Slørdahl, 2004; Wisloff *et al*., 2007), endothelial function (Tjønna *et al.,* 2008; Wisloff *et al*., 2007), enhanced muscle strength and endurance (Daussin *et al*., 2008; Nemoto *et al*., 2007; Tjønna *et al.,* 2008), and improved QoL (Wisloff *et al*., 2007). Moderate to high intensity interval training might also be associated with lowering cardiac risk factors such as: increasing insulin sensitivity (Tjønna *et al.,* 2008), increasing high-density lipoprotein cholesterol (HDL-C) (Tjønna *et al.,* 2008), and decreasing mean arterial pressure (MAP) (Daussin *et al.,* 2008). However, there is not enough data regarding interval training and cardiac risk factors among CAD patients (Elliott *et al.,* 2015).

The mechanism through which interval training can induce better clinical outcomes is still not fully clear, even though the relationship between intensity and peak $VO_2$ was established (Elliot *et al.,* 2015). Tjønna *et al. (*2008) and Wisloff *et al.* (Wisløff, Ellingsen & Kemi, 2009) found that endothelial function was improved more after interval training. They suggested that interval training increases the availability in nitric oxide (NO) which contributes to muscle relaxation. This effect might be due to the different shear stress on the walls of blood vessels which occurs with higher intensity of exercise (Tjønna *et al.,* 2008). Additionally, some studies have shown increased skeletal muscle mitochondrial capacity along with an improved exercise performance following interval training (Little, Safdar, Wilkin, Tarnopolsky & Gibala, 2010; Pattyn et al., 2014; Tjønna *et al.,* 2008), which also contributes to the enhanced ability of the muscle to turn energy source to energy. Others reported improved stroke volume (Helgerud *et al.,* 2007), systolic (Wisloff *et al.,* 2009) and diastolic LV function (Amundsen, Rognmo, Hatlen-Rebhan & Slørdahl*,* 2008), along with improved $VO_2$ peak. These changes imply that both central and peripheral factors are responsible for the higher improvements following interval training, though none of these studies investigated these theories thoroughly (Elliot *et al.,* 2015) and the data was based on relatively small sample sizes which elicit the need for larger and more elaborated trials (Pattyn et al., 2014).

While it is recognized that high intensity levels of exercise can elicit more favorable cardiovascular outcomes (Tanasescu *et al.,* 2002), it is also known that vigorous exercise can increase the risk of sudden cardiac death or MI in some patients (Thompson *et al.,* 2007). In the majority of interval training research that was performed with CAD patients, high-intensity levels of exercise were prescribed for the IE group reaching up to 95% maximal HR (MHR) or 90% of peak $VO_2$ (Rognmo *et al.,* 2004; Rocco *et al.,* 2012). Although it seems that the overall risk of interval exercise is low, prescribing high-intensity exercise to these patients requires careful attention (Elliot *et al.,* 2015).

**The effect of interval training on exercise capacity in cardiac populations**

Interval training in CR facilities has been investigated predominantly among heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF). Only a few studies compared this modality of training with the traditional continuous training method. These clinical trials found contradictory outcomes related to the

advantages of interval training over continuous training. On one hand Rocco *et al*. (2012), Moholdt *et al*. (2009), Currie *et al*. (Currie, Dubberley, McKelvie & MacDonald, 2013), and Warburton *et al*. (Warburton, McKanzie & Haykowsky, 2004) found no differences in $VO_2$ peak between interval and continuous training among CAD patients. However, Munk *et al*. (Munk, Staal & Noreen, 2009), Moholdt *et al*. (2012), Amundsen *et al.* (2008), and Rognmo *et al*. (2004) showed a significant improvement in $VO_2$ peak among CAD patients who have engaged in interval training compared to those who have exercised continuously. Improvements in peak $VO_2$ following interval exercise, though not always significantly different from the traditional continuous training, were consistently significant over time ranging between 12% to 25% enhancements post interval training. Various methodologies were used in these studies in terms of different sample sizes, diverse training methods, numerous lengths of programs, and inconsistent intensities; which might explain the diversity of the results. Table 2 presents the diverse training protocols and subsequent outcomes of the clinical trials examining interval training in a CR setting. It is important to note the two of the articles were published with the same subjects; one was published 4 years later with additional data of echocardiography (Amundsen *et al*., 2008; Rognmo *et al*., 2004).

**The effect of interval training on cardiac structure and function**

Indices of ventricular systolic function include LVEF, end diastolic volume (EDV), and end systolic volume (ESV) and are considered to be important predictors of cardiac disease and death due to their effect on LV remodeling post a cardiac event (Mancini *et al*., 2013; St John Sutton *et al*., 1997; White *et al*., 1987). However, it is still not clear how exercise can affect systolic function (Haykowsky *et al*., 2011). Previous studies that have examined the effect of exercise on systolic function among CAD patients reached different conclusions depending on study methodology, training protocols, baseline resting systolic and diastolic functions, and patient selection. With so little research on interval training in CAD patients in CR programs, there is even less information regarding LV function following interval exercise in this population. These studies demonstrate inconsistent evidence related to the effect of interval modality on systolic function. A few studies reported a positive change in resting LVEF with interval training (Molmen, Wisloff,

Aamot, Stoylen & Ingul, 2012; Wisloff *et al.,* 2007), while others demonstrated no change in LVEF after training (Amundsen *et al*., 2008; Moholdt *et al*., 2009; Yu *et al*., 2004).

In addition to functional characteristics, left atrial (LA) size is considered as a strong predictor of mortality, hence it is an important factor among CAD patients post MI (Laukkanen, Kurl, Eränen, Huttunen & Salonen., 2005; Moller *et al*., 2003). Additionally, LA enlargement is associated with adverse cardiovascular outcomes, atrial fibrillation and stroke, and is a marker of severity of diastolic dysfunction (Lang *et al.,* 2015). Furthermore, it was also found to be correlated with poor exercise capacity (Acarturk, Koc, Bozkurt & Unal, 2008; Laukkanen, Kurl, Salonen, Rauramaa & Salonen 2004). It is not clear if exercise can change the volume of LA, since some studies have shown a decline in LA volume (Giallauria *et al*., 2009), whereas others have demonstrated no change (Molmen *et al*., 2012).

During exercise, with the increasing HR, the duration of diastole is shortened compared to systole. Thus, adequate diastolic function is vital to sustain or improve preload during exercise (Amundsen *et al*., 2008). The most common indices that represent LV diastolic function are LV filling factors. Among these parameters are included mitral flow variables counting early mitral valve diastolic filling (MV-E), late mitral valve diastolic filling (MV-A), and E/A ratio (Appleton, Hatle & Popp, 1988); also mitral annulus velocities are essential diastolic function factors including septal e', lateral e' (and the consequent average), and E/e' ratio. Aging affects LV systolic and diastolic functions resulting also in a reduced MV-E and increased MV-A, hence E/A is decreased (Molmen *et al*., 2012; Nagueh *et al*., 2009). When E/A is decreased below 0.96 among adults (over 60 yr), it might indicate a diastolic dysfunction (Nagueh *et al*., 2009). These changes with age might suggest a decline in myocardial relaxation rate, which might result in diastolic heart failure. Also, e' velocity decreases with increasing age while the E/e' ratio is increased and might result in an elevated LV end-diastolic pressure (Ho & Solomon, 2006); Thus, assessing diastolic function using echocardiography can provide important prognostic information (Nagueh *et al*., 2009).

Some studies were able to show that exercise training in CR resulted in increased mitral E-wave (Giallauria *et al*., 2009; Molmen *et al*., 2012; Yu *et al*., 2004), and an increased E/A ratio (Giallauria *et al*., 2009; Molmen *et al*., 2012) in contrast to

sedentary patients that have demonstrated increased mitral A wave and decreased E/A ratio (Yu *et al*., 2004). Sakate *et al*. (2001) found that E/A ratio can be useful in assessing exercise capacity in patients with mild diastolic dysfunction. As mentioned earlier there is only scarce and conflicting data related to interval exercise and diastolic function in cardiac patients. For instance, Amundsen *et al*. (2008) found that mitral E-wave increased following continuous and interval training, however, in the continuous exercise group the mitral A-wave also increased while it did not change in the interval exercise group. Wisloff *et al*. (2007) demonstrated reduced mitral E and A waves in the continuous exercise group, whereas E/A ratio was increased by 15% in the interval exercise group. On the other hand, Moholdt *et al*. (2009) found no changes in the cardiac function parameters post interval or continuous training among CAD patients.

Mitral valve inflow velocities are often affected by HR, preload and afterload; conversely, measurements of mitral valve annular velocities (lateral e' and septal e') are considered to be less affected by the hemodynamic indices. The subsequent ratio between E-wave and the average e' (E/e') is therefore closely correlated with LV filling pressure (Nagueh *et al*., 2009; Ommen *et al*., 2000). Studies have found that an increased E/e' is correlated with lower functional capacity (Grewal, McCully, Kane, Lam & Pellikka, 2009; Otto, Pereira, Beck & Milani, 2011). As far as is known to us only one trial involving interval training with CR patients measured mitral valve annulus velocities, though all 27 subjects had HF and substantially decreased LVEF (mean 29%). In that study e' was increased significantly only within the interval exercise group and E/e' was significantly reduced with both modalities of training, but the interval exercise group had considerably reduced values compared to the CE group (Wisloff *et al.,* 2007).

In summary, due to little research and equivocal findings, it is not clear whether exercise in general or interval training specifically, can change resting systolic function, LA atrial size, or diastolic indices. However, since cardiac function and structure can be changed with increasing age and following a cardiac event, some parameters are important to be investigated; especially due to some evidence that exercise can prevent the deterioration of several indices that can result in diastolic dysfunction and subsequently heart failure.

### The effect of interval training on body composition

According to the American Heart Association (AHA), obesity in considered to be one of the central cardiac risk factors which is associated with several other comorbidities including type II diabetes, hypertension, and cancer (Poirier *et al.,* 2006). Obesity can be assessed using various body composition components including body mass index (BMI), body fat%, and waist circumference (WC). It was found that body fat% was independently associated with cardiovascular risk factors (Zeng, Dong, Sun, Xie & Cui, 2012), and that WC was significantly associated with the risk of cardiovascular events (de Koning, Merchant, Pogue & Anand, 2007). Nevertheless, not many studies reported the effect of interval training on these parameters. In the majority of the studies that reported the effect of training, no change was observed in BMI (Moholdt *et al*., 2009; Moholdt, Aamot, Garnoien & Gjerde, 2011; Rocco *et al*., 2012; Rognmo *et al*., 2004). In contrast, interval training was found to be effective in decreasing BMI, though it was compared to a control group who did not engage in physical activity (Munk *et al.,* 2009). When interval training was compared to continuous exercise significant body weight and BMI reductions were observed in both exercise groups (Warburton *et al.,* 2004). None of these studies obtained additional measurements of body composition such as body fat% and WC. In a study examining interval versus continuous training in patients with the metabolic syndrome, it was found that body weight, body fat%, and WC decreased significantly in both groups, whereas control patients had no changes in these parameters (Tjønna *et al*., 2008).

### The effect of interval training on hemodynamic parameters

Resting heart rate (RHR) has been suggested to be an independent risk factor for sudden CHD death (Nauman, Nilsen, Wisløff & Vatten, 2010), and associated with other cardiovascular risk factors (Dyer *et al*., 1980). Furthermore, according to the AHA hypertension is a major independent risk factor for the development of CAD (Rosendorff *et al*., 2007). It seems that exercise has diverse effects on RHR and blood pressure (BP) in CR programs regardless of training method. For instance, some interval trials reported a lowered resting HR after both training modalities (Currie *et al*., 2013; Moholdt *et al*., 2009). Whereas, others have found no changes in RHR (Keteyian *et al*., 2014; Rognmo *et al*., 2004; Warburton *et al.,* 2004). Munk *et al*. (2009) reported a significant reduction in RHR within an interval training

group compared to non-exercising group. Also, diastolic BP (DBP) was found to be decreased in CR programs after both continuous and interval exercise (Currie *et al*., 2013; Keteyian *et al*., 2014).

**The effect of interval training on blood chemistry**

*Lipid profile and glucose metabolism*

Serum triglycerides (TG), blood glucose, glycosylated hemoglobin (HbA1C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), have been recognized by the AHA as indicators of dyslipidemia (Smith *et al*., 2006), and thus these are usually monitored in CR programs for the purpose of establishing whether these risk factors are modified (Jolliffe *et al*., 2001; Lavie *et al*., 2009; Reid *et al*., 2005). Exercise may have favorable effects on blood lipids and glucose metabolism, but the range of intensity levels that were used is wide (Fletcher *et al*., 2001). To our knowledge only two studies that looked at interval exercise in CR programs measured blood lipids and demonstrated no changes in blood glucose, TG, LDL-C, and HDL-C among patients post coronary artery bypass graft (CABG) (Moholdt *et al*., 2009). However, patients post MI demonstrated an elevation in HDL-C with interval training only (Moholdt *et al*., 2011). HDL-C was also raised significantly after interval exercise among patients with metabolic syndrome along with increased insulin sensitivity, and decreased blood glucose, when compared to continuous training or no exercise (Tjønna *et al*., 2008).

*High-sensitive C-Reactive protein (hs-CRP)*

High-sensitive C-Reactive Protein (hs-CRP) is an inflammatory marker that indicates the pathogenesis of atherosclerosis in coronary arteries (Ridker, 2007). Its importance as a cardiovascular marker is also known due to the fact that it was found significantly correlated with CAD independently of other coronary risk factors (Ridker, 2005). It is still considered by many researchers as the gold standard for monitoring inflammation and infective disease. Hs-CRP has been shown to predict the recurrence of cardiac events such as MI and the need for revascularization and it is most extensively used in prognostic studies (Biasillo, Leo, Della Bona & Biasucci, 2010). However, we were able to find only one interval study in CAD patients that included hs-CRP as a cardiac marker. This study demonstrated a

decrease in hs-CRP levels only after interval training with a significant difference compared to non-exercisers (Munk *et al.,* 2009).

*Cardiac Troponin T - cTnT*

Cardiac troponins are released into the blood stream after cell injury. Troponin T (cTnT) assay was developed to detect concentrations that are ten-fold lower compared to previous troponin markers. CTnT was found to be higher among cardiac patients with diabetes, high blood pressure, patients with multivessel CHD, among patients post CABG, and among patients with impaired LV function. Also, cTnT can predict the occurrence of fatal and recurrence of nonfatal CVD events (Koenig *et al.,* 2012). As far as known to us, none of CR-interval trials examined the levels of cTnT following exercise-based CR and beyond the program. Nonetheless, one study demonstrated abnormal levels of cTnT in the beginning of CR program that was significantly reduced following 3 weeks of training, supporting the known effectiveness of CR programs (Ferratini *et al.,* 2012).

**The effect of Interval training on quality of life (QoL)**

It is widely known that the diagnosis of CAD has major psychological consequences and that depressed patients with CAD have a higher rate of mortality compared to non-depressed patients (Milani & Lavie, 2007); hence CR programs were designed to comply with the needs for improving QoL status. It has been demonstrated that an increase in QoL was associated with an increased exercise capacity post a cardiac event following a CR program (Lavie & Milani, 1997; Seki *et al*., 2003). Even so, only a few studies involving interval training in a CR setup examined the effect of interval exercise method on QoL. Moholdt *et al*. (2009) found that QoL was improved following 4 weeks of training in both continuous and interval groups similarly. Other studies were able to show that interval training had a superior influence on QoL in a CR program, but these studies included HF patients only (FU *et al*., 2013; Wisloff *et al.,* 2007).

**Long-term benefits**

Long term benefits of CR programs are, in most cases, evaluated by occurrence of cardiac events, hospitalizations, cardiac related mortality, and total mortality. However, most studies do not report long-term status of functional capacity and cardiac risk factors, including body composition, central hemodynamic variables

(HR and BP), glucose metabolism, blood lipids, and QoL. It was found that exercise capacity that had been improved during a CR program, was preserved during a follow-up of 1 -2 years (Blum, Schmid, Eser & Saner, 2013; Boesch *et al*., 2005). As mentioned before, only a few studies examined systolic and diastolic cardiac function following interval training, and even fewer followed the patients after the intervention. A study that performed a follow-up for 8 months after an 8-week standard exercise-based CR program yielded no effects on systolic or diastolic function (except for patients with abnormal relaxation pattern), while patients who did not participate in the program presented negative changes in several diastolic indices (Yu *et al.,* 2004). Panovsky *et al*. (2011) reported that improved LVEF can be sustained 12 months after graduating a 3-months CR program, however, it was only observed among patients who had continued to exercise throughout this time.

There are inconclusive findings concerning the long term effects of CR programs on cardiac risk factors. Some studies reported that cardiovascular risk factors were significantly worsened during 18 - 24 months of follow-up compared to the end of the program (Hansen *et al*., 2010) including TC, TG, BP (Blum *et al*., 2013; Boesch *et al*., 2005), and BMI (Blum *et al*., 2013). Conversely, others demonstrated improvements in several blood lipids after a follow-up phase (Blum *et al*., 2013; Willmer & Waite, 2009). Long-term psychosocial benefits are usually consistent showing that QoL is improved significantly during CR programs and can be sustained for long periods (Willmer & Waite, 2009; Yu *et al*., 2004).

The long-term effects of CR consisting of interval training within CAD patients have not been explored sufficiently. Of the few studies conducted in CR programs, only 3 performed follow-up measurements, including one involving HF patients. One study reported that only patients in the interval training group continued to improve their peak $VO_2$ during the follow-up time (at 6 months) which was significantly different from the control continuous exercise group (Moholdt *et al*., 2009). However, another study, by the same researchers, demonstrated that both training groups had a reduced value of peak $VO_2$ at 6 and 30 months follow-ups. Nonetheless, in the interval exercise group peak $VO_2$ values were comparable with baseline levels while in the continuous exercise group they were deteriorated to lower values than baseline. In a study that followed HF patients for one year after

CR, exercise capacity parameters remained improved within the interval exercise group compared to the non-exercise group throughout that year (Nilsson *et al*., 2008). In the same study QoL scores were also significantly improved within the interval training group compared to the control group during the follow-up, while in studies published by Moholdt *et al*. (2009, 2011), QoL variables remained elevated throughout the follow-up period in both exercise groups. Adherence to exercise during the period of follow-up was reported to be generally low (27%) (Hansen *et al*., 2010) or significantly higher among IE participants compared to continuous exercise subjects (82% and 58%, respectively) (Moholdt *et al*., 2011).

In summary, according to past research, high-intensity interval training seems to be more effective compared to the standard continuous training for elevating maximal aerobic capacity in CAD (non-HF) patients. The small number of trials with the relatively small sample sizes raised the need for further research. Moreover, other cardiovascular factors including cardiac risk factors (blood lipids and body composition), cardiac function, and psychological status, were not sufficiently explored in these studies. Also, two studied evaluated some of the cardiovascular outcomes after a follow-up period (Moholdt *et al.,* 2009., Moholdt *et al.,* 2011).

**Objectives and hypothesis**

The objectives of this PhD thesis were to compare the effects of moderate-high intensity aerobic interval training with moderate intensity continuous aerobic training on physiological, clinical and psychological outcomes in coronary patients. Another objective was to further look at the differences in the same outcome measurements after a follow-up period of 6 months. The hypothesis was that the primary outcome of $VO_2$ peak would improve significantly more within the interval exercise group compared to the continuous exercise group and that other cardiac related variables would be favourably more affected by interval training compared to the standard exercise. It was also postulated that after 6 months follow-up, favourable changes that would be found following 12 weeks of interval training, would be preserved or even further be improved during 6 months follow-up.

**Table 2. Overview of Interval training studies among CAD patients in CR programs**

| | Study population | | Training protocols | | | Outcomes | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | N, Age (years, mean ± SD) | Inclusion | Length of study. Exercise instruments | Continuous exercise prescription | Interval exercise prescription | Exercise capacity | Left ventricular function | Body composition | Hemo-dynamic variables | Lipid and inflammation profile | Quality of life |
| **Amundsen et al., 2008** | N=17<br>IE: 63 ± 11yr<br>CE: 61 ± 7yr | CAD patients (not including MI in past 3 months or CABG in past 12 months) | 10 weeks<br>Uphill treadmill walking<br>5 min warm-up and 5 min cool-down<br>Isocaloric | 41 min<br>50-60% VO2 peak | 4 X 4 min at 80 -90% VO2 peak, 3 X 4 50-60% VO2 peak | Peak $VO_2$ ↑: IE: 17%, CE: 8%. Significant between the groups | No change in LVEF<br>E wave ↑ both<br>A wave ↑ CE | ---- | HR no change | ---- | --- |
| **Conraads et al., 2015** | N = 174<br>IE: 57 ± 8.8<br>CE: 60 ± 9.2 | CAD patients post MI, CABG, or PCI EF>40% | 12 weeks<br>3 session per week<br>Stationary bike | 47 min (including 10min warm-up and cool-down)<br>>60-70% peakVO2 | 38 min (including 10min warm-up and cool-down)<br>4X4 min 85-90% peakVO2 3X4 60-70% peak VO2 | Peak $VO_2$ ↑: IE: 20%, CE: 23%. Not significant between the groups<br>Peak workload increased within both groups | Was not reported | Did not change | HR and DBP ↓<br>SBP tended to decrease | TC, HDL-C ↑ in both groups<br>hs-CRP ↓ in both groups | QOL ↑ in both groups |

| | Study population | | Training protocols | | | Outcomes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Reference | N, Age (years, mean ± SD) | Inclusion | Length of study. Exercise instruments | Continuous exercise prescription | Interval exercise prescription | Exercise capacity | Left ventricular function | Body composition | Hemo-dynamic variables | Lipid and inflammation profile | Quality of life |
| **Currie et al., 2013** | N=22<br>IE: 62 ± 11yr<br>CE: 68 ± 8yr | CAD patients: MI, PCI, CABG, positive stress test<br>Recruited on entry to CR. | 12 weeks<br>2 sessions per week<br>1 additional session a week<br>Cycling only<br>. | 30 to 50 min gradually<br>THR: 51-65% PPO<br>Patients were instructed to add an unsupervised session a week | 20 min<br>10 X 1 min 80-104% PPO. 10 X 1 min 10% PPO | Peak $VO_2$ ↑: IE: 24%, CE: 19%. Significant within the groups<br>PPO ↑: IE: 19%, CE: 23%. Significant within the groups | --- | --- | HR and DBP ↓ both<br>SBP no change | --- | --- |
| **Keteyian et al., 2014** | N=39<br>IE: 60 ± 7yr<br>CE: 58 ± 9yr | MI, PCI, CABG | 10 weeks (+2 weeks run –in)<br>3 sessions per week<br>Treadmill only | 30 min (not including 5 min warm-up and cool-down)<br>THR: 60-80% HRR | 31 min (not including 5 min warm-up and cool-down)<br>4 X 4 min at 80-90% HRR<br>3 X 4 min at 60-70% HRR | Peak $VO_2$ ↑: IE: 16%, CE: 8%. Significant between the groups<br>Test time ↑: IE: 13.5%, CE: 13.3%. Significant within the groups<br>$VO_2$ at VT ↑: IE: 21%, CE: 5%. Significant between groups | --- | --- | DBP ↓<br>HR and SBP no change | --- | --- |

| | Study population | | Training protocols | | | Outcomes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Reference | N, Age (years, mean ± SD) | Inclusion | Length of study. Sessions per week | Continuous exercise prescription | Interval exercise prescription | Exercise capacity | Left ventricular function | Body composition | Hemo-dynamic variables | Lipid and inflammation profile | Quality of life |
| **Moholdt et al., 2009** | N=69<br><br>IE: 60.2 ± 6.8yr<br><br>CE: 62.0 ± 7.6yr | 4-6 weeks post CABG | 4 weeks. Inpatient CR<br>5 times a week<br>Follow-up at 6 months Treadmill only. Isocaloric | 46 min<br><br>THR: 70% MHR | 38 min<br><br>4 X 4 min at 90% MHR<br><br>3 X 3 min at 70% MHR | 4 weeks: peak $VO_2$ ↑ : IE: 12%, CE: 9%.<br>Significant within the groups<br>6 months: Peak $VO_2$ ↑: IE: 5.9%, CE: 3.5%. Sig between | No changes in systolic variables<br>IE: MV-E ↓. different from CE.<br>No other diastolic changes | No changes | HR rest ↓ within groups.<br>BP N/A | No changes in LDL-C, HDL-C, TG, and Glucose | ↑ within both groups |
| **Moholdt et al., 2011 + Follow-up (2011)** | N=107 Baseline: IE: 60.2 ± 6.8yr. CE: 62.0 ± 7.6yr<br><br>6 mo: N=83,<br>30 mo: N = 69 | 2-12 weeks post MI | 12 weeks 2 sessions per week 1 session at home<br><br>6 months and 30 months follow-up | Usual care: 60 min Warm-up, cool down, stretching 35 min of aerobic exercises | 38 min Warm-up and cool-down<br>4 X 4 min at 85-95% MHR. 3 X 4 min at 70% MHR | Peak VO2 ↑: IE: 14%, CE: 7.5%. Significant between groups<br>6 months: IE: peak $VO_2$↓ NS UC: peak $VO_2$↓ NS<br>30 months: IE $VO_2$↓ similar to baseline. UC: $VO_2$↓ lower than baseline<br>Sig between the groups | | No changes<br><br>No changes | HR rest ↓ only in usual care BP N/A<br>No changes in HR<br>No changes in HR | HDL-C ↑ only in IE group<br><br>No changes at 6 months. Not measured at 30 months | QOL ↑ in both groups<br><br>↑ within sig vs. baseline in both groups |

| | Study population | | Training protocols | | | | Outcomes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | N, Age (years, mean ± SD) | Inclusion | Length of study. Exercise instruments | Continuous exercise prescription | Interval exercise prescription | Exercise capacity | Left ventricular function | Body composition | Hemo-dynamic variables | Lipid and inflammation profile | Quality of life |
| **Munk et al., 2009** | N=40<br><br>IE: 57 ± 14yr<br><br>Control: 61 ± 10yr | > 11 ± 4 days post PCI | 26 weeks (6 months)<br><br>3 sessions per week<br><br>Control: no exercise | N/A | 60 min: 10 min warm-up, 20 cool-down and exercises<br><br>30 min jogging or cycling<br><br>4 min at 90-95% MHR, 3 min at 60-70% MHR | Peak $VO_2$ ↑: IE: 17%, Control: 8%. Significant between groups<br><br>PPO ↑: IE: 12.2%, Control: 3%. Significant between groups<br><br>$VO_2$ at VT ↑: Significant between groups | --- | BMI: Significant between groups (in favor IE). | HR rest: Significant between groups (IE > CE).<br><br>BP no change | hs-CRP ↓ only in IE. Significant between groups | --- |
| **Rocco et al., 2012** | N=37<br><br>IE: 56.5 ± 3yr<br><br>CE: 62.5 ± 2yr | Stable CAD patients | 3 months<br><br>3 sessions per week | 60 min including 5 min warm-up and cool-down<br><br>50 min at VT | 42 min.<br><br>7 X 3 min at 80-90% Peak $VO_2$<br><br>7 X 3 min at 70-80% Peak $VO_2$ | Peak $VO_2$ ↑: IE: 25%, CE: 23%. Significant within the groups | --- | No changes | --- | --- | --- |

| | Study population | | Training protocols | | | Outcomes | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | N, Age (years, mean ± SD) | Inclusion | Length of study. Exercise instruments | Continuous exercise prescription | Interval exercise prescription | Exercise capacity | Left ventricular function | Body composition | Hemo-dynamic variables | Lipid and inflammation profile | Quality of life |
| **Rognmo et al., 2004** | N=21<br><br>IE: 62.9 ± 11.2yr<br><br>CE: 61.2 ± 7.3yr | CAD patients:<br><br>post MI, CABG or PCI (>12 months) | 10 weeks<br><br>3 sessions per week<br><br>Treadmill only. Isocaloric programs | 41 min<br><br>50-60% peak $VO_2$ | 33 min including warm-up and cool-down<br><br>4 min at 80-90% peak $VO_2$<br><br>3 min at 50-60% peak $VO_2$ | Peak $VO_2$ ↑: IE: 18%, CE: 8%. Significant between the groups | -- | No changes | No changes | --- | --- |
| **Warburton et al., 2004** | N=14<br><br>IE: 55 ± 7yr<br><br>CE: 57 ± 8yr | CAD patients:<br><br>post CABG or PCI (>6 months)<br><br>Only fit patients (> 9 METS) | 16 weeks<br><br>2 sessions per week, 3 various machines. 3 more days/week at 65% HRR. | 50 min including warm-up and cool-down<br><br>30 min at 65% HRR | 50 min including warm-up and cool-down<br><br>8 X 2 min at 90% HRR<br><br>7 X 2 min at 40% HRR | Peak $VO_2$ ↑: IE and CE (no data was presented). Significant within groups<br><br>Time to exhaustion ↑: IE improved significantly more than CE. | --- | Body weight ↓ within both groups. | No changes | --- | --- |

**CAD**: coronary artery disease; **CE**: continuous exercise; **IE**: interval exercise; **HR**: heart rate; **BP**: blood pressure; **SBP**: systolic blood pressure; **DBP**: diastolic blood pressure; **MI**: myocardial infarction; **PCI**: percutanuous coronary intervention; **CABG**: coronary artery bypass graft; **PPO**: peak power output; **THR**: target heart rate; **HRR**: heart rate reserve; **VT**: ventilatory threshold; **LDL**: low density lipoprotein; **HDL**: high density lipoprotein; **TG**: triglycerides; **MHR**: maximal heart rate; **MV-E**: mitral valve E wave; **hs-CRP**: high sensitive C-reactive protein; **NS**: non-significant; **N/A:** non-applicable.

# Chapter 3
# General Methods

## Settings

The typical cardiac rehabilitation (CR) program in Israel lasts for 3 months minimum and the main component of the CR program is the exercise training. Patients attend the CR program twice a week for 60 minutes of exercise. The exercise session is comprised of a 5-10 minutes dynamic warm up, 40 minutes of aerobic training on different instruments and a 5-10 minutes cool-down. An exercise trainer and a nurse are always present in the exercise room. The medical staff in the CR includes a cardiologist; a nurse who monitors the patients and assists with medical issues during the exercise class; an exercise physiologist who prescribes and updates the exercise plan; and an exercise trainer who follows the patient's program and assists with recording the data in the patient's personal training file. The personal training file consists of a training form (Appendix B) which specifies a brief medical observation, cardiac risk factors, orthopaedic limitations, and also includes the individualized exercise program. All training files are located in a room and are accessible for the patients before their sessions.

The exercise physiologist supervises the sessions frequently while being constantly updated by the trainer. In this study, since all trainers guided patients from both groups, they were instructed by the exercise physiologist to treat all patients equally, in terms of encouragement and assistance during the sessions in order to prevent bias. Due to the circumstances that the trainers were responsible for training all subjects according to their exercise programs, they could not have been blinded for group allocations.

## Participants

Eighty-four cardiac patients were recruited for a parallel-group study between May 2011 and May 2014. All patients were enrolled in a CR program within the Coronary Rehabilitation and Cardiovascular Disease Unit, Division of Cardiology, Assaf Harofeh Medical Center, affiliated to the Sackler School of Medicine, Tel

Aviv University, Israel. Patients were eligible for inclusion if they were aged between 40-75 years, and had undergone MI, percutaneous coronary intervention (PCI) or CABG during the previous ten months. Patients were excluded if they had previously confirmed chronic heart failure according to the New-York Heart Association (NYHA at stages II, III), uncontrolled arrhythmias, severe ischemia and or angina, severe valve disease, implantable cardioversion device (ICD), pacemakers, severe LV dysfunction (LVEF < 25%), or orthopaedic limitations as indicated in their medical notes and /or questioning during the initial consultation. Participants provided written informed consent and the study complied with the Declaration of Helsinki (World Medical Association, 2013). The study protocol was approved by the Assaf Harofeh Medical Center Institutional Review Board (Study ID Number 175/10).

## Study design

The study was held at the outpatient cardiac rehabilitation centre, where all patients were pre-screened by the same exercise physiologist. Detailed medical histories were obtained, including evaluation of the cardiac history. All patients underwent an assessment of height, weight and body composition, and resting haemodynamics. In addition, demographic information was collected from the patients by a questionnaire. The Short Form 36 (SF-36) quality of life (QoL) questionnaire (Ware, Kosinski & Keller, 1994) was completed. Eligible patients entered the study after one month of supervised exercise-based cardiac rehabilitation. This “lead in” period enabled the participants to become familiar with exercise across a range of activities. Safety considerations were emphasized in terms of potentially adverse cardiovascular events and musculoskeletal injury (Scheinowitz & Harpaz, 2005). Furthermore, due to a negative dose-response relationship between physical fitness and cardiac risk (Giri *et al*, 1999; Hallqvist *et al*, 2000; Mittleman *et al.*, 1993), an important feature of the design was to establish appropriate baseline fitness before reaching higher intensity levels.

Each patient underwent assessment at three discrete time points; at the end of the lead-in phase (Baseline), immediately upon completion of a 3-month exercise intervention (Post), and 6-months after completion (Follow-up) of the intervention. Follow-up testing was irrespective of whether or not the patient was still attending for exercise-based cardiac rehabilitation. Any appearances of symptoms, cardiac

events and subsequent hospitalization during the 3-month training phase and/or 6-month follow-up phase were documented as required. In cases of symptoms manifesting during exercise sessions a nurse examined the patient and documented the event. On occasions when a patient was hospitalized during either the intervention or follow-up period, he or she was instructed to notify the medical staff at the CR centre and to send the hospital's documents immediately post discharge. During the follow-up phase patients were asked to report changes in their health status including appearance of symptoms, cardiac events and or hospitalizations due to cardiac symptoms/events.

## Protocol

Preceding the day of measurements patients were instructed to refrain from food and beverages for 12 hours, as well as avoiding strenuous physical activity for 72 hours, and to avoid the consumption of caffeine and alcohol 72 hours before their visit. Also, for safety reasons, patients were instructed to take their cardiac medications as normal on medical assessment day. On the day of testing participants reported to the Department of Cardiology at 8 am. A fasting venous blood sample was drawn by a research nurse, after which the patients had a small breakfast. Approximately 30 minutes later patients underwent an echocardiographic examination, undertaken by a trained sonographer. Finally, a cardiopulmonary exercise test (CPET) was performed under the supervision of the exercise physiologist in a temperature controlled laboratory at the Pulmonary Institute, Assaf Harofeh Medical Center, which is located in a separate building close to the Department of Cardiology. Patients completed their medical assessments by approximately 11 am. All measurements, except for CPET, were conducted by researchers blinded to the patients' group allocation and time point of the study. CPET were performed by the exercise physiologist who was not blinded to group allocation, but was the only available qualified person in the hospital to conduct these tests.

## Measurements

### Blood Analyses

*Sampling procedure*

Upon arrival to the Cardiology Institute, fasting venous blood was drawn from the patient by a nurse. Phlebotomy was performed after 12 hours of overnight fasting. A 23G butterfly needle was used to draw the patient's blood from the antecubital area of the arm .One 4cc Serum Separator Clot Activator Gel Vacuette ® tube was used to collect blood for the assessment of TG, blood glucose, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), cardiac troponin-T (cTnT), and high sensitivity C-reactive Protein (hs-CRP). Also, one 3cc EDTA K2 Vacuette® tube was used to collect blood for analyzing HbA1C. Once the tubes were obtained, they were transferred by the nurse to the chemistry laboratory in the Division of Laboratories, Assaf Harofeh Medical Center. The laboratory staff placed a unique barcode on each tube and entered the data into the records system. The tubes were then put in the Modular Pre–Analytics analyzer (MPA) (Cobas, Rozkreuz, Switzerland) for the centrifuge process (not including HbA1c which is not being centrifuged). Subsequently, the tubes were transported by a conveyor belt to the analyser. Quality control including precision and coefficients of variation of the blood analysers is presented in Appendix H.

*Laboratory Analyses*

Blood samples were analysed for glucose, HbA1c, lipids (HDL-C, LDL-C, and TG), cardiac biomarkers (cTnT), and Hs-CRP. All of the laboratory staff were blinded for group allocation and time point in the study. A Roche ® Modular Clinical Chemistry analyzer (Cobas ® E170, Cobas, Rozkreuz, Switzerland) was used to measure TG, HDL-C and glucose. The method used was an in vitro enzymatic colorimetric assay for the quantitative determination of the different analyses in the human plasma. A Cobas ® Integra 800 Clinical analyzer was used to measure glycosylated hemoglobin (HbA1c by whole blood application- standardized according to IFCC transferable to DCCT/NGSP). The anticoagulated whole blood specimen was hemolyzed automatically on the Cobas ® Integra 800 with Cobas ® Integra hemolyzing reagent. All hemoglobin variants which are glycated at the beta

chain N-terminal and which have antibody-recognizable regions identical to that of HbA1c were determined by this assay.

*Cardiac markers*

Measurement of the cardiac biomarker cTnT was performed using a Roche Modular E170 analyzer (Cobas ® E170, Cobas, Rozkreuz, Switzerland). The electro-chemiluminescence Immunoassay "ECLIA" was used for in vitro quantitative determination of cardiac cTnT in human plasma on the cobas E. The modern Roche analyzer can detect cTnT levels as low as 0.013 ng/ml. Thus, values from the lab were accepted as either < 0.013 ng/ml, or a valid value equal and above it. Therefore, data will not be presented as mean and SD, but as the number and percentage of patients below and above 0.014 ng/ml; which is the 99th percentile of a healthy reference population recommended as a positivity threshold for the diagnosis of acute myocardial infarction with the Cobas E (Koerbin, Tate & Hickman, 2010; Zhelev *et al.,* 2015).

Measurement of hs- CRP was also carried out in the Roche Modular Clinical Chemistry analyzer using a particle enhanced immunoturbidimetric assay. Human CRP agglutinates with latex particles coated with monoclonal anti- CRP antibodies. The aggregates were determined turbid metrically.

**Anthropometric measurements**

Height was measured to the nearest centimetre using a standard measurement tape (FT-041, Wintape Measuring Tape, Foshan, China). Patients stood upright, barefoot, with their heels pressed against the wall. Weight, body composition and body mass index were measured using an Omron BF-508 Bioelectrical Impedance Analysis (BIA) (Omron BF-508, Hoofddorp, Netherlands). The Omron BF-508 estimates body composition by sending electrical currents through the hands via handheld electrodes and the feet via electrodes on the scale's surface. The combination of handheld and scale electrodes take into account both the upper and lower body when percent of body fat (BF) is estimated (Pribyl, Smith & Grimes, 2011). After inputting the subjects' data, including age, gender, and height, subjects stood barefoot on the scale while holding the hand sensors parallel to the ground. At this time an extremely weak electrical current of 50 kHz and less than 500 µA was passed through their body. BIA measures the impedance or resistance

to the signal as it travels through the water that is found in muscle and fat. The more muscle a person has, the more water their body can hold, hence the easier it is for the current to pass through it. The more fat in the body, the more resistance to the current exists and the percentage is increased.

Waist circumference (WC) was measured using a measurement tape (BWT-006, Wintape Measuring Tape, Foshan, China) that was placed in a horizontal plane around the abdomen at the midway point between the iliac crest (hip bone) and the lower rib. The patients were instructed to stand up straight, arms besides the body and the legs are slightly spread apart. The measurement was made at the end of a normal expiration (NIH, NHLBI, 2000). Abdominal fat is an independent risk factor for disease. Men who have WC greater than 102 cm and women who have WC greater than 88 cm are at greater risk for diabetes, hypertension, dyslipidemia and cardiovascular disease (NIH, NHLBI, 2000).

**Resting Hemodynamics**

Following at least five minutes of seated rest, resting heart rate and systolic and diastolic blood pressures were recorded by an automatic blood pressure monitor (Connex® ProBP™ 3400 Digital Blood Pressure Device, Welch Allyn, USA). The measurement was performed at least twice (with 2-3 minutes apart) in order to confirm validity and reliability and the average result was recorded (Pickering et al., 2005).

**Quality of Life**

Quality of life was measured by the Hebrew translation of the Medical Outcomes Study (MOS) Short Form 36 (SF-36) Health Survey. The SF-36 was developed by the Rand Corporation (Santa Monica, CA, USA) and has been tested and validated in various national cardiac populations (Brown *et al.,* 1999). The Hebrew version was translated and validated by Lewin-Epstein *et al. (*Lewin-Epstein, Sagiv-Schifter, Shabtai & Shmueli,1998).

*The SF-36 structure*

The SF-36 questionnaire consists of 36 items which are divided into eight dimensions (Brown *et al.,* 1999; Dempster & Donnelly, 2000; Ware *et al.,* 1994): physical functioning (ten items); social functioning (two items); general health perception (five items); physical role limitations (four items); emotional role

limitations (three items); bodily pain (two items) energy/vitality (four items); and mental health(five items). Three summary measures are calculated (Shmueli, 1998): overall score: mean of all eight scales; physical health measure (PH): the mean of three scales including the physical functioning, role physical and bodily pain; mental health score (MH); the mean of three scales including mental health, role emotional, and social functioning. An example of the SF-36 QoL questionnaire and the model of the questionnaire can be found in appendix A. Each of the scores for the domains are coded, summed, and transformed on to a scale of 0-100, with zero being the worst health and one hundred being the best health (Brown *et al.,* 1999). The SF-36 is commonly used to differentiate physical and emotional aspects of quality of life before and after a disease had occurred using a time frame of previous four weeks or during the past year.

*SF-36 uses and advantages*

The SF-36 questionnaire was selected as an assessment tool in this current study due to its substantial validity (Brazier *et al.*, 1992), good internal consistency, and high test-retest reliability (Brazier *et al.,* 1992; Dempster & Donnelly, 2000). Even though it is not a disease specific tool, it has been used in 24% of the studies involving patients in cardiac rehabilitation programs (Dempster & Donnelly, 2000). In a review that had examined the SF-36 questionnaire among cardiac rehabilitation patients, it seems clear that the SF -36 is a sensitive, valid tool that is appropriate for using with this population (Brown, 2003; Lindsay, Hanlon, Smith & Wheatley). Additionally, the SF-36 questionnaire had been reported to be easily administrated, requires minimal staff time for explaining, scoring and interpreting, preferably self-administered, cost effective and with relatively high response rates (Brazier *et al.,* 1992; Brown, 2003). It is also the one of the shortest generic health related QoL questionnaire since it takes approximately 5-10 minutes to complete it, which makes it very tolerable among patients (Brazier *et al.,* 1992; Dempster, Donnelly & O'Loughlin, 2004).

In the present study the SF-36 questionnaire was self-administered. The patient sat in a quiet room and paid a close attention to the questions in the questionnaire, especially to the different time frames. The exercise physiologist was in an adjacent room, prepared to answer any questions that had risen.

**Echocardiography**

Standard echocardiography was performed at rest using a Vivid 9 scanner and M5S cardiac probe (General Electric, Horton, Norway) with a frame velocity of >50 FPS (frame per second). Data were obtained and analysed by two separate experienced operators (R.S. experienced for 20 years, and C.B. experienced for 10 years) who were both blinded for group allocation and time points in the study. Both sonographers are thoroughly experienced with the Vivid 9 scanner. The technician performed the examination using a two-chamber and four-chamber apical views and recorded the results both on the scanner and on a disc. For each patient 14 echograms were performed during each time point. All measurements were obtained and analysed by the sonographer. Following the test, a cardiologist specializing in echocardiography re-analysed the results. Appendix H describes the intra-observer and inter-observer reliability of both sonographers. Figure 1 demonstrates an echocardiography examination.

*Systolic function*

End diastolic volume (EDV), end systolic volume (ESV) and left ventricular ejection fraction (LVEF) were measured using the method of discs (Simpson's Rule) according to the recommendations of the American Association of Echocardiography (ASE). In this method the multiple cylinders that are measured along the LV are summed. LVEF is calculated as the difference between end diastolic and end systolic volume divided by end diastolic volume (Gottdiener *et al.,* 2004). LVEF $\geq$ 55% is considered to be normal value of left ventricular systolic function (Lang *et al.,* 2005).

*Diastolic function*

Pulse wave (PW) Doppler, obtained from a four-chamber apical view, was used to evaluate early (E) diastolic mitral inflow velocity, late (A) diastolic mitral inflow velocity, and mitral valve deceleration time (MV-DT) of early filling velocity. A subsequent E/A ratio was computed as a marker of relaxation patterns. Up to age around 60 years, E/A ratio of > 1.0 is considered normal, while a ratio < 1.0 may imply diastolic dysfunction. In some guidelines the reference value of E/A > 0.8 is also considered to be normal (Nagueh *et al.,* 2009). In older individuals E/A ratio is more complex and is even more affected by hemodynamic factors, therefore,

additional indices were included in the echocardiography measurements (Nagueh *et al.,* 2009). Normal values of MV-DT included durations between 160 – 200 ms (Nagueh *et al.,* 2009) or 140 to 220 ms (Moller *et al.,* 2003). For obtaining mitral inflow velocity values, a sample volume was placed 2 mm above the tip of the mitral valve leaflets (Estefania *et al.,* 2011; Nagueh *et al.,* 2009).

Pulse wave tissue Doppler imaging (TDI) was performed in the apical views to obtain mitral annular velocities. The primary measurement was early diastolic annular velocity that is expressed as e'. Provided LV relaxation is impaired the e' velocity is reduced. Following to this measurement the ratio of the mitral inflow E velocity to tissue Doppler e' was calculated (E/e'). The sample volume was placed once at the basal septum and once at the lateral insertion site of the mitral leaflets. The e' velocities attained from the septal and the lateral sides of the mitral annulus were averaged, since septal e' is usually lower compared to lateral e' velocity. Using only one side would change the E/e' ratio and thus the reference values would not be relevant. A ratio $\leq$ 8 is considered to indicate normal LV filling pressures, while a ratio $\geq$15 usually indicates an increased LV filling pressures (Nagueh *et al.,* 2009). When the ratio is between 8 and 15, additional indices should be used such as pulmonary artery pressure, and the left atrial (LA) volume. Diastolic dysfunction was graded in 4 levels according to established guidelines: normal function, impaired relaxation (Grade I), pseudonormal relaxation (Grade II), and restrictive filling (Grade III) (Khouri, Maly, Suh & Walsh, 2004; Nagueh *et al.,* 2009) (Figure 2).

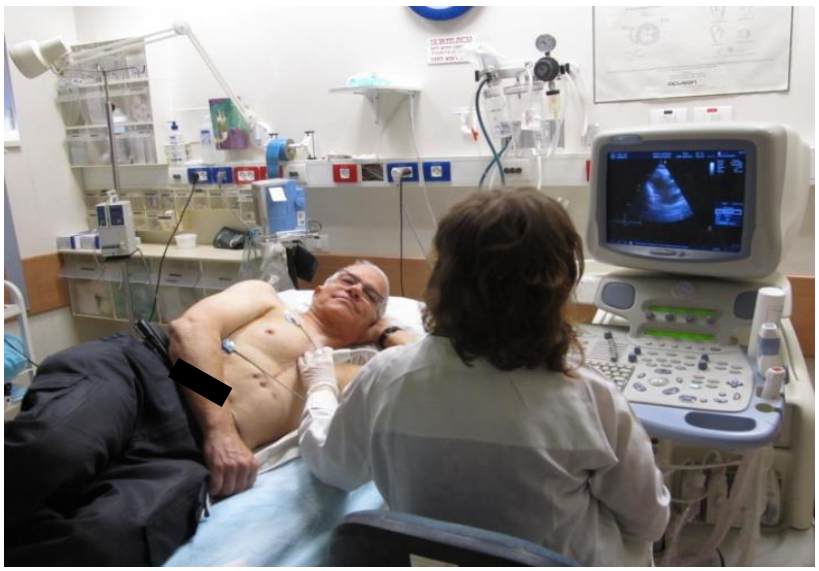


Figure 1 A photograph of a patient undergoing echocardiography.

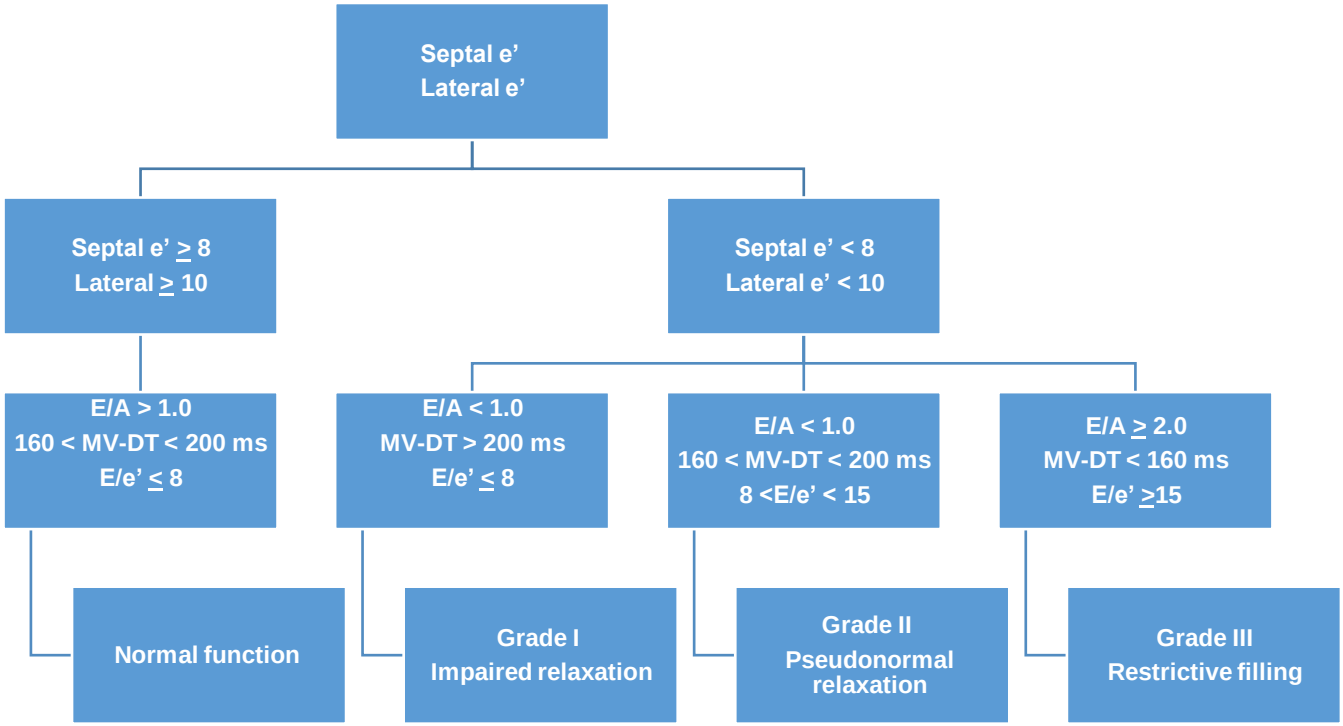
**Table 3. Variables included in echocardiography assessment**

| Variable | Description |
|---|---|
| LA area ($mm^2$) | The size of the left atrium. An indicator of severity of diastolic dysfunction. |
| **Systolic function** | |
| EDV (ml) | The frame in the cardiac cycle in which LV dimension is the largest |
| ESV (ml) | The frame in the cardiac cycle in which the cardiac dimension is the smallest |
| SV (ml) | The difference between EDV and ESV |
| Calculated LVEF(%) | LVEF = (EDV-ESV)/EDV |
| **Diastolic function** | |
| MV-E (cm/s) | Represents the early passive filling of the left ventricle |
| MV-A (cm/s) | Represents the late and active filling of the left ventricle |
| E/A ratio | The ratio of peak early to late diastolic filling velocities which is used to assess diastolic filling and function. |
| MV-DT (ms) | The time taken from the maximum point of MV-E wave to baseline |
| e' (ms) | The average of the lateral and septal mitral annulus velocities. Reflects the velocity of early myocardial relaxation during early rapid LV filling |
| E/e' | The ratio between MV-E wave and e' which correlates with LV filling pressures during diastole |

**LA:** left atrium; **EDV**: end diastolic volume. **ESV**: end systolic volume. **LVEF**: left ventricular ejection fraction. **SV**: stroke volume; **MV-E**: early diastolic mitral inflow velocity. **MV-A**: late diastolic mitral inflow velocity. **MV-DT**: mitral valve deceleration time. **e'**: average of septal and lateral e'

(Lang *et al.,* 2015; Nagueh *et al.,* 2009; Khouri *et al.,* 2004)

**Figure 2. Grading of diastolic dysfunction**




(Khouri *et al.,* 2004; Nagueh *et al.,* 2009)

Left atrium area was measured from the apical four chamber view at the end of systole, just before the opening of the mitral valve when the left atria is in its greatest dimension (Lang *et al.,* 2005). The reference value of normal LA area is <20 $cm^2$, with abnormal values of LA area > 40 $cm^2$ (Lang *et al.,* 2005) that might indicate poor prognosis for cardiac patients (Moller *et al.,* 2003).

**Cardiopulmonary exercise test –CPET**

*Equipment and preparations*

The patients were instructed to take their medications as usual, including the beta-blockers, in order for the test to be under safe conditions and for the exercise physiologist to be able to prescribe an exercise program under normal conditions. The exercise test was conducted between 9:30-10:30 in the morning following the other measurements and after a small breakfast. The patients were instructed to avoid strenuous physical activity 72 hours before the exercise test.

Maximal exercise capacity ($VO_2$ max) was determined using an automated metabolic system (ZAN600 CPET, nSpire Health GmbH, Oberthulba, Germany) and a progressive incremental test on a cycle ergometer (Ram, 660 BP) until volitional exhaustion. Before each test, the gas analyser was calibrated using a calibration gas mixture with accurately known concentration (16% $O_2$ and 4% $CO_2$) and ambient air. The turbine flow meter was calibrated before each test using a 3 litter tank at several flow rates. Room temperature was monitored as well and set between 21-23$^{o}$c. The seat of the bike was adjusted to each participant according to their leg length, while their feet were strapped to the pedals. Subjects were instructed to hold the hand bar gently, and to sit during the entire test. Participants breathed through a facemask attached to a one-way valve. Figure 3 demonstrates a patient undergoing a CPET.

*Exercise test protocol*

The CPET was performed according to the AHA, the American College of Chest Physicians (ACCP), and the American Thoracic Society (ATS) guidelines (ATS/ACCP, 2003; Balady *et al.,* 2010). A ramp test protocol was used including 2 minutes of rest and 2 min of a warm-up at 10 watts followed by 15 watts increments every minute for men and 10 watts increments for women. The ramp protocol was designed so the exercise test will be terminated after 8-12 minutes as recommended by the AHA (Fletcher *et al.,* 2013). The patients were asked to exercise to exhaustion while maintaining a constant pedalling pace of 60-70 RPM. Gas exchange data were collected breath-by-breath while a 12- lead ECG was continuously monitoring the patients.

Subjects were instructed to avoid talking during the test for eliminating electrocardiogram (ECG) artifacts and gas exchange interferences. An ECG recording was printed every 2 minutes for better observation. Blood pressure was measured manually (Tycos® 509 Manual Blood Pressure Device, Welch Allyn, USA) during rest and every 2 minutes. The patients were asked to let go of the hand bar and straighten their arm for each measurement. Blood pressure was also taken during the first minute of recovery and during the last minute of the recovery. The rating of perceived exertion (RPE) using the 6-20 Borg scale was explained to the subjects before the exercise test. Then, it was presented to the patients during the test every 2 minutes and the patients had to point at the number and/or the

description, which was next recorded on the ECG printout. The test was terminated with subjective rating of perceived exertion (RPE)≥ 17 using the Borg scale 6-20, appearance of symptoms, or ECG changes. Recovery parameters were obtained for 3 minutes. A physician was present in the adjacent room for an event of emergency. Following the test a cardiologist examined the ECG for abnormal manifestations.

*Variables obtained*

The outcomes that had been selected were based on earlier published CPET guidelines (Arena & Sietsema, 2011; Balady *et al.,* 2010; Guazzi *et al.,* 2012; Mezzani *et al.,* 2009; Milani, Lavie, Mehra & Ventura, 2006). These parameters had also been used in previous studies that examined interval training among CAD patients (Moholdt *et al.,* 2009; Munk *et al.,* 2009; Rognmo *et al.,* 2004; Warburton *et al.,* 2004; Wisloff *et al.,* 2007). The parameters that were obtained during the test are presented in Table 4.

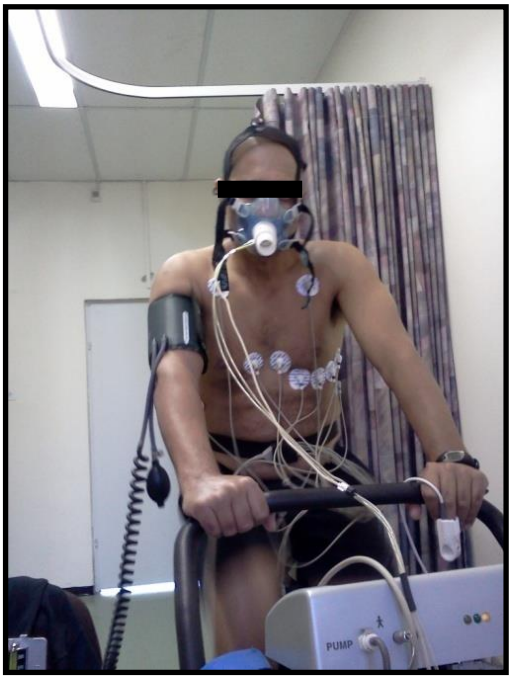



Figure 3. A photograph of a patient undergoing CPET.

**Table 4. Parameters obtained during the CPET**

| Parameters | Description |
|---|---|
| $VO_2$ peak (ml/min/kg) | Defines the limits of the cardiopulmonary system. It is usually expressed in millilitres of $O_2$ per kilogram body weight per minute, in order to detect differences between subjects (Balady *et al.,* 2010). Since $VO_2$max is rarely achieved within CAD patients, it is common to use the peak $VO_2$ achieved during the exercise test (Fletcher *et al.,* 2013; Balady *et al.,* 2010). |
| Maximal heart rate (beats per minute) | The highest heart rate reached at the end of the test using the ECG monitor and pulse oximeter. |
| Maximal blood pressure (mm/Hg) | Blood pressure was measured manually every 2 minutes throughout the test. The maximal blood pressure was the highest blood pressure recorded at the end of the exercise. |
| Maximal rate pressure product (RPP) | The product of maximal heart rate and maximal systolic blood pressure. It reflects myocardial $O_2$ uptake which is correlated linearly to coronary blood flow (Fletcher *et al.,* 2013). |
| Respiratory exchange ratio (RER) | The ratio between $VCO_2$ and $VO_2$ ($VCO_2$/ $VO_2$). It is a reliable estimate of subject's effort with a peak RER of > 1.10 as an excellent indication of a maximal effort. |
| Duration of the test (min) | Duration of tests was obtained as an indicator of exercise endurance changes. |
| Maximal load (watt) | The maximal load that was reached at the end of the test was recorded as reflection of maximal effort and capacity. |
| Ventilatory threshold (VT, ml/kg/min) | Reflects the anaerobic threshold. The methods for detecting the VT that were used included the following: 1. The departure of $VO_2$ from a line of a plot of $VCO_2$ versus $VO_2$ (the V-slope). 2. The point at which there is an increase in the ventilatory equivalent for $O_2$ (VE/ $VO_2$) without an increase in the ventilatory equivalent for $CO_2$ (VE/$VCO_2$) (Balady, 2010; ATS, 2003). VT was expressed as percentage of predicted maximal $VO_2$ peak. |
| Rating of perceived exertion (RPE) | Was measured every 2 minutes. Test termination at an RPE $\geq$ 17 is usually used as an indication of a maximal exercise test. |
| Submaximal variables | These were collected at three different loads (30, 60, and 90 watts). These variables included RPE, $VO_2$, HR, and RER. The purpose was to be able to detect changes that occur during submaximal levels that might indicate cardiorespiratory improvements. |

## Symptoms, cardiac related events, and hospitalizations

Patients were instructed to report of any occurrences of cardiac symptoms, cardiac related events and or hospitalizations. Data was recorded throughout the whole study. Additionally, the exercise physiologist asked about these occurrences at the beginning of the intervention, at the monthly meetings, following the intervention, and at the end of the 6 months follow-up.

## Data handling and Statistical Analyses

Power analysis was conducted to determine the optimal sample size for this study. To detect a statistically significant effect of training on the primary outcome variable, peak $VO_2$, it was determined that a difference of 2 ± 2.45 ml/kg/min was required. This value is based on the findings reported in previous studies (Moholdt *et al.,* 2009; Moholdt *et al.,* 2011; and Rognmo *et al.,* 2004). With a two-tailed 5% significance level and a power of 90%, a sample size of 33 patients per group was necessary. Given a dropout rate of at least 10%, we had planned to recruit 84 patients.

Statistical analysis was conducted using SPSS 20 (SPSS Inc, Chicago, Illinois). In chapters 4 and 5, T-tests and Chi-squared tests were used for baseline comparisons (according to the type of variables). Mixed ANOVA repeated measures analysis was used for detecting differences between the groups following the intervention. For the analysis presented in Chapter 6, multiple regression using the “Enter” method was applied on different parameters for the purposes of finding the strongest associations that can explain changes in cardiorespiratory fitness. Specific descriptions of the statistical analysis are presented in each experimental chapter separately.

# Chapter 4

# Comparison between moderate continuous exercise and moderate-high interval exercise over 3 months of intervention


## Summary

Exercise-based CR increases peak $VO_2$, which is an important predictor of cardiac related mortality. However, it is still unclear what the optimal prescription is for the most beneficial effects of exercise-based CR. The purpose of this single-site, prospective, randomized controlled trial was to compare the effects of two different training prescriptions on peak $VO_2$, clinical parameters and health-related quality of life in a real-life CR setting. Cardiac patients (N = 84), recruited after 4 weeks of standard centre-based CR training, were randomized to a 12-week program of twice weekly sessions of either moderate aerobic continuous exercise (CE) training or moderate-high aerobic interval exercise (IE) training. Seventy-two patients (68 men and 5 women) completed the exercise training. Peak $VO_2$ (ml/kg/min) increased significantly in both groups (CE 6.3% versus IE 6.3%, $p < 0.05$), with no differences between them ($P = 0.84$). In contrast, improvements in exercise test duration and maximal output were greater in the IE group compared to the CE, along with several submaximal variables that were improved within the IE group solely, suggesting augmented exercise tolerance and improved activities of daily living following interval training. No systolic or diastolic changes occurred in the echocardiography measurements for either group. In addition, body composition and hemodynamic variables were not affected, except for a small reduction in waist circumference within the IE group only. Blood lipids did not change over time; however, HbA1c decreased slightly following interval training (by 0.17%, $p < 0.005$) which might have some clinical relevance. Also, hs-CRP was reduced in the IE group alone (by 21.8%, $p < 0.05$) which might have a beneficial effect on cardiovascular risk. QoL indices increased in both groups significantly, including their physical and mental scores ($p < 0.05$) regardless of group affiliation. In conclusion, a 12-week IE and CE intervention in a CR setting are equally effective to improve cardiorespiratory fitness and QoL. However, using IE may result in

greater improvements in some cardiovascular risk factors. These conclusions should be taken into account when prescribing training programs in a standard centre-based CR setting.

## Introduction

Previous clinical trials of interval training with CAD patients in CR have used various designs and training methods (Table 2). In fact, all reviewed interval training studies report different durations of interventions, various training protocols, different frequencies of exercise sessions, assorted exercise instruments, and even various cardiac populations. These multiple and dissimilar interventions have made the comparison between these trials difficult. Due to the different protocols used in relatively few studies, and due to the different outcomes achieved in these trials, it is still not clear whether interval training is more beneficial for cardiac patients when compared to the traditional recommended continuous training. This experimental chapter describes the use of a practical interval training protocol versus the standard used continuous modality, while maintaining a real-life setting.

The objectives of this chapter were to compare the effects of 12 weeks of moderate-high intensity aerobic interval training with moderate intensity continuous aerobic training on cardiorespiratory, cardiac function, cardiac risk factors and QoL in CAD patients. The hypothesis was that interval training would be more beneficial in improving $VO_2$ and perhaps other cardiac related outcome variables compared to the continuous training.

## Methods of training

Baseline measurements were performed as described in chapter 3 (General Methods). Then, patients were allocated to either an aerobic *Interval Exercise* group (IE) or a *Continuous Exercise* group (CE). Group allocation was achieved using a sequentially-randomized dynamic adaptive computer algorithm developed by the North Wales Organisation for Randomised Trials in Health (NWORTH), Bangor University and incorporating stratification by age, gender and diagnosis following initial assessment including cardiac event and presence of type II diabetes.

**Exercise sessions**

The intervention consisted of twenty six supervised exercise sessions completed over a 12 week period. Both training groups attended two supervised exercise sessions per week lasting for sixty minutes each time. Sessions took place between 7 AM and 3 PM, and contained up to 15 patients per hour. Patients exercised on the same days of the week and at a time they had chosen before entering the study. Cardiac patients who were not participating in the study also took part in classes. The rationale for this was based on an assumption that patients would be more motivated to complete their intervention period provided they are able to attend the program at their comfortable time. Additionally, it was felt that it was important to conduct the study within a real-life setting in which patients exercise in heterogeneous groups. Once the patients arrived to the CR centre they took their personal exercise file from the ECG room and rested while seated for a few minutes. Then, a nurse measured their resting heart rate and blood pressure and assisted them with wearing the heart rate monitor (Polar FT1, Kempele, Finland).

Following the warm-up patients exercised on three various ergometers including: motorized treadmill (T655, SportsArt, Tainan, Taiwan), stationary bicycle (C532U, SportsArt, Tainan, Taiwan), rowing machine (model D, Concept II, Morrisville, Vermont, USA), cross trainer (E825, SportsArt, Tainan, Taiwan), and combined upper body and lower body bicycles (XT20, SportsArt, Tainan, Taiwan). The ergometers used were offered to the participants according to their cardiac and/or orthopedic limitations, if existing, and the availability of the devices. All subjects used the motorized treadmill and two other ergometers. The exercise on the treadmill lasted 18 or 21 minutes (for the patients in the IE group and the CE group respectively), while the other two instruments were used for 10 minutes each. Approximately 5 minutes after the cool-down, HR and blood pressure were obtained and recorded again by the nurse. Each patient was requested to stay seated until their HR was decreased below 100 beats per minute (bpm). When BP was high ($\geq$ 150 SBP and or DBP $\geq$ 95) or low ($\leq$ 80 SBP and or DBP $\leq$ 50) (SBP = systolic blood pressure), the patient was requested to maintain seated while a nurse conducted repeated measurements until adequate values were achieved.

All exercise data including speed, resistance levels, METS, watts, and calories, were self-recorded in the patient's personal file, with the assistance of the trainer. Additionally, after being trained for monitoring their exercise HR and their RPE levels during exercise, subjects recorded training HR and RPE at the end of exercise on each device, under the supervision and assistance of the trainer. The subjects were instructed to record the highest HR during their work out on each instrument provided it was stable, and to record their highest RPE level that was reached during that time. In the IE group, patients recorded these parameters twice on each machine, once during the low intensity bout and the second time during the high intensity bout. The patients in the IE group were instructed to record the highest HR during the low and high bouts (Moholdt *et al.,* 2011). An example for an exercise form of each group is presented in Appendix B. By using the heart rate monitors, patients could control their heart rate during exercise and adjust their efforts according to the recommended intensity, including prescribed training HR and RPE levels. The trainers encouraged the patients continuously to reach the upper limit of their target heart rate as much as possible (Rognmo *et al.,* 2004).

The trainer and the nurse were also responsible for taking the patients' blood pressure during exercise twice a month using a manual sphygmomanometer (Tycos® 509 Manual Blood Pressure Device, Welch Allyn, USA). Exercise blood pressure was obtained on the stationary bike approximately between 6-8 minutes into the exercise. A monthly appointment with the exercise physiologist took place in order to modify the exercise program according to the patient's progress and to encourage the participants to reach their intensity goals. During these appointments, anthropometric and hemodynamic data were being collected and recorded. Patients were offered access to supplementary professional consultations including a nutritionist and a psychologist.

**Exercise prescription**

The exercise physiologist prescribed the exercise plan according to the group affiliation and the patient's personal physical condition. Exercise intensity was prescribed using both target HR and the RPE scale of 6-20 by Borg (Borg, 1982). Using the HR alone is not always sufficient or accurate, thus it is helpful to be assisted by the RPE scale which also helps to define the intensity level (Fletcher *et al.,* 2001; Moholdt *et al.,* 2011). The target heart rate was calculated using the

Karvonen Formula: [($HR_{max}$ – $HR_{rest}$) X %target HR] + $HR_{rest}$ (Karvonen, Kentala & Mustala, 1957), where $HR_{max}$ was taken from the $VO_2$ max test, and $HR_{rest}$ was taken from hemodynamic measurements at baseline. It was explained to the subjects that both parameters including target HR and RPE should be closely monitored throughout their exercise routine. In addition to the exercise regimen in CR, patients were requested to exercise at home twice a week for 30-60 minutes, at a moderate continuous intensity level of RPE 11-13. This information was self-reported during the monthly appointments with the exercise physiologist.

Even though exercise prescription focused on aerobic exercise, resistance training was offered to all patients after the first month of the study, as accustomed in this facility. It is widely established that resistance training is safe and important for cardiac patients for achieving cardiovascular, musculoskeletal, and QoL benefits (Adams *et al.,* 2006; Pollock *et al.,* 2000; Williams *et al.,* 2007). Each patient was instructed to perform 2-3 exercises at the end of their exercise routine under the supervision of the trainer. Type of exercises, intensity, repetitions, and sets were prescribed individually according to the AHA recommendations (Pollock *et al.,* 2000; Williams *et al.,* 2007).

*The IE group*

Patients in the IE group performed ten bouts of exercise per training session. Each bout consisted of two minutes of moderate to high intensity exercise, using RPE 14-16 (corresponding to approximately 60-85% $VO_2$ max) (Fletcher *et al.,* 2001), followed by two minutes of lower intensity at RPE 11-13 (corresponding to approximately 40-60% $VO_2$ max) (Fletcher *et al.,* 2001). Total time of aerobic exercise was 38 min including 8 bouts of moderate-high intensity and 11 bouts of lower intensity. Duration of each bout was based on our past experience with this population of cardiac patients that demonstrated poor tolerance and motivation over 2 minutes of strenuous exercise (Conraads et al., 2015). Moreover, the duration prescribed in this study was in consistence with a previous study (Warburton *et al.,* 2004)

*The CE group*

Patients in the CE group performed continuous aerobic exercise for 41 minutes. Intensity level of RPE 12-14 (consistent with 50-60% $VO_2$ max) was prescribed.

This level of intensity is being used on a regular basis at our CR program following the guidelines of the American College of Sports Medicine (ACSM) (Thompson, Gordon & Pescatello, 2010) and the AHA (Fletcher *et al.,* 2013). Also, similar exercise prescription for continuous exercise was seen in other trials that had compared interval and continuous training in a CR setting (Moholdt *et al.,* 2009; Rognmo *et al.,* 2004). Different durations of exercise sessions for each group were determined in an attempt to equalize total work (Rognmo *et al.,* 2004; Wisloff *et al.,* 2007). The calculation of estimated energy expenditure is presented in Appendix C. Caloric expenditure was recorded from each exercise instrument in order to be compared between the groups to verify equality.

### Post intervention measurements

Once completing 3 months of training, post intervention measurements were scheduled for the following week. Procedures of measurements were similar to baseline testing, thus patients received the same instructions as they did before baseline measurements.

### Statistical analysis

Baseline comparisons in the statistical analysis were performed using T-tests for continuous variables and Chi-squared for categorical variables. When comparisons between groups over time were conducted the mixed ANOVA repeated measures analysis was used. All relevant assumptions were tested, including normal distribution using the Shapiro-Wilk's test, and the Leven's test of homogeneity of variance. When an assumption was violated, the appropriate adjustment was made and reported.

## Results

### Participants

Eighty four patients were recruited for this study between May 2011 and April 2014, including 77 men and 7 women. Of the 84 patients recruited twelve patients did not complete the first phase (10 men and 2 women); therefore, 72 patients were included in the statistical analysis following 3 months of training. Patients' characteristics are presented in Table 5. The common reasons for dropping out involved: non-cardiac medical conditions, work related issues, and personal

reasons. Patients who dropped out from the study had similar characteristics as their counterparts who had completed the study. The sample is presented in the participant flow diagram (Figure 4). There were no major complications or acute cardiac events during the study period. Two patients had felt weakness immediately after their CPET. Both patients recovered after a few minutes while being treated by the medical staff. Two other patients (one male and one female) experienced chest discomfort at their homes and consequently were hospitalized. Subsequently, they underwent angiography that revealed no significant narrowing in the coronary arteries. They were discharged on the following day and were instructed to continue their medical treatment of exercise and medications. A summary of occurrence of symptoms and hospitalizations during this time can be found in Appendix D.

**Baseline comparisons**

Thirty-six patients in each group completed 3 months of training. Out of 26 sessions that were prescribed, adherence rate in the IE group was 89.5%, with number of sessions ranging from 19 - 26 (73.1% to 100%); the mean number of sessions was 23.3 ± 2.0. The CE group completed 88.4% of the sessions ranging between 18 - 26 sessions (69.2% to 100%); number of sessions in average was 23.0 ± 2.2. There were no differences between the groups in compliance to the exercise program ($p = 0.546$). Baseline characteristics are described in Table 5; groups were matched in all variables except of diabetes mellitus type 2 (DM2) which was almost statistically different between the groups ($p = 0.052$), with 12 diabetic patients in the CE group compared to 5 diabetic patients in the IE group. When all 84 patients are included, there are no differences between the groups in DM2 ($p = 0.174$).

**Figure 4. Flow diagram of enrollment and participation in the study**

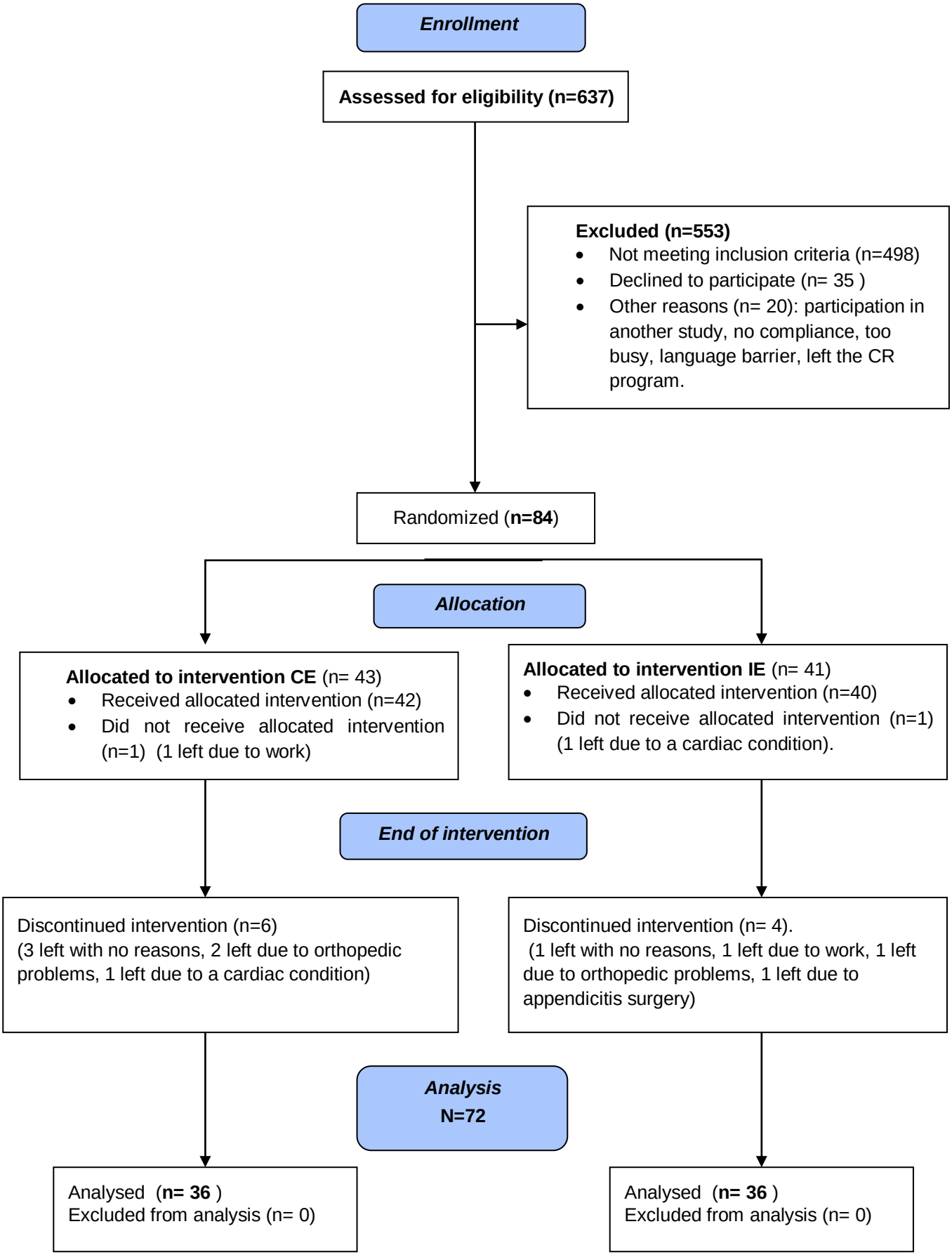


**Table 5. Characteristics of patients and baseline comparisons between the IE and CE groups**

| | All patients | CE | IE | P value |
|---|---|---|---|---|
| **N** | **72** | **36** | **36** | |
| **Subject Characteristics** | | | | |
| Age (years) | 58.4 ± 7.4 | 59.6 ± 7.1 | 57.2 ± 7.5 | 0.17 |
| Men (%) | 67 (93) | 33 (92) | 34 (94) | ----- |
| Women (%) | 5 (7) | 3 (8) | 2 (6) | ----- |
| Weight (kg) | 81.8 ± 12.1 | 81.3 ± 11.4 | 82.3 ± 13.0 | 0.743 |
| BMI ($kg/m^2$) | 28.3 ± 4.0 | 28.4 ± 3.8 | 28.3 ± 4.2 | 0.861 |
| **Coronary disease and risk factors** | | | | |
| MI (%) | 47 (65) | 27 (75) | 22 (61) | 0.206 |
| CABG (%) | 14 (19) | 5 (14) | 9 (25) | 0.234 |
| PCI (%) | 11 (15) | 4 (11) | 7 (19) | 0.326 |
| Type 2 DM (%) | 17 (24) | 12 (33) | 5 (14) | 0.052 |
| HTN (%) | 37 (51) | 22 (61) | 15 (42) | 0.099 |
| Overweight, BMI>25 (%) | 54 (75) | 26 (72) | 28 (78) | 0.786 |
| Obese, BMI>30 (%) | 23 (32) | 12 (33) | 11 (31) | 1.000 |
| Dyslipidemia (%) | 56 (78) | 27 (75) | 29 (81) | 0.571 |
| Smoking (current/recent) (%) | 26 (36) | 13 (36) | 13 (36) | 1.000 |
| Lack of physical Activity (%) | 33 (46) | 17 (47) | 16 (44) | 1.000 |
| **Drugs** | | | | |
| ARB (%) | 6 (8) | 3 (8.3) | 3 (8.3) | |
| CCB (%) | 4 (6) | 2 (5.4) | 2 (5.4) | 0.451* |
| ACE Inhibitors (%) | 39 (54) | 16 (44.4) | 23 (63.9) | |
| Beta blockers (%) | 65 (90) | 31 (86) | 34 (94) | 0.233 |
| Statins (%) | 71 (97) | 36 (100) | 35 (97) | 0.314 |

Values are presented as mean ± SD or frequencies (percentage), as appropriate.
**BMI**: body mass index; **MI**: myocardial infarction; **CABG**: coronary artery bypass graft; **PCI**: percutaneuous coronary intervention. **DM**: diabetes mellitus; **HTN**: hypertension; **ARB**: Angiotensin II receptor blockers; **CCB**: calcium channel blockers; **ACE**: angiotensin converting enzyme.
* P value represents differences between the groups of anti-ischemic medications.

## Outcome measurements

*Cardiorespiratory variables*

The primary outcome of peak $VO_2$ and cardiorespiratory data is presented in Table 6. Mixed ANOVA repeated measures analysis revealed that peak $VO_2$ was not statistically different between the groups before and after the intervention. However, each group separately had improved its $VO_2$ peak by 6.3% ($p < 0.05$) (Figure 5). Exercise treatment resulted in larger improvements in maximal time of the test and maximal power output in the IE group compared to the CE group ($p < 0.05$). The main effect of time revealed that test duration improved in 3.5% and 10.1% within the CE and the IE groups, respectively ($p = 0.015$, and $p < 0.001$, correspondingly). Rate pressure product (RPP) was found to be increased following treatment only within the IE group ($p = 0.025$). There were no significant differences between the groups in the other cardiorespiratory variables.

*Submaximal variables*

Submaximal variables including HR, $VO_2$ and RPE were recorded at different submaximal levels of exercise during the CPET at baseline and 3 months (Table 7). Repeated measures ANOVA was applied in order to see whether differences between the groups or within the groups exist at submaximal levels of the exercise test. Though no differences were found between the groups in any of these parameters, the results of the main effect of time demonstrated that HR was lowered with time only within the IE groups at 90 and 120 watts (Figure 6.A). RPE levels declined within both groups at 60 watts, while a significant decline was further seen within the IE group alone at 90 watts and almost at 120 watts (Figure 6.B). Submaximal $VO_2$ decreased from baseline to 3 months within the same group, however that was demonstrated at 120 watts only (Figure 6.C)

**Table 6. Cardiorespiratory variables**

| | CE | | IE | | | |
|---|---|---|---|---|---|---|
| | **Baseline** | **3 months** | **Baseline** | **3 months** | **P value** | **Partial Eta$^2$** |
| **N** | **36** | **36** | **36** | **36** | | |
| $VO_2$ peak (ml/kg/min) | 22.2 ± 5.6 | 23.6 ± 5.6* | 23.8 ± 5.8 | 25.3 ± 6.6* | 0.839 | 0.001 |
| Maximal output (watt) | 127.9 ± 33.0 | 134.2 ± 34.0* | 133.6 ± 24.0 | 146.9 ± 30.3* | 0.012 | 0.086 |
| Duration of test (min) | 8.6 ± 2.0 | 8.9 ± 2.1* | 8.9 ± 1.6 | 9.8 ± 2.0* | 0.005 | 0.109 |
| Maximal HR (bpm) | 133.4 ± 17.5 | 133.1 ± 16.8 | 134.0 ± 18.2 | 138.0 ± 19.2 | 0.106 | 0.037 |
| Maximal SBP (mmHg) | 186.7 ± 24.2 | 190.7 ± 23.4 | 184.6 ± 20.7 | 190.0 ± 23.5 | 0.728 | 0.002 |
| VT of predicted $VO_2$ max (%) | 45.8 ± 11.9 | 50.4 ± 11.7* | 48.2 ± 12.3 | 51.6 ± 12.7 | 0.452 | 0.000 |
| $VO_2$ peak / predicted VO2 max (%) | 80.3 ± 18.4 | 85.0 ± 17.9* | 83.2 ± 20.4 | 87.7 ± 23.9* | 0.931 | 0.000 |
| Maximal VE (l/min) | 67.3 ± 16.3 | 72.3 ± 17.6* | 72.3 ± 19.6 | 78.9 ± 22.6* | 0.452 | 0.009 |
| $VE/VCO_2$ at VT | 30.5 ± 3.7 | 29.7 ± 3.4 | 30.1 ± 4.2 | 29.4 ± 3.8 | 0.872 | 0.000 |
| RPP (mmHg X bpm) | 24398 ± 6663 | 25628 ± 5579 | 24683 ± 5306 | 26426 ± 5603* | 0.397 | 0.019 |
| RER | 1.1 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.1 ± 0.1 | 0.186 | 0.025 |
| Maximal RPE | 17.3 ± 0.6 | 17.4 ± 0.6 | 17.4 ± 0.6 | 17.6 ± 0.6 | 1.000 | 0.000 |
| HR recovery difference at 1 min (bpm) | 22.9 ± 8.8 | 28.2 ± 21.9 | 22.9 ± 10.4 | 23.9 ± 10.4 | 0.276 | 0.004 |

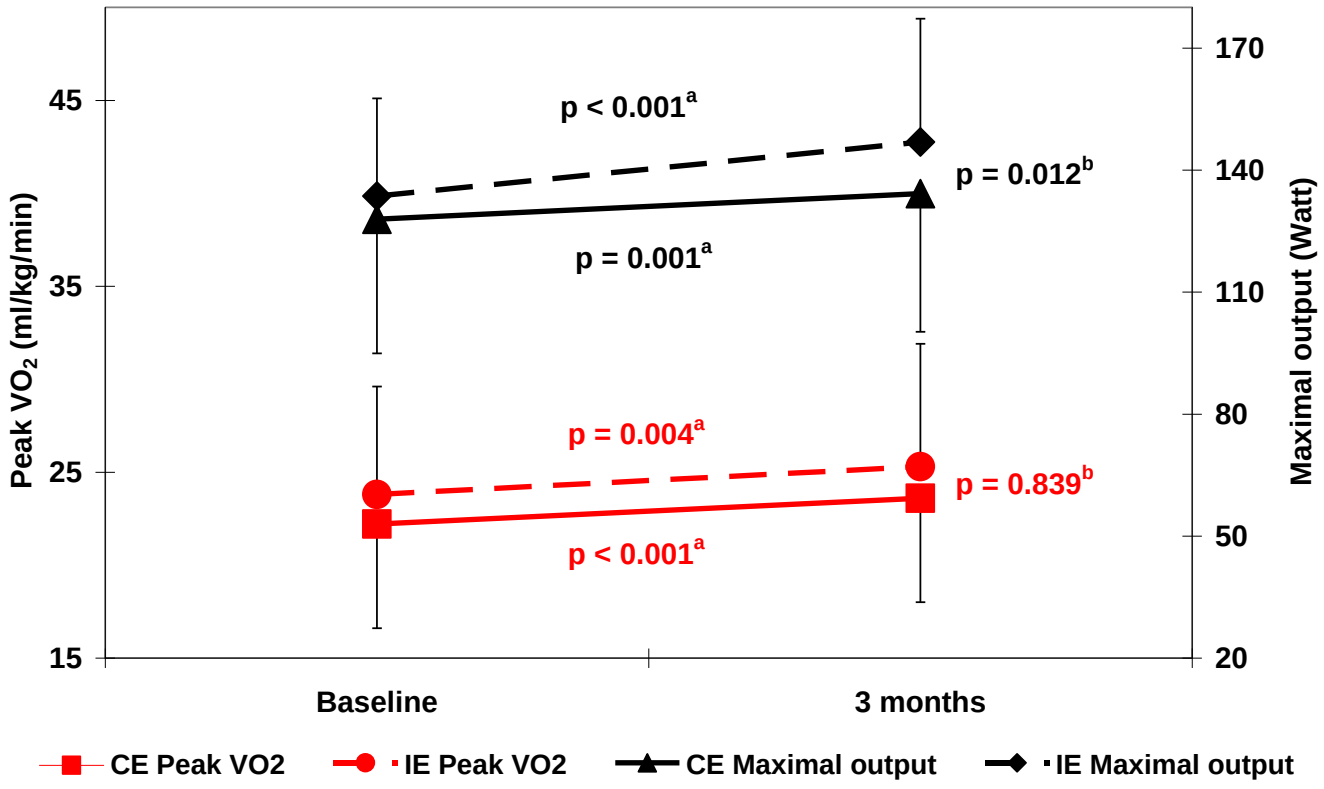
Values are means ± SD.

*Within $p < 0.05$.

P value represents differences between the groups

**HR**: heart rate **; SBP:** systolic blood pressure; **VT**: ventilatory threshold; **VE**: ventilation; **RPP**: rate pressure product**; RER:** respiratory exchange ratio; **RPE:** Rating of perceived exertion

**Figure 5. Comparison of changes between CE and IE groups in peak oxygen uptake ($VO_2$ peak) and maximal output from baseline to 3 months**




[a] Within the group change from baseline to 3 months

[b] differences between the groups

**Table 7. CPET submaximal variables at different load levels (watts)**

| | CE | | | IE | | | P value | Partial Eta$^2$ |
|---|---|---|---|---|---|---|---|---|
| | N | Baseline | 3 months | N | Baseline | 3 months | | |
| HR at 60 watts (bpm) | 33 | 94.3 ± 11.3 | 93.0 ± 12.3 | 28 | 92.4 ± 11.1 | 91.9 ± 15.3 | 0.765 | 0.002 |
| HR at 90 watts (bpm) | 33 | 109.6 ± 13.7 | 108.6 ± 17.5 | 27 | 108.4 ± 12.0 | 104.4 ± 14.9* | 0.259 | 0.022 |
| HR at 120 watts (bpm) | 10 | 118.9 ± 12.8 | 115.6 ± 9.7 | 14 | 122.6 ± 16.7 | 116.6 ± 17.1* | 0.508 | 0.020 |
| $VO_2$ at 60 watts (ml/kg/min) | 33 | 12.4 ± 2.2 | 12.7 ± 2.4 | 26 | 12.7 ± 2.9 | 12.5 ± 2.7 | 0.400 | 0.012 |
| $VO_2$ at 90 watts (ml/kg/min) | 33 | 16.5 ± 3.2 | 17.3 ± 3.2 | 25 | 17.3 ± 3.6 | 16.9 ± 3.3 | 0.072 | 0.057 |
| $VO_2$ at 120 watts (ml/kg/min) | 10 | 20.9 ± 2.4 | 20.5 ± 2.7 | 14 | 23.6 ± 4.9 | 22.0 ± 3.7* | 0.257 | 0.061 |
| RPE at 60 watts | 33 | 12.2 ± 1.7 | 11.5 ± 1.9* | 28 | 12.4 ± 1.5 | 11. 9 ± 1.4* | 0.402 | 0.012 |
| RPE at 90 watts | 33 | 14.3 ± 1.7 | 13.9 ± 1.7 | 27 | 14.4 ± 1.5 | 13.8 ± 1.3* | 0.339 | 0.016 |
| RPE at 120 watts | 10 | 14.6 ± 1.2 | 14.4 ± 1.5 | 14 | 15.4 ± 1.2 | 14.9 ± 1.1 | 0.432 | 0.028 |

Values are means ± SD.

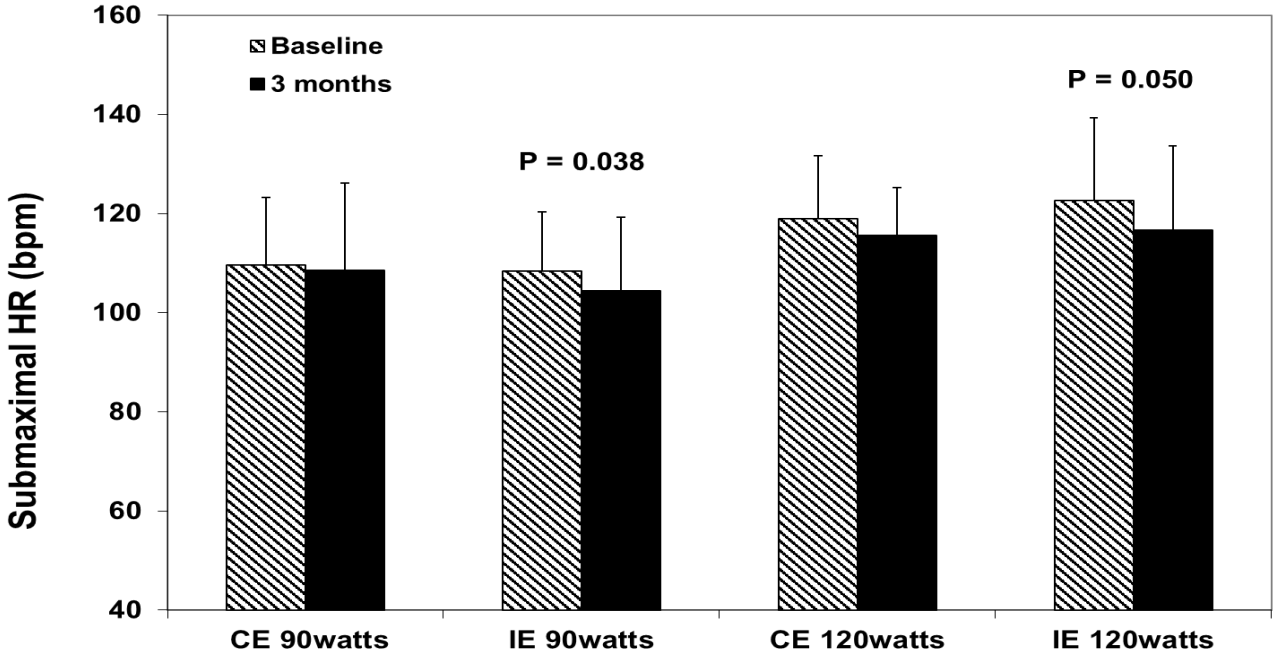
*Within $p < 0.05$.

P value represents differences between the groups

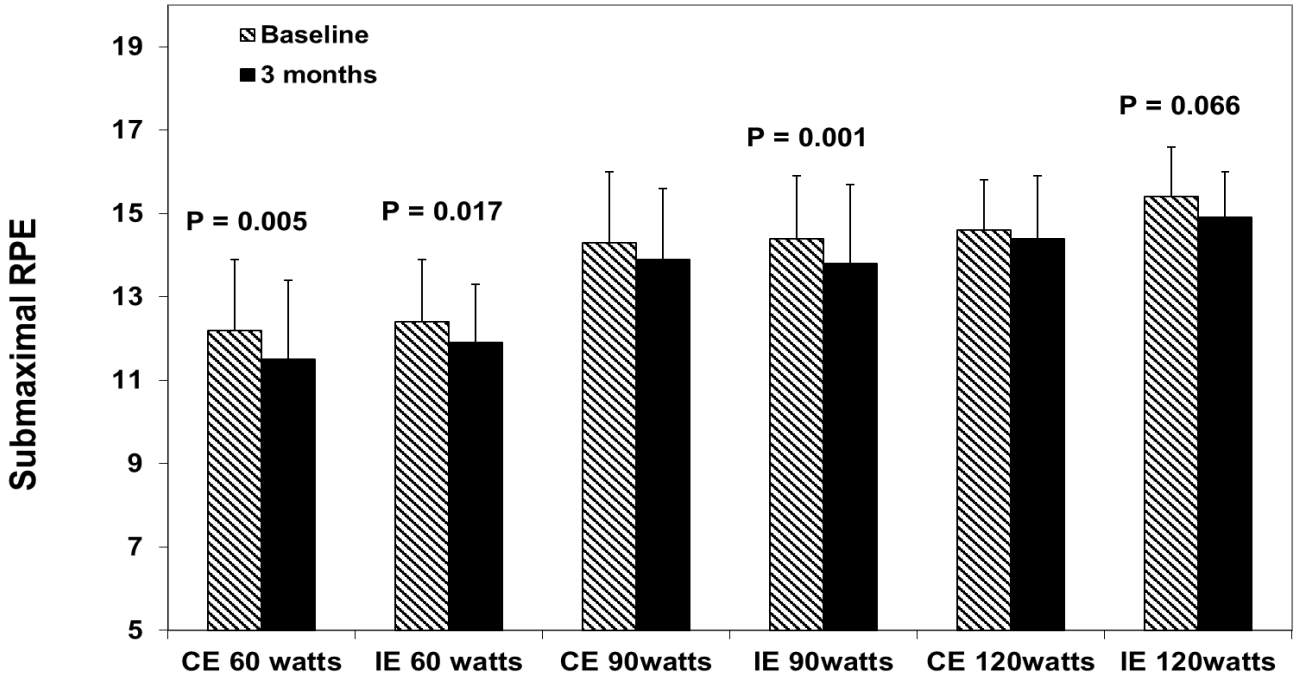
**HR**: heart rate; **RPE:** Rating of perceived exertion

**Figure 6. Changes in submaximal variables at different load levels during CPET at baseline and 3 months.**

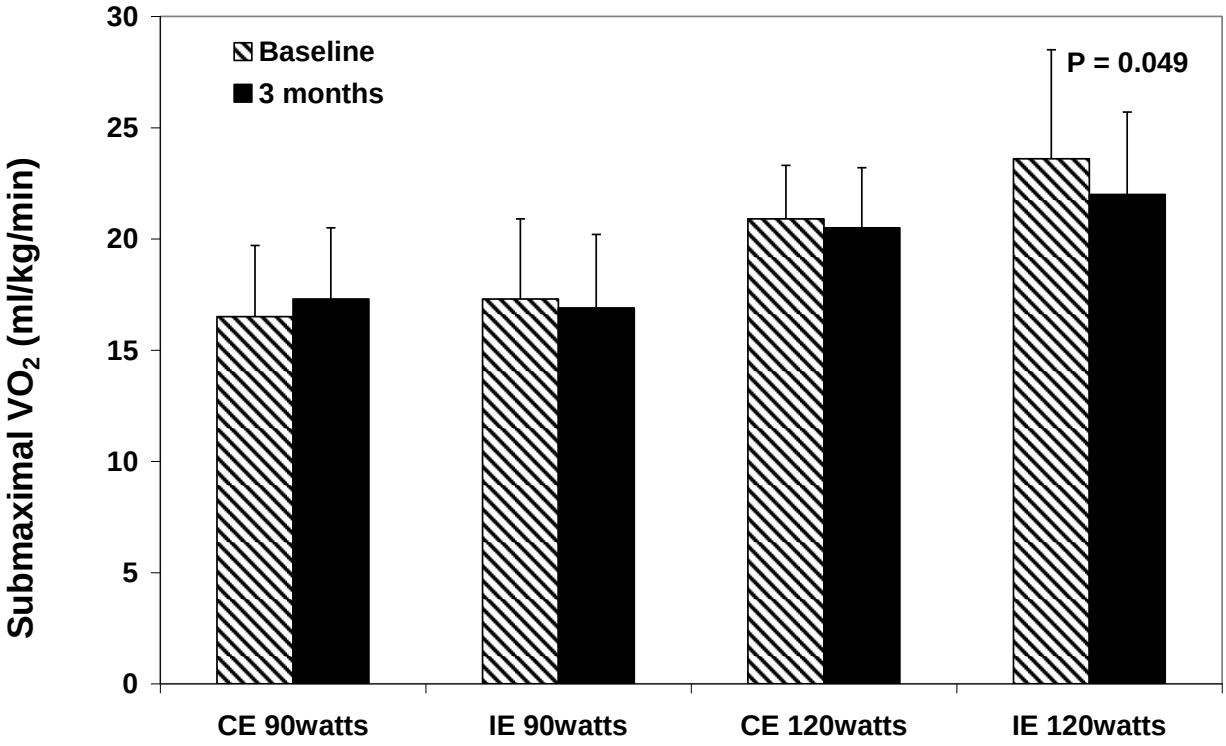
**A. Submaximal HR**




**B. Submaximal RPE**



**C. Submaximal $VO_2$**




P values represent changes within the groups over time.

**A.** HR significantly decreased over time within the IE group only at 90 and 120 watts during the CPET.

**B.** RPE significantly decreased over time within both groups at 60 watts; it was significantly lowered at 90 watts within the IE group only; and it was almost significantly lowered within the IE group at 120 watts.

**C.** VO2 significantly decreased over time within the IE group only at 120 watts during the CPET

*Blood parameters and CVD risk biomarkers*

Five patients were excluded from some of this analysis due to outliers that caused the results to change drastically once included. Additionally, due to violation of the Leven's test of equal variance the results were considered as if equal variance had not been assumed. Data is presented in Table 8. Triglycerides decreased over time in the CE group ($p = 0.039$, partial $eta^2 = 0.116$), while it increased in the IE group ($p = 0.006$, partial $eta^2 = 0.199$), resulting in significant differences between the groups. HbA1c was changed significantly post intervention among the IE group ($p < 0.005$, partial $eta^2 = 0.232$), with no differences between the groups after training. Reduction in hs-CRP within the IE group was significant over time ($p = 0.047$, partial $eta^2 = 0.118$). No other differences were detected between or within the groups after the intervention in the remaining variables. At baseline, cTnT was below the cut-off point of 0.014 ng/ml in most cases. However, values above the cut-off point were evident in 6 patients (17.6%) and 5 patients (14.3%) from the CE and the IE groups respectively (mean 0.0217 ± 0.0041 ng/ml; and 0.0200 ± 0.000 ng/ml, respectively). At 3 months, only 2 subjects (5.6%) from the CE group and 1 patient (2.8%) from the IE group had higher values than 0.014 ng/ml. Due to the low frequencies of abnormal values, a group comparison was deemed to be inappropriate. It is important to note that consulting the nutritionist had no effect on any of the blood parameters and biomarkers within or between the training groups (Appendix G).

**Table 8 - Blood parameters and CVD risk biomarkers**

| | CE | | | IE | | | P value | Partial Eta$^2$ |
|---|---|---|---|---|---|---|---|---|
| | N | Baseline | 3 months | N | Baseline | 3 months | | |
| TC (ml/dl)[a] | 36 | 128.8 ± 19.8 | 131.5 ± 19.7 | 35 | 134.8 ± 33.5 | 136.9 ± 26.5 | 0.921 | 0.000 |
| Blood glucose (ml/dl)[b] | 35 | 110.3 ± 19.0 | 107.3 ± 16.1 | 35 | 102.5 ± 11.1 | 100.3 ± 12.6 | 0.742 | 0.002 |
| HbA1c (%) | 33 | 5.98 ± 0.57 | 5.88 ± 0.55 | 36 | 6.06 ± 0.63 | 5.89 ± 0.6* | 0.368 | 0.012 |
| TG (ml/dl)[c] | 36 | 96.2 ± 33.1 | 88.2 ± 33.1* | 35 | 92.8 ± 32.2 | 105.3 ± 44.0* | 0.001 | 0.158 |
| LDL-C (ml/dl)[a] | 36 | 66.4 ± 18.5 | 69.0 ± 16.9 | 35 | 69.9 ± 28.0 | 69.1 ± 22.4 | 0.545 | 0.005 |
| HDL-C (ml/dl)[d] | 36 | 43.2 ± 9.7 | 44.7 ± 12.3 | 35 | 45.7 ± 11.8 | 46.7 ± 10.8 | 0.756 | 0.001 |
| HS-CRP (mg/l)[e] | 33 | 1.81 ± 1.59 | 1.80 ± 1.43 | 34 | 2.46 ± 2.64 | 1.94 ± 1.96* | 0.103 | 0.041 |
| cTnT < 0.014 (ng/ml) | --- | 34 (82.4) | 34 (94.4) | --- | 35 (85.7) | 36 (97.2) | --- | --- |

*Within p value< 0.05

Values are means and SD. ** Values are presented as number of patients and percentage (%).

**TC**: total cholestrol. **HbA1c**: glycosylated hemoglobin. **TG**: triglycerides. **LDL-C**: low density lipoprotein cholesterol. **HDL-C**: high density lipoprotein cholesterol. **HS-CRP**: high sensitive C-reactive protein. **cTnT**: Troponin-T

[a] Patients number 85 and 14 (IE group) were excluded

[b] Patients number 84 (CE group) and 28 (IE) were excluded

[c] Patient number 9 (IE) and 77 (CE group) were excluded

[d] Patient number 57 (CE group) was excluded

[e] Patients number 63 (CE group), 29 and 76 (IE) were excluded

*Body composition and hemodynamic variables*

Table 9 presents characteristics of weight and hemodynamic variables. Outliers of body fat percentage were seen due to the presence of females in the study. None of them were excluded since their exclusion did not change the outcomes. After the exercise program, the groups did not differ from each other in any of the weight nor the hemodynamic variables. However, with time a significant decrease in waist circumference was found within the IE group ($p = 0.028$, $eta^2 = 0.130$). These results were not influenced by nutritional guidance as can be seen in Appendix G. Resting HR and BP did not differ between the groups, nor did they change over time.

**Table 9. Body composition and hemodynamic variables**

| | CE | | IE | | P value | Partial Eta$^2$ |
|---|---|---|---|---|---|---|
| | Baseline | 3 months | Baseline | 3 months | | |
| N | 36 | 36 | 36 | 36 | | |
| Weight (Kg) | 81.3 ± 11.4 | 80.8 ± 11.2 | 82.3 ± 13.0 | 81.4 ± 11.8 | 0.617 | 0.004 |
| BMI (Kg/m$^2$) | 28.4 ± 3.8 | 28.2 ± 3.9 | 28.3 ± 4.2 | 28.0 ± 4.0 | 0.458 | 0.008 |
| Percent of body fat (%) | 28.1 ± 7.0 | 27.8 ± 7.1 | 28.3 ± 8.2 | 28.0 ± 7.8 | 0.873 | 0.000 |
| WC (cm) | 99.2 ± 9.6 | 99.0 ± 9.2 | 100.8 ± 10.6 | 99.9 ± 9.4***** | 0.337 | 0.013 |
| Resting HR (bpm) | 65.2 ± 8.5 | 63.8 ± 8.5 | 67.5 ± 10.1 | 65.3 ± 10.5 | 0.583 | 0.004 |
| Resting SBP (mmHg) | 121.3 ± 11.6 | 120.5 ± 12.8 | 117.7 ± 11.6 | 117.2 ± 11.7 | 0.895 | 0.000 |
| Resting DBP (mmHg) | 73.0 ± 6.7 | 73.1 ± 7.1 | 71.7 ± 8.4 | 72.1 ± 8.0 | 0.858 | 0.000 |

Values are means and SD

* Within p value< 0.05

**BMI**: body mass index. **WC**: waist circumference. **HR**: heart rate. **SBP**: systolic blood pressure. **DBP**: diastolic blood pressure

*Echocardiography parameters*

As shown in Table 10 the echocardiography parameters did not differ between the groups following training. Seventy five percent from the CE group and 71% from the IE group had normal LVEF (LVEF≥55) with no differences between the groups. Resting stroke volume (SV) was calculated as EDV – ESV, and resulted in almost a significant small increase in the IE group alone following the intervention (p = 0.051). Due to several extreme outliers (≥2 SD), patients were excluded from specific analyses (as noted in the Table) provided their exclusion resulted in different outcomes. LA area was abnormal (> 20 mm$^2$) among 18 and 19 patients from the CE and the IE groups respectively, but no differences were found between the groups at both time points of the study and none of the patients had LA area > 40 mm$^2$. Measurements of mitral inflow did not change over time. The only noticeable (but small) change included the decrease in MV-A within the CE group (p = 0.032, partial eta$^2$ = 0.128) that did not occur in the IE group. Mitral

annulus velocities as were measured by TDI (e' and E/e') did not demonstrate changes with training. Due to technical difficulties, these variables were obtained for only 26 patients from the CE group and 27 patients from the IE group.

Figures 7 and 8 illustrate the changes in the proportion of patients with normal and abnormal diastolic function at baseline and 3 months in each group. Since the number of patients in each diastolic function group was rather low, diastolic function was divided into 2 categories: normal diastolic function and diastolic dysfunction. Diastolic dysfunction includes patients with impaired relaxation, pseudonormal relaxation, and restrictive pattern. There were no differences between the groups in the prevalence of diastolic function categorizations in baseline ($p = 0.330$) and at 3 months ($p = 0.155$), as was proven by a Chi-Square analysis. As shown in the Figures 7&8, in both groups the percent of subjects with normal diastolic function was increased while number of subjects with diastolic dysfunction was lowered with time. However, most patients did not change their diastolic function classification from baseline to 3 months and there was also no difference in the change of diastolic function between the groups (Table 11).

**Table 10 - Echocardiography variables**

| | CE | | | IE | | | P value | Partial Eta$^2$ |
|---|---|---|---|---|---|---|---|---|
| | N | Baseline | 3 months | N | Baseline | 3 months | | |
| LA area ($mm^2$) [a] | 36 | 20.5 ± 4.1 | 20.7 ± 4.2 | 34 | 20.2 ± 4.5 | 20.4 ± 4.5 | 0.683 | 0.002 |
| **Diastolic function** | | | | | | | | |
| MV-E (cm/s) [a,b] | 35 | 70.3 ± 12.2 | 71.4 ± 15.8 | 33 | 73.1 ± 12.6 | 75.4 ± 12.8 | 0.742 | 0.002 |
| MV-A (cm/s) [a,b] | 35 | 68.9 ± 15.4 | 65.4 ± 12.3* | 33 | 63.5 ± 15.4 | 66.0 ± 15.3 | 0.020 | 0.080 |
| E/A ratio [a,b] | 35 | 1.1 ± 0.3 | 1.1 ± 0.4 | 33 | 1.2 ± 0.6 | 1.2 ± 0.5 | 0.182 | 0.027 |
| MV-DT (ms)[c] | 34 | 180.4 ± 38.8 | 183.7 ± 50.0 | 33 | 179.6 ± 32.2 | 181.4 ± 36.8 | 0.794 | 0.001 |
| e' (ms) | 26 | 9.2 ± 1.3 | 9.1 ± 1.3 | 27 | 9.5 ± 1.7 | 9.4 ± 1.7 | 0.993 | 0.000 |
| E/e' | 26 | 7.6 ± 1.7 | 8.1 ± 1.7 | 27 | 9.7 ± 2.7 | 10.0 ± 3.3 | 0.753 | 0.002 |
| **Systolic function** | | | | | | | | |
| EDV (ml) [a,b] | 35 | 96.0 ± 13.9 | 96.1 ± 12.2 | 34 | 98.7 ± 14.2 | 100.9 ± 14.9 | 0.134 | 0.033 |
| ESV (ml) [a,b] | 35 | 43.1 ± 10.2 | 42.1 ± 9.2 | 34 | 43.6 ± 12.7 | 43.8 ± 13.7 | 0.550 | 0.005 |
| SV (ml) [a,b] | 35 | 52.9 ± 9.7 | 53.9 ± 8.7 | 34 | 55.1 ± 9.4 | 57.0 ± 9.7 | 0.393 | 0.011 |
| Calculated LVEF(%)[a,b] | 35 | 55.2 ± 7.3 | 56.3 ± 6.6 | 34 | 56.3 ± 8.7 | 57.1 ± 9.2 | 0.763 | 0.001 |

P values represent differences between the groups

Values are means and SD.

* Significant within the group over time ($p < 0.05$)

[a] Patient number 29 (IE group) was excluded

[b] Patient number 35 (CE group) was excluded

[c] Patients number 3 (IE group) and 10 (CE group) were excluded

**MV-E**: early diastolic mitral inflow velocity. **MV-A**: late diastolic mitral inflow velocity. **MV-DT**: mitral valve deceleration time. **e'**: average of septal and lateral e'. **EDV**: end diastolic volume. **ESV**: end systolic volume. **LVEF**: left ventricular ejection fraction.

**Figure 7. Percent of patients from the CE group with normal diastolic function and diastolic dysfunction at baseline and 3 months.**

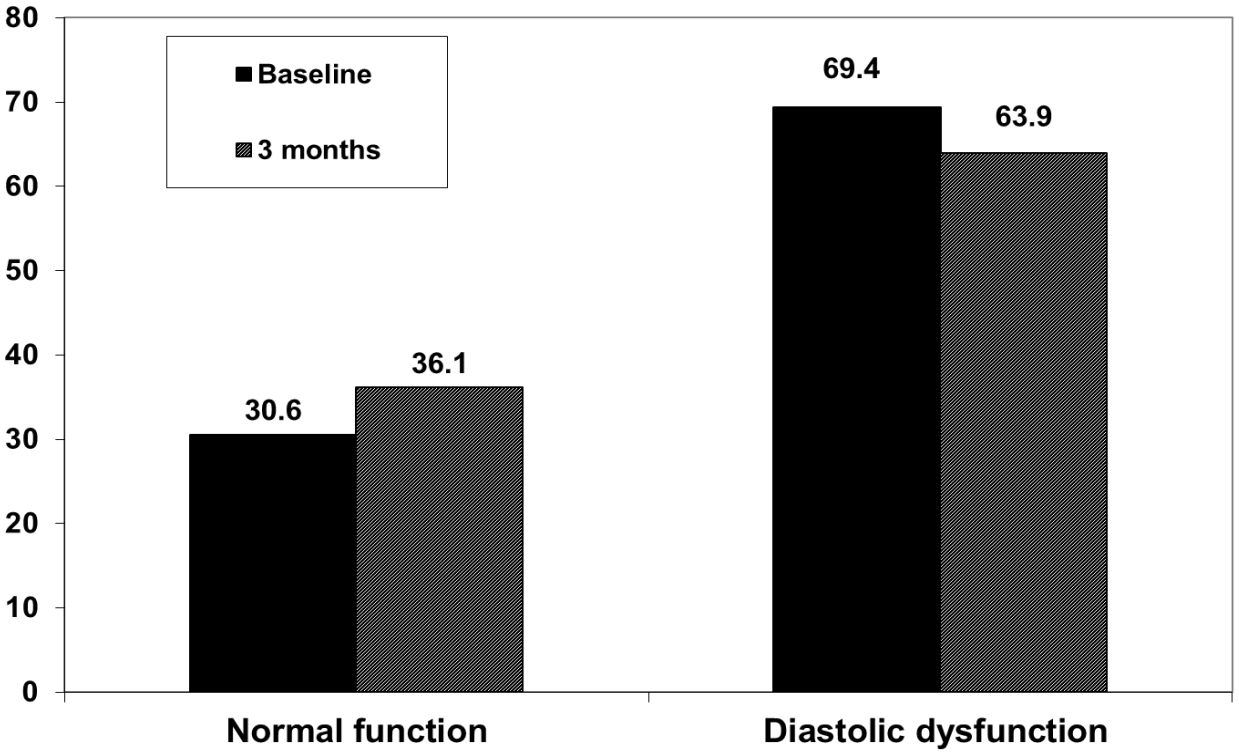



**Figure 8. Percent of patients from the IE group with normal diastolic function and diastolic dysfunction at baseline and 3 months.**

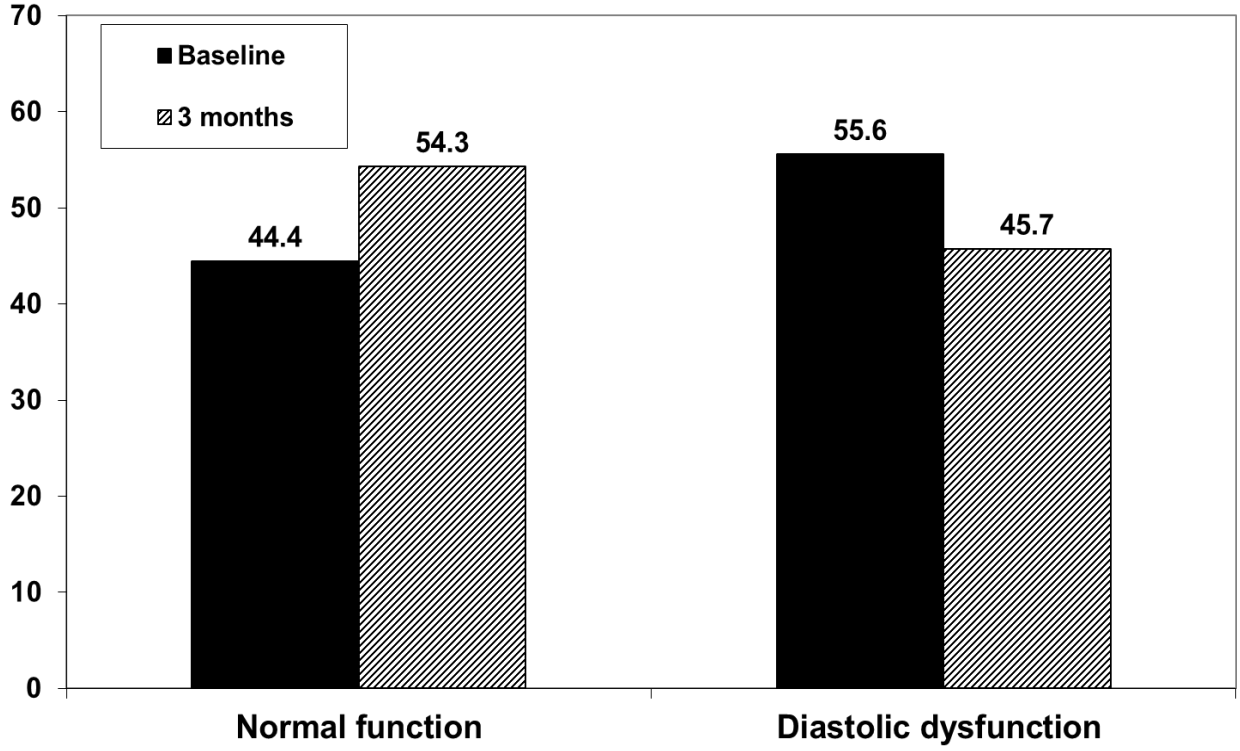


**Table 11. Numbers and percentages of patients who have changed their diastolic function classification from baseline to 3 months**

| | CE | IE | P value* |
|---|---|---|---|
| N | 36 | 35 | |
| No change | 31 (86.1) | 27 (77.1) | |
| Improvement in diastolic function | 4 (11.1) | 5 (14.3) | 0.503 |
| Worsening in diastolic function | 1 (2.8) | 3 (8.6) | |

Data is presented in number of patients and percentages (%)

*Chi-Square analysis

*Quality of life*

Four patients did not complete the SF-36 QoL questionnaire. Two of the patients could not read or understand Hebrew fluently, while two other patients had declined to complete the questionnaire for personal reasons. Furthermore, during the study 3 patients had experienced personal problems not related to their recent cardiac event. Subsequently, all three patients had extremely low scores in the SF-36 questionnaire and they were excluded from this current analysis. Following the intervention the results demonstrated significant changes over time in the 2 major domains of physical and mental health within each group regardless of group participation (CE: $p < 0.001$; IE: $p < 0.05$). Data is presented in Table 12. QoL subscale scores did not differ between the groups. Separately, the CE group improved scores in 6 of the 8 subscales including physical functioning, role physical, role emotional, social functioning, vitality, and general health; whereas IE group improved only 2 of the subscales including role physical and role emotional.

Cronbach's alpha test was employed to measure internal consistency of the different subscales. Six of the 8 subscales were tested for reliability; bodily pain and social functioning were excluded since they consist of only two items each. Internal consistency coefficients for all 6 constructs ranged between 0.764 and 0.866, which are considered highly reliable (DeVillis, 2003).

**Table 12 - SF- 36 Quality of Life Questionnaire variables**

| | CE | | IE | | P value | Partial Eta$^2$ |
|---|---|---|---|---|---|---|
| | Baseline | 3 months | Baseline | 3 months | | |
| N | 34 | 34 | 30 | 30 | | |
| PH score* | 68.6 ± 18.9 | 76.7 ± 15.8 | 78.0 ± 11.8 | 82.5 ± 7.3 | 0.138 | 0.035 |
| MH score* | 69.0 ± 20.3 | 76.7 ± 15.6 | 78.6 ± 12.4 | 83.3 ± 6.4 | 0.242 | 0.022 |
| Total score* | 69.6 ± 19.1 | 78.2 ± 15.5 | 80.5 ± 11.4 | 85.9 ± 6.1 | 0.139 | 0.035 |

Values are means and SD.

*Within groups, p value< 0.05

**PH**: physical health. **MH**: mental health

Patients 44, 69, and 71 were excluded from this analysis due to non-cardiac related personal issues.

### Symptoms, cardiac events, and hospitalizations

Data related to occurrences of safety variables is presented in Appendix D.

## Discussion

*Cardiorespiratory outcomes*

Exercise-based cardiac rehabilitation improves cardiorespiratory fitness and cardiovascular health outcomes in patients with coronary artery disease. However, uncertainty exists surrounding exercise prescriptions that are most effective for improving cardiorespiratory fitness. This study evaluated the impact of two aerobic exercise prescriptions (IE and CE) on indices of cardiorespiratory fitness, clinical variables and self-reported quality of life in cardiac patients receiving outpatient, centre-based CR. Training intensity was based on subjective perception of effort (i.e. RPE) integrated with objective indices (i.e. HR) based on percentage of baseline peak $VO_2$. The primary objective was to compare the effects of IE with CE on $VO_2$ peak. As expected, exercise-training elicited an increase in $VO_2$ peak (around 6%) in both groups, though this change was relatively low compared to other CR studies (Lavie *et al.,* 2009). However, post-intervention $VO_2$ peak was similar for both training groups, a finding that indicates that IE is no more effective than CE in eliciting an increase in $VO_2$ peak. This is a similar finding to Warburton *et al.* (2004), Rocco *et al.* (2012), Conraads *et al.* (2015), Currie *et al.* (2013), and

Moholdt *et al.* (2009), but different from studies by Moholdt *et al.* (2012), Rognmo *et al.* (2004), Keteyian *et al.* (2014), and Amundsen *et al.* (2008).

The 10 % increase in maximal output recorded during CPET within the IE group was significantly higher compared to the increase within the CE group and is similar to the change with interval training following PCI reported by Munk *et al*. (2009). Furthermore, the present observation that interval training has a superior effect on CPET duration, without a similar effect on $VO_2$ peak, when compared with continuous training is consistent with a previous finding reported in a study by Warburton *et al.* (2004). In that paper, the authors concluded that although interval training did not elicit $VO_2$ peak, it may have improved aerobic tolerance and activities of daily living (Warburton *et al.,* 2004). The increased maximal RPP with interval training was not thoroughly evaluated before, and it may indicate physiological changes in the myocardium which can result in increased maximal work capacities (May & Nagle, 1984).

Possible explanations of the results could rest on the fact that the interval training protocol consisting of two-minute intervals was designed following years of experience with cardiac patients who frequently demonstrated difficulties to maintain high intensity exercise for longer durations. However, it is possible that those 2- minute intervals were not sufficient for producing higher improvements compared to continuous training, as was explained in a study that had used a similar protocol (Warburton *et al.,* 2004). Additionally, CR programs usually consist of 2 exercise sessions per week with further recommendations for additional individual physical activity for at least 3 days a week (Fletcher *et al.,* 2001). In reality, our patients reported being physically active for 1.8 days a week in average; it is possible that with higher frequency of physical training, greater benefits could have been found as seen in a study done by Moholdt *et al.* (2009). Nonetheless, adding supervised or individual sessions does not necessary guarantee different outcomes (Warburton *et al.,* 2004).

Perhaps the most critical element of this study, and its kind, is the prescription of training intensities. Previous interval studies compared high intensity interval training (HIIT) to moderate continuous training. HIIT is defined as vigorous exercise performed at a high intensity (>95% $VO_2$ max) for a brief period of time interposed with recovery intervals at low-moderate intensity. In contrast to those studies, it

was never our intension to prescribe high intensity exercise for the patients in the IE group but only moderate – high intensity level. Thus, we aimed for lesser extreme intensities of 70-85% $VO_2$ peak as was previously described elsewhere (Iellamo *et al.,* 2013). Our concerns included the medical condition (safety) and mental state of the patients, and the lack of physical activity history among many of the patients, which accounted for almost half of our cohort. It has been reported before that vigorous exercise may be associated with an increased risk for MI, and thus be avoided, especially for habitually inactive adults with elevated cardiac risk (Giri *et al.,* 1999; Willich *et al.,* 1993).

Since not many interval training studies involved CAD populations (and those which had, recruited rather small numbers of subjects), safety of the patients is still not clear enough (Wisloff *et al.,* 2009). Moreover, from our experience, CAD patients in CR programs are usually less motivated to exercise and are often more anxious with engaging in an exercise program. Such patients effectively would need a personal trainer in order to reach and maintain high levels of exercise intensity. This is not feasible in our facility and in most standard programs.

Despite the encouragement and supervision throughout the training program, the patients in the IE group did not reach the intensity levels that were prescribed. The professional staff reported that while patients belonging to the CE group were cooperative and easy to monitor, subjects from the IE group needed their full devoted attention and encouragement throughout their exercise sessions. Nillson *et al.* postulated that interval training is an individualized modality that should be guided individually by a certified professional who should motivate each patient until he reaches his intensity goals. This supervision is very difficult to be implemented in exercise groups (Nillson *et al*., 2008a). Given that, exercise-based CR programs in Israel and in the UK are generally group-based (Israeli Society of cardiology, 2000; Thow, 2006), interval training might not be suitable for all programs. As presented in Appendix E reported average %HRR and RPE levels were lower than expected within this group creating only a relatively small gap in intensity levels between the training groups. This small gap might have been a contributor to the absence of differences between them in $VO_2$ peak post training (Rocco *et al.,* 2012; Warburton *et al.,* 2004).

Iellamo *et al.* (2013) who have looked at the effects of interval training on heart failure patients, suggested that a lack of differences between these training modalities can be explained by the use of $VO_2$ max percentages. This prescription method might result in different physiological outcomes as a consequence of various individual internal adaptations to the training load, even if the patients have similar aerobic capacity at baseline. Also, the usage of beta-blocker agents among 90% of the cohort may have resulted in underestimation of HR prescription and thus reduced levels of training intensity (Tabet *et al.,* 2007). Even though it is valid to prescribe training intensity while taking these drugs (Chaloupka, Elbl, Nehyba, Tomaskova & Jedlicka, 2005), an assortment of beta blockers and various dosages were used which might have affected subjects differently. In light of this reason, RPE was also prescribed and it was found to be significantly higher in the IE group versus the CE group ($p = 0.013$) (Appendix E); meaning, in their subjective feeling, patients in the IE group trained harder than their peers in the CE group. Also, it is imperative to note that absolute (estimated) caloric expenditure was equal between the groups, an important element while designing the study for preventing one group from reaching superior energy expenditure (Moholdt *et al.,* 2009; Wisloff *et al.,* 2007).

Similarly to other trials, exercise prescription was based on the pre-intervention $VO_2$ max test. Moholdt *et al.* (2011) have reported that only 16% of their subjects have reached the same MHR during both exercise tests, while the other subjects either increased or decreased their MHR during the repeated test. Consequently, prescribing the intensity levels according to the first test might seriously underestimate or overestimate the levels of effort needed to be achieved. In this current study despite all patients reaching RPE levels of 17-19 during both exercise tests, only half of the patients were able to reach $\geq$85% of predicted MHR (with no differences between the exercise groups), which can be explained by the use of beta blockers medications).

Another explanation can be related to the exercise equipment. The exercise program in our CR centre incorporates various exercise modes including treadmills, stationary bikes, rowing machines, and elliptical machines. It is our belief that it is important for the patients to activate as many muscles as possible in order to improve not only their aerobic functional capacities but also their daily

functional capabilities. Most studies had only used one device, for example the treadmill (Keteyian *et al.,* 2014; Moholdt *et al.,* 2009; Rognmo *et al.,* 2004), or the stationary bike (Conraads *et al.,* 2014; Currie *et al.,* 2013). It is possible that changing exercises devices during the session caused a diminished effect versus other studies that did not use different instruments and had their patients exercising with no interruptions. Nevertheless, Keteyian *et al.* concluded that it is important to incorporate various modes of exercise devices in order to evaluate the benefits of training in CR programs (Keteyian *et al.,* 2014).

An additional reason can be associated with the fact that our study included a heterogeneous population of CAD patients. Most studies recruited patients with similar cardiac characteristics, which might reflect a minority of patients referred to CR programs who could be more motivated to exercise (Cornish *et al.,* 2011). For example, one study included only patients post CABG (Moholdt *et al.,* 2009), while other studies looked at patients who underwent PCI only (Munk *et al.,* 2009; Warburton *et al*., 2004). The current study included all cardiac patients for the purpose of generalization to the real CR population that participates in these programs (Keteyian *et al.,* 2014). It might be that the diversity of our cohort that included patients post MI, PCI or CABG, that made it more difficult in reaching larger differences between the groups given that not all patients may tolerate a training modality such as intervals.

Last but not least, in an attempt to conduct the study in a real– life setting, patients were recruited after a 4-week exercise adjustment period (as reported elsewhere) (Keteyian *et al.,* 2014). Thus, it is possible that greater improvements in both groups would have been found post training if the baseline CPET was performed on the day of admission to the CR programme. Even so, it is our belief it was imperative to maintain the standard conditions as well as consider safety issues. Furthermore, it is not clear whether differences between the groups would have been found with an early initiation of the intervention

*Submaximal cardiorespiratory variables*

While other interval studies did not look at submaximal cardiorespiratory factors, the present results demonstrated that following interval training submaximal HR and $VO_2$ can be reduced. This may suggest that aerobic tolerance was improved

(Leon et al., AHA, 2005) which can be supported by the parallel reduction in RPE within the same training group at the same effort levels. The fact that both groups had a reduced RPE at a lower load level (60 watts) can imply to improved tolerance during lighter activities, or improved confidence during the second exercise test. The fact that $VO_2$ was reduced during higher levels of the exercise test implies that at a higher work load the patients were more efficient in performing the same effort while consuming less oxygen.

*Blood parameters and CVD risk biomarkers*

The effect of interval training on blood lipids is not clear, since most studies investigating interval training with CAD patients did not examine these variables. In our study, most blood lipids, including total cholesterol, blood glucose, LDL-C, and HDL-C did not change with exercise, as was also described by Moholdt *et al.* (2009). As was explained before, it is possible that adjustments in drug therapy have interfered with possible favourable effects of exercise. A few interval training studies that included middle-aged adults reported no changes in blood lipids (Schjerve *et al.,* 2008; Wallman, Plant, Rakimov & Maiorana*.,* 2009). In both of these studies, treatment by medications for lipids were not mentioned and cholesterol levels were slightly elevated. It is important to note that the levels of total cholesterol, LDL-C, and HDL-C in this current study were normal at baseline according to the National Cholesterol Education Program (NCEP, 2002), which might partially explain the absence of improvements in these lipids (Kessler, Sisson & Short, 2012; Ståhle, Mattsson, Rydén, Unden & Nordlander,1999). An unexpected response was seen in triglycerides with increased values among the IE patients. However, since triglycerides values were within the normal range at both times, it is assumed that these changes are not clinically relevant. Also, it is important to recall that normal distribution and homogeneity of variance were violated within these variables; hence it is difficult to draw conclusive conclusions regarding these changes or lack of them during the intervention period.

Although there is a great inconsistency in the effect of interval training on blood glucose within CAD population, the lack of change in our study is consistent with other studies (Moholdt *et al.,* 2009; Wisloff *et al.,* 2007). None of the previous studies of interval training in CAD patients looked at HbA1c changes. In this current study, HbA1c was decreased significantly only after interval exercise.

However, the reduction was by only 0.17%, and the clinical importance of this small change is uncertain. A study done by Hansen *et al.* (2010) reported 0.3% reduction in HbA1c which, according to the researchers, was translated to a 6% reduction in the risk of premature death and an 11% reduction in the risk of microvascular disease. The authors based their conclusion on the UK Prospective Diabetes Study (UKPDS) that found that each 1% reduction in mean HbA1c can be associated with 14% reduced MI events and 37% reduced microvascular diseases (Stratton *et al.,* 2000). A study by Mitranun *et al.* (Mitranun, Deerochanawong, Tanaka & Suksom, 2013) found greater reductions in HbA1c following interval training, however, baseline levels of HbA1c (7.2%) were much higher compared to those found in the current study, due to the diabetic study population that participated in that study. To sum up, since in this present study the change in HbA1c was smaller than formerly reported, and since the number of patients with DM2 was not equal between the groups, clinical relevance cannot be established.

Despite the known importance of exercise-based CR, the effects of different exercise prescriptions on commonly measured biomarkers in CAD patients has received relatively little attention. Since hs-CRP has been considered an independent predictor of future cardiovascular events (Ridker, 2007), several studies have tried to examine the effect of exercise on this biomarker. One study demonstrated a 35.6% decrease in hs-CRP among CAD patients during CR program (Milani, Lavie & Mehra, 2004). In this study, the IE group experienced a significant reduction in hs-CRP (21%), which was not apparent in the CE group; however, the effect size was small, and hs-CRP values at baseline were higher for the IE group. The only previous study in a CR setting that evaluated the influence of aerobic interval training (for 6 months) on hs-CRP also reported a significant reduction (Munk *et al.,* 2009), but there was np CE group to compare to. Milani *et al.,* (2004) also found that the effect of exercise on hs-CRP levels was similar whether the patients had been under statins therapy or not. They emphasized the additional effect of the exercise over the effect of the drug therapy. Given that in our study almost all patients were taking statins, we could not have compared both situations. Data related to the changes in statins therapy can be found in Appendix F.

It has been described that hs-CRP levels of less than 1 mg/l, between 1 to 3 mg/l, and greater than 3, are associated with lower, moderate, and higher cardiovascular risks, respectively (Bassuk, Rifai & Ridker, 2004). Also, patients with hs-CRP levels between 1-3 mg/l have a noticeable higher risk for death when compared to patients with levels < 1 mg/l (Morrow *et al.,* 2006). In our study, approximately 60% of the patients (in both groups) had hs-CRP > 1 mg/l at baseline and at 3 months. Consequently, clinically, it seems that most of the patients are considered to have moderate – high cardiovascular risk; thus, it is important to continue exploring whether interval training can assist in lowering hs-CRP levels.

Only a very small number of patients from each group had abnormal values of cTnT; however, even fewer subjects had abnormal levels after the intervention. Being a dominant predictor of major adverse cardiac events (MACE), it is encouraging that cardiac cTnT can possibly be reduced with training, though the clinical importance cannot be determined from this current trial. Ferratini *et al.* (2012) demonstrated a significant reduction in cTnT following a short (3-week) CR program within CAD patients undergoing CABG. Additionally, in this present study, since no acute levels of cTnT were observed after training, it can be assumed that neither of the exercise modalities facilitates damage to the cardiac muscle.

*Body composition and hemodynamic variables*

In accordance with former studies, no weight reduction was observed following intervention or differed between the groups (Keteyian *et al.,* 2014; Rocco *et al.,* 2012; Moholdt *et al.,* 2009; Moholdt *et al.,* 2011; Rognmo *et al.,* 2004). Ades *et al.* (Ades, Savage & Harvey-Berino, 2010) explained that while most new patients in CR programs are willing to undertake the exercise plan, only a minority are prepared to take action to reduce their dietary intake. In our study WC decreased significantly within the IE group, though the change seems to be small (- 0.9 cm). This change could have resulted from the relative higher (non-significant) number of patients from the IE group that consulted the dietitian during the 3 months of training, compared to the number of patients from the CE group ($X^2 = 0.077$), which emphasizes the need for nutritional guidance in such programs (Appendix G). It was demonstrated that every 1 cm decrease in WC is associated with a 2% decrease in risk of future cardiovascular disease (de Koning *et al.,* 2007), thus

more attention should be paid to weight loss (and specifically fat loss) in these programs.

Hemodynamic variables did not change in our study within or between the groups, a finding that is in agreement with several former trials (Guimaraes *et al.,* 2010; Rognmo *et al.,* 2004; Warburton *et al*., 2004), except for the reduction in BP within both training groups in the study done by Guimaraes *et al.* (2010), in which mean BP was elevated at baseline. The lack of changes in these indices could be attributed to the drug therapy that was closely regulated or to the normal values (Kessler *et al.,* 2012) that are defined by the Joint National Committee (JNC7) (Chobanian *et al.,* 2003). Drug therapy was supervised by the patient's physician (not in the CR facility); when desirable values were obtained and/or when side effects had appeared, adjustments were made. Consequently, it is possible that the lack of changes seen in these variables was due to therapy modifications. Data related to the changes in beta-blockers and anti-ischemic drug therapy can be found in appendix F which demonstrates no significant alterations in drug therapy.

*Echocardiography - Systolic function*

None of the systolic parameters were changed with training except for SV, for which there was an increasing trend within the IE group, with a small non-clinical mean change of 1.9 ml/beat (partial $eta^2 = 0.111$). Otherwise, no differences between the groups were observed in these values, a finding that is similar to that of a previous study by Moholdt *et al. (*2009). Only a few studies have investigated the effects of exercise-based CR on systolic function and compared IE with CE. Some of these studies lacked control groups, included small sample sizes, or used various protocols and cardiac populations. For instance, Amundsen *et al.* (2008) used interval training alone (with no CE group) on 17 CAD patients who had participated in a CR program and found no changes in LVEF. Another study that compared 19 healthy seniors with young males using interval training alone, demonstrated an increased systolic function (EDV, SV and LVEF) within the seniors (Molmen *et al.,* 2012). Wisloff *et al.* (2007) demonstrated a 35% increase in LVEF within HF patients (N=9) after interval training; however, it should be noted that baseline LVEF in that study was 29 % and the sample included only 27 patients. In another study (Giallauria *et al.,* 2009) improved LV systolic function was observed among patients post MI following exercise-based CR (6 months, no

interval component); however, baseline LVEF values (average LVEF = 44%) were also lower than those recorded in the present study.

Ehsani *et al.* (Ehsani, Ogawa, Miller, Spina & Jilka, 1991) reported that 10 cardiac patients exhibited an increased LVEF after high intensity interval training, but these changes were demonstrated only during exercise and not during rest. According to Panovski *et al.* (2011) it is possible that 3 months of intervention are not sufficient in inducing favourable systolic changes. In their study, only patients who trained for additional 9 months demonstrated improved resting LVEF. Yu *et al.* (2004) argued that cardiac function is more affected by drug therapy, especially in light of the progression of drug treatment for cardiac patients in past years.

*Echocardiography - Diastolic function*

Of the 72 patients that completed the intervention, more than half (18 CE and 19 IE) had a large LA area (>20 cm) at baseline and this proportion was not affected by training. In the current study mitral inflow variables (MV-E, E/A ratio and MV-DT) and mitral annular velocities were not changed with training, as was seen elsewhere (Moholdt *et al.,* 2009), and no group differences were detected in most of these variables. The only noticeable change was the decrease in MV-A within the CE group that was significantly different from the IE group which is in agreement with one interval training study (Wisloff *et al.*, 2007). In contrast to our findings, the same study by Wisloff *et al.* (2007) found improvements in e' and E/e' with interval training among considerably reduced LVEF HF patients, a cardiac population which was not included in this present study.

As far as known to us, no studies with interval training examined the effect on the grade of diastolic function. In this present study, most of the patients from both groups had no change in their diastolic function classification; however there seems to be a slight improvement in the diastolic function status in both groups. That is, while the number of patients having a normal diastolic function was increased, there was a decrease in the number of subjects presenting with diastolic dysfunction of all grades. This finding was similar to the one found in a previous trial done by Wuthiwaropas *et al. (*2013), however this study was not looking at interval training interventions. Thus, it is possible that exercise is valuable in preventing LV diastolic dysfunction progress in CAD patients (Yu *et al.,* 2004).

While it is not proven substantially that exercise can improve diastolic function among patients with abnormal diastolic function, Grewal *et al.* (2009) explained that even mild abnormalities of diastolic function can be related to a lower exercise capacity. They added that diastolic function is modifiable and can prevent the development of exercise intolerance provided it is identified and treated.

*Quality of life*

As has been widely reported in the literature, exercise-based CR produces a moderate improvement in health related QoL. While before the study the IE group had higher scores in all 3 scores, no group differences were found after the 12-week training period,. This lack of an effect of training type is consistent with the findings of the relatively few studies that have reported the effects of interval training on indices of QoL (Moholdt *et al.,* 2009; Moholdt *et al., 2*011). Other studies (that included HF patients) reported superior improvements in QoL indices along with cardiorespiratory variables within the interval training group (Fu *et al.,* 2013; Wisloff *et al.,* 2007). The researchers suggested that due to greater physiological adaptations, their subjects enjoyed from improved daily activities, thus improving their psychosocial state as well. Perhaps, if substantial differences in maximal aerobic capacity were found between the groups in the current study, QoL indices would have been different between the groups as well. Comparing the SF-36 questionnaire scores to academic grading in Israel (as suggested by Shmuelly, 1998), where a score < 54 is considered as 'fail' and a score > 95 is 'excellent', it is apparent that the CE subjects improved their scores from 'fair' to 'good' whereas the IE subjects improved their scores from 'good' to 'very good' and even to an 'excellent' total score.

In conclusion, twelve weeks of IE is equally effective for increasing relative peak $VO_2$ and more effective for improving indices of exercise tolerance and activities of daily living (ADL) compared with CE in cardiac patients. Neither IE nor CE alters LV ejection fraction. Indices of diastolic filling are not different between IE and CE after training, although there seems to be a reduction in the proportion of patients with a diagnosis of diastolic dysfunction in both training groups. IE was no more effective than CE in improving health-related QoL. However, IE may have some beneficial effects in several cardiac risk factors such as waist circumference and hs-CRP. In our opinion, although IE seems to be safe and relatively easy to

administer in a CR setting, there are various training protocols which include different intensity levels, duration of programs, frequency of sessions, and type of exercise instruments that have been documented before. It seems that our training protocol was not able to present unequivocal substantial advantages in favor of interval training, and that further designs and protocols should be explored before determining if interval exercise should be the preferable training method in CR programs. In the meantime, it is perfectly clear that moderate-high intensity exercise at any form of training, is valuable for cardiac patients.

# Chapter 5

# Comparison of outcomes 6 months after exercise-based CR: aerobic interval training versus moderate continuous training


## Summary

The extent to which benefits of exercise-based cardiac rehabilitation are sustained is poorly documented. Furthermore, most reports of studies that have investigated the efficacy of interval training in CR programs usually to do not include follow-up measurements. This chapter presents results from follow up tests performed six months after conclusion of the 12-week prospective randomized controlled trial described in Chapter 4. The main of objective of follow-up testing was to determine whether any of the differences apparent between CE and IE groups at the end of the 12-week training period persisted after a further 6 months (i.e. 9 months after the start of the intervention). Sixty-one subjects (56 men) underwent the follow-up measurements, 30 from the CE group and 31 from the IE group. At 6 month follow-up, $VO_2$ peak remained significantly higher compared to baseline only within the IE group. Former IE subjects demonstrated better results in several blood lipids including HbA1c, TG, and HDL-C, while increased levels of TC, LDL-C, and hs-CRP were observed in the former CE group. Although no differences were found between the training groups in body composition and hemodynamic variables, CE patients exhibited increased values of BF%. It was also found that QoL domains improved significantly more within the CE group, which can be explained by the higher QoL scores at the beginning of this phase within the IE group. Thus, both groups improved their QoL values significantly throughout the 9 months of the study. At 6 months follow-up the systolic indices ESV and LVEF and diastolic parameter of MV-A were slightly increased in the CE group, but clinical importance is questioned. Compared with at the end of 12-weeks training,there was an equal number of patients from the CE group and more patients from the IE group, who had a diagnosis of diastolic dysfunction at 6 months-follow up.

In conclusion, only IE patients were able to maintain higher functional capacity and several cardiovascular disease risk factors compared to CE subjects, which may suggest that interval training possibly have long-term benefits.

## Introduction

It is well established that cardiac rehabilitation participants improve aerobic capacity, reduce cardiovascular risk burden and improve QoL following exercise based rehabilitation (Lavie *et al.,* 2009; Swift *et al,.* 2013). Furthermore, improvements in aerobic capacity can be maintained for up to two years (Bosch *et al.,* 2005) and there are reports that exercise-based CR programs prevent the deterioration of diastolic dysfunction with time (Yu *et al.,* 2004), and preserve the important feature of QoL for long durations (Moholdt *et al.,* 2011). However, in contrast to the sustained effects on aerobic capacity, cardiac function and QoL, it seems that the cardiac risk factors profile does not necessarily remain improved (Blum *et al.,* 2013; Wilmer & Waite, 2009).

To date, relatively few studies that looked at the effects of aerobic interval exercise training in cardiac rehabilitation participants have evaluated the physiological and psychosocial effects over the longer term following completion of the intervention. However, one study did investigate exercise capacity, cardiac function and QoL six months after completion of a four-week IE training intervention at a CR facility (Moholdt *et al.,* 2009). In this study patients continued to train at home for the period between the end of the intervention and the follow-up measurements. Moholdt *et al.* (2009) found $VO_2$ peak, which was increased between baseline and 4 weeks, to be further increased in IE trained patients. In contrast, in another exercise group that trained using moderate continuous exercise, $VO_2$ peak was no greater at follow-up than at the end of the 4 weeks intervention, although the intervention resulted in greater aerobic capacity compared to baseline. Quality of life, which was increased from baseline to 4 weeks in both IE and CE groups, remained improved at 6 months in each training group.

The previous chapter of this thesis presented a prospective randomized controlled 3-month trial that examined the effect of moderate to high intensity, aerobic IE training on physiological and psychosocial outcomes in cardiac patients undergoing exercise-based rehabilitation in Israel. The current chapter presents an

extended follow-up at 6 months post intervention. The primary purpose of this chapter, therefore, is to evaluate any differences in the outcomes of aerobic capacity, resting cardiac function and QoL six months after completion of either IE or CE training. In light of findings by Mohdolt *et al.* (2009) it was hypothesized that the primary outcome, $VO_2$ peak, in the patients that had undergone 3 months of interval training would remain elevated at 6 months follow-up compared with baseline. In contrast, it was hypothesized that for patients that previously engaged in continuous training, $VO_2$ peak at 6 follow-up would be similar to baseline. Also, other variables that were found to be favourably changed within the IE group as was seen in Chapter 4 (such as maximal output, duration of exercise test, and hs-CRP), were expected to be preserved for 6 months by the same group.

## Methods

The data presented in this chapter were collected as a follow-up to the prospective randomized controlled trial described in Chapter 4. Upon completion of the supervised exercise intervention, patients were recommended to continue to exercise for 40-60 minutes at least 4 times a week. The prescription consisted of continuous training with moderate intensity levels of RPE 12-14. These guidelines were similar for all patients including to patients who have chosen to continue at the CR centre and for those who have decided to leave the CR program. CR programs in Israel last for 3 months; thereafter, patients can choose to continue to attend the program for up to a year with a partial financial contribution. As the study reported here sought to reflect the “real life” scenario, the decision whether to continue the program or not was made by the subjects without the intervention of the principal researcher. Patients who opted to remain, continued to receive professional care including: monthly monitoring of body weight and hemodynamic parameters, updating their exercise program every 3 months, and supervised exercise sessions by the trainer, the nurse, and the exercise physiologist.

Nine months after entering the study (6 months post intervention), all patients were invited to return to the Medical Centre for follow-up measurements. Testing day procedures are explained in Chapter 3 and included phlebotomy, hemodynamic and body composition measurements, QoL questionnaire, echocardiography, and $VO_2$ max test using the CPET. Furthermore, the exercise physiologist interviewed

patients regarding their habitual physical activity for the past 6 months, as well as the occurrence of symptoms, cardiac related events and subsequent hospitalizations.

### Statistical analysis

Repeated measures ANOVA was used to analyse differences between the groups during the follow-up period. When significant changes were found for the main effect of time, the statistical test was performed again after splitting the groups for finding where the changes have occurred. Independent T-tests were applied for comparing between the groups at 3 months or at 6 months follow-up. When categorical variables were compared Chi-square tests were used. For each statistical analysis the relevant assumptions were tested, and in any case for a violation, it was treated appropriately and stated in the text. Also, when necessary, exclusions of specific subjects were also stated in this chapter.

## Results

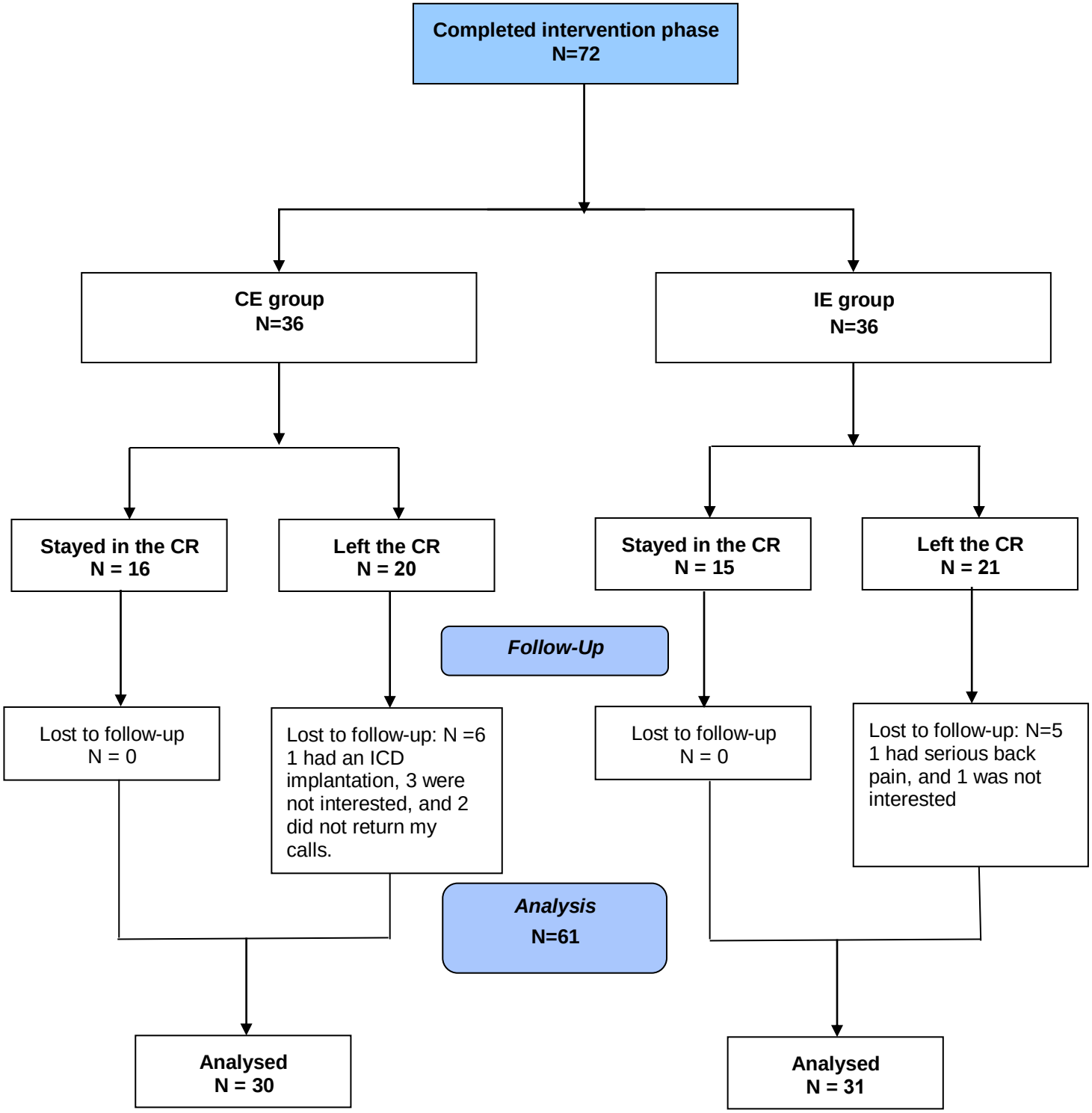
### Participants

Follow-up measurements took place between February 2012 and February 2015. Eleven patients were not able to complete the second phase of the study, thus 61 patients were incorporated in the statistical analysis. Reasons for not accomplishing the follow-up measurements included medical complications, patients who did not return phone calls, and also patients who were not interested in performing the tests. Two patients did not show up to the CPET at 9 months; one patient was suffering from serious back pain and was not able to perform any kind of activity around this time. The other subject claimed he was feeling too tired at the day of testing and he was unreachable since that day forward. Both patients performed the other tests including blood tests, echocardiography, body composition and hemodynamic measurements, and completed the SF-36 QoL questionnaire. There were no major complications or acute cardiac events during the follow-up period.

Out of the 61 subjects who have completed the follow-up measurements, 30 patients were from the CE group, and 31 were from the IE group. A new baseline comparison between the groups using the smaller sample size (N = 61) was

performed and is presented in Table 13. Most variables did not differ between the training groups before the intervention. However, QoL scores of physical health and total score were still significantly higher within the IE group compared to the CE group, as they were with the larger and original sample size at baseline. Patients' characteristics and flow diagram are presented in Table 14 and in Figure 9, respectively. At 3 months the groups were comparable in all variables including age, type of cardiac event, presence of cardiac risk factors, weight, BMI, hemodynamic variables, blood lipids, cardiorespiratory fitness, and use of cardiac medications. Presence of DM type 2 was the only risk factor that was different between the groups ($p = 0.031$) with 11 diabetic patients in the CE group compared to 4 diabetic patients in the IE group. As was explained in Chapter 4, this inequality between the training groups in DM2 did not exist with the initial sample of 84 subjects and occurred after some patients dropped out from the study during the intervention.

**Figure 9. A flow diagram of the number of patients during 6 months follow-up**




**ICD:** implantable cardioverter defibrillator

**Table 13. Baseline variables using N = 61**

| | All patients | CE | IE | P value |
|---|---|---|---|---|
| **N** | **61** | **30** | **31** | |
| **Cardiorespiratory parameters** | | | | |
| $VO_2$ peak (ml/kg/min) | 23.4 ± 5.7 | 22.9 ± 5.9 | 24.4 ± 6.0 | 0.293 |
| Maximal output (watt) | 131.5 ± 30.0 | 127.5 ± 34.6 | 135.3 ± 24.8 | 0.318 |
| Duration of test (min) | 8.9 ± 2.0 | 8.7 ± 2.1 | 9.2 ± 1.90 | 0.334 |
| Maximal HR (bpm) | 134.6 ± 17.7 | 133.3 ± 17.6 | 135.7 ± 18.0 | 0.600 |
| VT/predicted $VO_2$max (%) | 48.2 ± 12.7 | 47.9 ± 12.7 | 48.5 ± 13.0 | 0.492 |
| Maximal RPP (mmHg X bpm) | 25258 ± 5712 | 25358 ± 5828 | 25162 ± 5692 | 0.526 |
| **Blood lipids and markers** | | | | |
| TC (ml/dl) | 129.5 ± 24.3 | 127.7 ± 21.1 | 131.3 ± 27.4 | 0.568 |
| Blood glucose (ml/dl) | 105.8 ± 15.7 | 111.0 ± 18.7 | 100.8 ± 10.0 | 0.013 |
| HbA1c (%) | 5.95 ± 0.62 | 5.91 ± 0.63 | 5.60 ± 0.62 | 0.595 |
| TG (ml/dl) | 90.5 ± 27.7 | 87.5 ± 24.3 | 93.3 ± 30.6 | 0.433 |
| LDL-C (ml/dl) | 69.2 ± 28.5 | 64.7 ± 19.4 | 73.5 ± 34.9 | 0.817 |
| HDL-C (ml/dl) | 45.1 ± 10.7 | 43.1 ± 8.0 | 46.9 ± 12.6 | 0.168 |
| HS-CRP (mg/l) | 2.14 ± 2.19 | 1.93 ± 1.69 | 2.33 ± 2.58 | 0.489 |
| cTnT < 0.014 (ng/ml) | 58 (95.1) | 28 (93.3) | 30 (96.8) | 0.844 |
| **Body composition** | | | | |
| Weight (Kg) | 81.0 ± 11.9 | 80.4 ± 10.8 | 81.5 ± 13.0 | 0.725 |
| BMI ($Kg/m^2$) | 27.9 ± 3.9 | 27.9 ± 3.5 | 28.0 ± 4.34 | 0.919 |
| Percent of body fat (%) | 28.0 ± 8.0 | 28.0 ± 7.4 | 28.0 ± 8.8 | 0.979 |
| WC (cm) | 99.0 ± 9.5 | 98.1 ± 8.4 | 100.0 ± 10.6 | 0.454 |
| Resting HR (bpm) | 65.5 ± 9.2 | 65.2 ± 9.0 | 65.8 ± 9.4 | 0.778 |
| Resting SBP (mmHg) | 118.9 ± 11.0 | 120.2 ± 9.9 | 117.6 ± 12.1 | 0.372 |
| Resting DBP (mmHg) | 71.9 ± 7.3 | 72.5 ± 6.3 | 71.4 ± 8.8 | 0.584 |

**Table 13. Continued.**

| | All patients | CE | IE | P value |
|---|---|---|---|---|
| **N** | **61** | **30** | **31** | |
| **Cardiac function** | | | | |
| LA area ($mm^2$) [a] | 20.3 ± 4.2 | 19.9 ± 3.8 | 21.2 ± 5.2 | 0.455 |
| MV-E (cm/s), | 72.1 ± 12.9 | 71.2 ± 12.2 | 73.1 ± 13.7 | 0.568 |
| MV-A (cm/s) | 66.2 ± 16.8 | 67.8 ± 15.0 | 64.5 ± 18.7 | 0.459 |
| E/A ratio | 1.18 ± 0.48 | 1.11 ± 0.33 | 1.26 ± 0.59 | 0.151 |
| e' (ms) | 9.4 ± 1.4 | 9.3 ± 1.4 | 9.5 ± 1.6 | 0.550 |
| E/e' [b] | 7.9 ± 1.9 | 7.7 ± 1.8 | 8.1 ± 2.0 | 0.253 |
| EDV (ml) | 98.4 ± 13.5 | 95.8 ± 13.1 | 101.1 ± 13.7 | 0.134 |
| ESV (ml) | 44.0 ± 11.4 | 42.8 ± 9.7 | 45.3 ± 13.0 | 0.403 |
| SV (ml) | 54.4 ± 9.8 | 53.1 ± 9.9 | 55.9 ± 9.8 | 0.281 |
| Calculated LVEF(%) | 55.5 ± 8.2 | 55.4 ± 7.4 | 55.6 ± 9.2 | 0.916 |
| **QoL scores** | | | | |
| PH score | 73.9 ± 16.6 | 68.5 ± 19.4 | 79.7 ± 10.6 | 0.010 |
| MH score | 74.7 ± 17.1 | 71.1 ± 19.8 | 78.5 ± 12.8 | 0.103 |
| Total score | 75.8 ± 16.9 | 70.5 ± 19.5 | 81.5 ± 11.3 | 0.012 |

**HR**: heart rate **; VT**: ventilatory threshold; **RPP**: rate pressure product; **TC**: total cholesterol; **HbA1c**: glycosylated haemoglobin; **TG**: triglycerides; **LDL-C**: low density lipoprotein cholesterol; **HDL-C**: high density lipoprotein cholesterol; **HS-CRP**: high sensitive C-reactive protein; cTnT: Troponin-T; **BMI**: body mass index**; WC**: waist circumference; **SBP**: systolic blood pressure; **DBP**: diastolic blood pressure; **MV-E**: early diastolic mitral inflow velocity; **MV-A**: late diastolic mitral inflow velocity; **e'**: average of septal and lateral e'. **EDV**: end diastolic volume. **ESV**: end systolic volume. **LVEF**: left ventricular ejection fraction; **PH**: physical health. **MH**: mental health

**Table 14. Characteristics of patients at 3 months**

| | All patients | CE | IE | P value |
|---|---|---|---|---|
| **N** | **61** | **30** | **31** | |
| **Age (years)** | 58.1 ± 7.4 | 59.0 ± 7.5 | 57.3 ± 7.3 | 0.389 |
| **Men** | 56 (92) | 25 (90) | 29 (93) | ----- |
| **Coronary disease and risk factors** | | | | |
| MI | 44 (72) | 22 (73) | 22 (71) | 0.837 |
| CABG | 12 (20) | 5 (17) | 7 (23) | 0.234 |
| PCI | 7 (11) | 3 (10) | 4 (13) | 0.722 |
| Type 2 DM | 15 (25) | 11 (37) | 4 (13) | 0.031 |
| HTN | 29 (47) | 16 (53) | 13 (42) | 0.373 |
| Overweight, BMI>25 | 44 (72) | 22 (73) | 22 (71) | 0.837 |
| Obese, BMI>30 | 18 (29) | 9 (30) | 9 (29) | 0.934 |
| Dyslipidemia | 47 (77) | 22 (73) | 25 (81) | 0.497 |
| Smoking (current/recent) | 20 (33) | 11 (37) | 9 (30) | 0.584 |
| **Drugs** | | | | |
| Beta blockers | 52 (85) | 25 (83) | 27 (87) | 0.679 |
| Statins | 60 (98) | 30 (100) | 30 (97) | 0.314 |

Values are presented as mean ± SD or frequencies and percentage (%), as appropriate.

**BMI**: body mass index; **MI**: myocardial infarction; **CABG**: coronary artery bypass graft; **PCI**: percutaneuous coronary intervention. **DM**: diabetes mellitus; **HTN**: hypertension;

## Outcome measurements

*Cardiorespiratory outcomes*

Data is presented in Table 15. A comparison between the CE and IE groups at 3 months (post intervention) revealed no difference in peak $VO_2$ or any other cardiorespiratory parameters. Furthermore, no differences in peak $VO_2$, or any other cardiorespiratory variable, were found between the groups from 3 months to 9 months. Also, no significant changes in these parameters were seen for the main effect of time in either of the groups. However, at 9 months follow-up peak $VO_2$ remained statistically higher compared to baseline levels only within the IE group ($p = 0.040$), while there were no differences between baseline and 9 months within the CE group ($p = 0.524$). Figure 10 represents the changes in peak $VO_2$ over the 3 time points of the study. Submaximal cardiorespiratory indices did not change or differ between the groups during the follow-up. It is important to report that the differences that were found between the groups in maximal output and duration of exercise test following the intervention did no longer exist with the smaller sample size (N = 61), which might affect the outcomes during the follow-up period.

**Table 15. Cardiorespiratory parameters at 3 and 9 months**

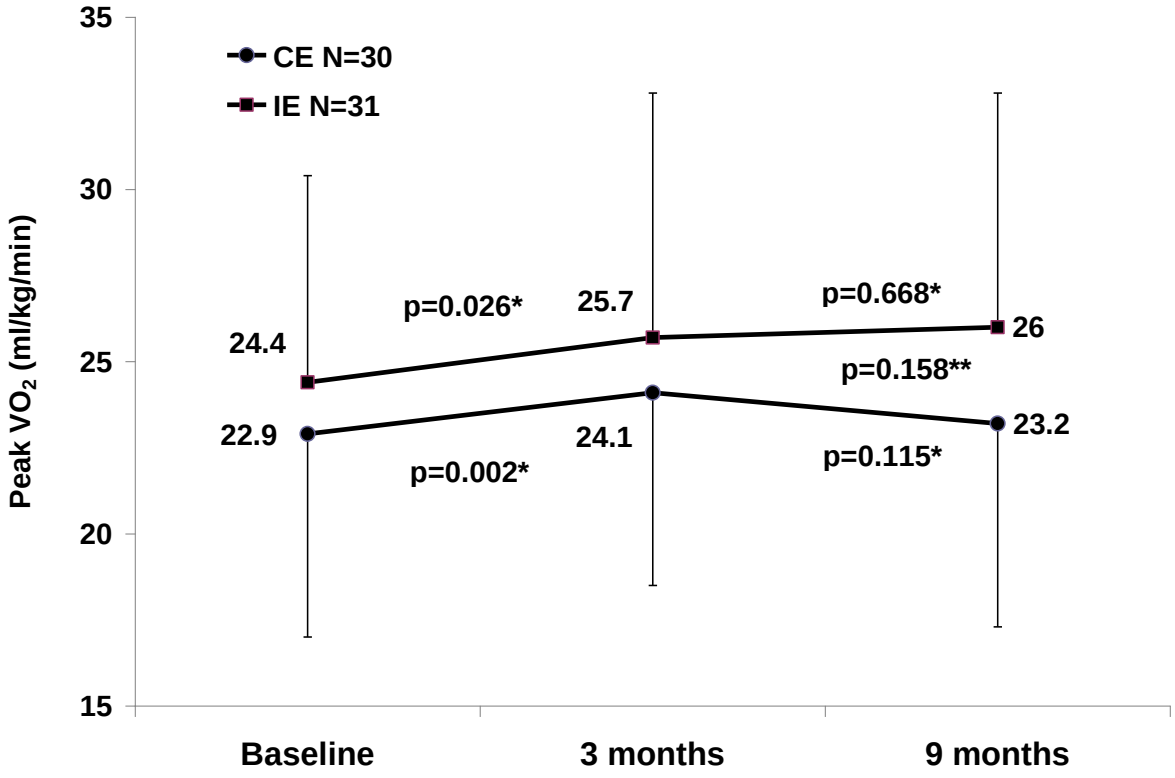
| | CE N = 30 | | IE N = 31 | | P value | Partial Eta$^2$ |
|---|---|---|---|---|---|---|
| | 3 months | 9 months | 3 months | 9 months | | |
| $VO_2$ peak (ml/kg/min) | 24.1 ± 6.0 | 23.2 ± 5.9 | 25.7 ± 7.1 | 26.0 ± 6.8 | 0.158 | 0.042 |
| Maximal output (watt) | 133.9 ± 36.0 | 132.7 ± 35.1 | 145.3 ± 31.0 | 139.4 ± 23.6 | 0.505 | 0.008 |
| Duration of test (min) | 8.7 ± 2.0 | 8.5 ± 2.7 | 9.9 ± 2.1 | 9.5 ± 1.8 | 0.530 | 0.007 |
| Maximal HR (bpm) | 134.2 ± 18.0 | 134.0 ± 18.8 | 137.2 ± 1.7 | 137.5 ± 18.3 | 0.845 | 0.001 |
| Maximal SBP (mmHg) | 190.5 ± 24.8 | 196.0 ± 27.4 | 189.3 ± 23.6 | 192.8 ± 29.3 | 0.625 | 0.004 |
| VT/predicted $VO_2$ max (%) | 51.8 ± 10.9 | 51.4 ± 12.4 | 50.4 ± 11.7 | 53.1 ± 10.6 | 0.142 | 0.041 |
| $VO_2$ peak / predicted $VO_2$ max (%) | 86.5 ± 18.9 | 83.4 ± 19.9 | 85.3 ± 25.6 | 86.5 ± 17.3 | 0.187 | 0.033 |
| Maximal VE (l/min) | 73.1 ± 19.1 | 72.8 ± 19.0 | 79.2 ± 23.8 | 72.3 ± 18.2 | 0.084 | 0.052 |
| Maximal RPP (mmHg X BP) | 25839 ± 5904 | 26560 ± 6374 | 26197 ± 5679 | 26817 ± 6492 | 0.916 | 0.000 |
| RER | 1.16 ± 0.12 | 1.15 ± 0.14 | 1.15 ± 0.09 | 1.10 ± 0.08 | 0.153 | 0.036 |
| Maximal RPE | 17.5 ± 0.6 | 17.3 ± 0.5 | 17.6 ± 0.7 | 17.4 ± 0.5 | 0.691 | 0.003 |

Values are presented as mean ± SD

P value represents differences between 3 months and 9 months

**HR**: heart rate **; SBP:** systolic blood pressure; **VT**: ventilatory threshold; **VE**: ventilation; **RPP**: rate pressure product; **RER:** respiratory exchange ratio; **RPE:** Rating of perceived exertion

**Figure 10. Peak $VO_2$ at baseline, 3 months, and 9 months in CE and IE groups**




*****p value represents changes over time within the group

**p value represents differences between the groups from 3 to 9 months

*Blood parameters and CVD risk biomarkers*

Due to several outliers and the violation of the assumption of normal distribution as was confirmed by boxplots, some cases were excluded during this analysis. The relevant data can be found in Table 16. Separated group analysis revealed an elevation in total cholesterol and LDL-C among CE patients over time ($p = 0.003$, $eta^2 = 0.267$; and $p = 0.027$, $eta^2 = 0.157$, respectively), while IE subjects increased HDL-C levels ($p = 0.034$, $eta^2 = 0.142$). There were group differences between the groups in favour of the IE group in triglycerides, though levels were within normal recommended values. HbA1c was different between the groups as a result of a small reduction in the IE group and a small increase in the CE group. Also, hs-CRP levels were elevated significantly at follow-up compared with the end of the intervention among CE subjects only ($p = 0.048$, $eta^2 = 0.132$). Only 1 patient from each group exhibited cTnT levels above the cut-off point, therefore group comparison seemed to be unnecessary.

When compared with baseline (before the intervention), there were group differences in HbA1c ($p = 0.015$, $eta^2 = 0.100$) with a reduction in the IE group alone (5.90 ± 0.50% at baseline and 5.66 ± 0.50% at 9 months, $p < 0.001$, $eta^2 = 0.381$). Also, group differences were observed in hs-CRP ($p = 0.009$) with significantly increased levels within the CE group (1.93 ± 1.69 mg/l at baseline and 3.12 ± 3.42 mg/l at 9 months, $p = 0.026$, $eta^2 = 0.176$). Additionally, an almost significant elevation was seen in the LDL-C within the CE group from baseline to the end of 9 months (64.7 ± 19.4 ml/dl and 70.0 ± 18.7 ml/dl, respectively, $p = 0.054$), while a non-significant decrease was observed in the IE group. Lastly, HDL-C was improved significantly in both groups from baseline to 9 months (CE: 43.1 ± 8.0 ml/dl and 45.5 ± 10.1 ml/dl, respectively, $p = 0.037$, $eta^2 = 0.133$; IE: 46.9 ± 12.6 ml/dl and 51.1 ± 13.3 ml/dl, respectively, $p = 0.040$, $eta^2 = 0.147$).

*Body composition and hemodynamic variables*

There were no differences in body composition and hemodynamic variables between the exercise groups during the follow-up phase (Table 17). BF% was increased significantly over time only in the CE group ($p = 0.035$, $eta^2 = 0.145$), No significant changes within each group or between the groups were observed during the 9 months of the study in any of the variables. There was a tendency towards reduction in WC within the IE group from baseline to 6 months follow-up (mean = -1.10 ± 3.31, $p = 0.079$). Also, there was a small non-significant reduction in RHR from baseline to 6 months follow-up in both the CE and the IE groups (mean = -2.38 ± 7.00, $p = 0.067$; and mean = -2.35 ± 6.90, $p = 0.078$, respectively).

**Table 16. Blood parameters and CVD risk biomarkers at 3 and 9 months**

| | CE 3 months N = 30 | CE 9 months N = 30 | IE 3 months N = 31 | IE 9 months N = 31 | P value | Partial eta$^2$ |
|---|---|---|---|---|---|---|
| **Blood lipids and markers** | | | | | | |
| TC (ml/dl) | 129.0 ± 18.8 | 136.4 ± 21.4* | 138.9 ± 32.6 | 138.0 ± 19.4 | 0.151 | 0.035 |
| Blood glucose (ml/dl)[a] | 110.8 ± 23.6 | 116.0 ± 35.2 | 101.6 ± 21.0 | 101.4 ± 11.7 | 0.728 | 0.002 |
| HbA1c (%)[b] | 5.87 ± 0.56 | 5.97 ± 0.86 | 5.73 ± 0.48 | 5.66 ± 0.50 | 0.018 | 0.096 |
| TG (ml/dl)[c] | 83.2 ± 33.3 | 91.8 ± 30.3* | 98.4 ± 37.5 | 92.6 ± 36.1 | 0.027 | 0.083 |
| LDL-C (ml/dl) | 66.1 ± 15.2 | 70.0 ± 18.7* | 70.9 ± 27.3 | 69.2 ± 12.3 | 0.227 | 0.026 |
| HDL-C (ml/dl)[d] | 44.0 ± 8.1 | 45.5 ± 10.1 | 47.5 ± 11.2 | 51.1 ± 13.3* | 0.312 | 0.017 |
| HS-CRP (mg/l)[e] | 2.07 ± 1.59 | 3.12 ± 3.42* | 1.72 ± 1.64 | 1.92 ± 1.56 | 0.114 | 0.045 |
| cTnT < 0.014 (ng/ml)** | 28 (93.3) | 29 (96.7) | 30 (96.8) | 30 (96.8) | ---- | ---- |

* Differences within the group from 3 months to 9 months ($p < 0.05$).

** Values are presented as number of patients and percentage (%).

[a] Patients number 84 (CE group) and 28 (IE) were excluded

[b] Patients number 47 (CE group) and 28 (IE) were excluded

[c] Patient number 9 (CE group) was excluded

[d] Patient number 57 (CE group) was excluded

[e] Patients number 63 (CE group) and 76 (IE) were excluded

**TC**: total cholestrol. **HbA1c**: glycosylated hemoglobin. **TG**: triglycerides. **LDL-C**: low density lipoprotein cholesterol; **HDL-C**: high density lipoprotein cholesterol; **HS-CRP**: high sensitive C-reactive protein; cTnT: Troponin-T

**Table 17. Body composition and hemodynamic variables at 3 and 9 months**

| | CE 3 months N = 30 | CE 9 months N = 30 | IE 3 months N = 31 | IE 9 months N = 31 | P value | Partial eta$^2$ |
|---|---|---|---|---|---|---|
| **Body composition and hemodynamic variables** | | | | | | |
| Weight (Kg) | 80.3 ± 10.8 | 80.9 ± 10.8 | 80.8 ± 12.0 | 81.2 ± 12.2 | 0.833 | 0.001 |
| BMI (Kg/m$^2$) | 27.8 ± 3.6 | 27.9 ± 3.5 | 27.7 ± 4.1 | 27.8 ± 4.1 | 0.761 | 0.002 |
| Percent of body fat (%) | 27.8 ± 7.5 | 28.5 ± 7.2* | 27.7 ± 8.5 | 28.0 ± 8.7 | 0.229 | 0.026 |
| WC (cm) | 98.1 ± 8.1 | 98.7 ± 8.1 | 99.3 ± 9.5 | 99.1 ± 9.4 | 0.186 | 0.031 |
| Resting HR (bpm) | 63.9 ± 8.9 | 62.8 ± 8.1 | 64.0 ± 9.4 | 63.5 ± 10.2 | 0.741 | 0.002 |
| Resting SBP (mmHg) | 118.0 ±10.7 | 119.9 ±11.4 | 117.5 ± 12.1 | 118.2 ± 11.3 | 0.591 | 0.005 |
| Resting DBP (mmHg) | 72.9 ± 6.6 | 71.3 ± 7.9 | 71.9 ± 8.4 | 72.6 ± 7.4 | 0.188 | 0.030 |

**BMI**: body mass index**; HR**: heart rate; **SBP**: systolic blood pressure; **DBP**: diastolic blood pressure

** Within differences p < 0.05*

*Echocardiography parameters*

At 6 months follow-up, LVEF was normal in approximately similar proportion of patients in both groups (74% of the CE and 78% of the IE groups). However, during the follow-up period, ESV was decreased and LVEF was increased only among CE patients (p = 0.028, eta$^2$ = 0.152, and p = 0.004, eta$^2$ = 0.246, respectively). Other LV systolic parameters were not changed significantly regardless of exercise group affiliation. At the time of follow-up measurements abnormal LA area (> 20 mm$^2$) was present among 15 (50%) subjects from the CE group and 18 (62%) from the IE group, corresponding to a total of 33 patients (56%) with LA enlargement. These proportions were similar to those determined at the end of the 3-month intervention. Comparisons of diastolic parameters did not reveal any changes with time, or between the groups, except for a significant increase in MV-A within the CE group at 6 months follow-up (p = 0.013, eta$^2$ = 0.189). Due to technical difficulties, data of e' could not have been obtained for all participants, thus the N number was smaller for these variables. Data is presented

in Table 18. Compared to measurements taken at the end of the exercise intervention, it was observed that overall there were only small changes in diastolic function classification at 6 months follow-up (Figures 11 and 12). Only 1 patient (3%) from the CE group had an improvement in diastolic function, while 3 patients (10%) from the IE group, who have been previously diagnosed with normal diastolic function, were classified with abnormal function at 6 months follow-up. Chi-square analysis demonstrated no differences between the groups in these changes (Table 19).

**Table 19. Numbers and percentages of patients who have changed their diastolic function classification from 3 months to 9 months**

| | CE | IE | P value* |
|---|---|---|---|
| N | 29 | 30 | |
| No change | 30 (96.8) | 26 (89.7) | |
| Improvement in diastolic function | 1 (3.2) | 0 (0) | 0.121 |
| Worsening in diastolic function | 0 (0) | 3 (10.3) | |

Data is presented in number of patients and percentages (%)

*Chi-Square analysis

**Table 18 - Echocardiography variables**

| | CE | | | IE | | | P value | Partial Eta$^2$ |
|---|---|---|---|---|---|---|---|---|
| | N | 3 months | 9 months | N | 3 months | 9 months | | |
| LA area ($mm^2$) [a] | 31 | 20.3 ± 3.7 | 19.8 ± 3.5 | 28 | 20.9 ± 4.7 | 20.7 ± 4.1 | 0.677 | 0.003 |
| **Diastolic function** | | | | | | | | |
| MV-E (cm/s), | 31 | 71.7 ± 16.5 | 69.8 ± 14.3 | 28 | 75.5 ± 12.7 | 72.7 ± 13.6 | 0.809 | 0.001 |
| MV-A (cm/s) | 31 | 64.7 ± 9.2 | 69.6 ± 12.5* | 28 | 62.5 ± 16.7 | 64.3 ± 18.1 | 0.217 | 0.027 |
| E/A ratio | 31 | 1.1 ± 0.3 | 1.0 ± 0.3 | 28 | 1.3 ± 0.6 | 1.2 ± 0.5 | 0.902 | 0.000 |
| MV-DT (ms) [a] | 30 | 175.3 ± 39.9 | 170.8 ± 40.2 | 28 | 184.1 ± 39.0 | 175.1 ± 35.3 | 0.701 | 0.003 |
| e' (ms) | 21 | 9.3 ± 1.3 | 9.2 ± 1.4 | 22 | 9.2 ± 1.6 | 9.1 ± 1.6 | 0.990 | 0.000 |
| E/e' [b] | 21 | 7.9 ± 1.8 | 7.7 ± 2.1 | 21 | 8.3 ± 1.8 | 8.3 ± 2.3 | 0.902 | 0.000 |
| **Systolic function** | | | | | | | | |
| EDV (ml) | 31 | 95.4 ± 11.9 | 95.7 ± 12.4 | 28 | 105.9 ± 20.4 | 106.0 ± 20.8 | 0.962 | 0.000 |
| ESV (ml) | 31 | 41.7 ± 8.9 | 40.8 ± 9.1* | 28 | 48.4 ± 20.2 | 47.7 ± 20.3 | 0.812 | 0.001 |
| SV (ml) | 31 | 53.7 ± 9.0 | 54.9 ± 8.9 | 28 | 57.4 ± 9.5 | 58.3 ± 9.3 | 0.790 | 0.001 |
| Calculated LVEF(%) | 31 | 56.4 ± 6.7 | 57.6 ± 6.7* | 28 | 55.4 ± 10.5 | 56.3 ± 10.5 | 0.587 | 0.005 |

Values are means and SD.

* Significant within the group over time ($p < 0.05$)

[a] Patient number 10 (CE group) was excluded

[b] Patient number 44 (IE group) was excluded

**MV-E**: early diastolic mitral inflow velocity. **MV-A**: late diastolic mitral inflow velocity. **MV-DT**: mitral valve deceleration time. **e'**: average of septal and lateral e'. **EDV**: end diastolic volume. **ESV**: end systolic volume. **LVEF**: left ventricular ejection fraction.

**Figure 11. Percent of patients from the CE group with normal diastolic function and diatolic dysfunction at baseline, 3 months, and 9 months.**

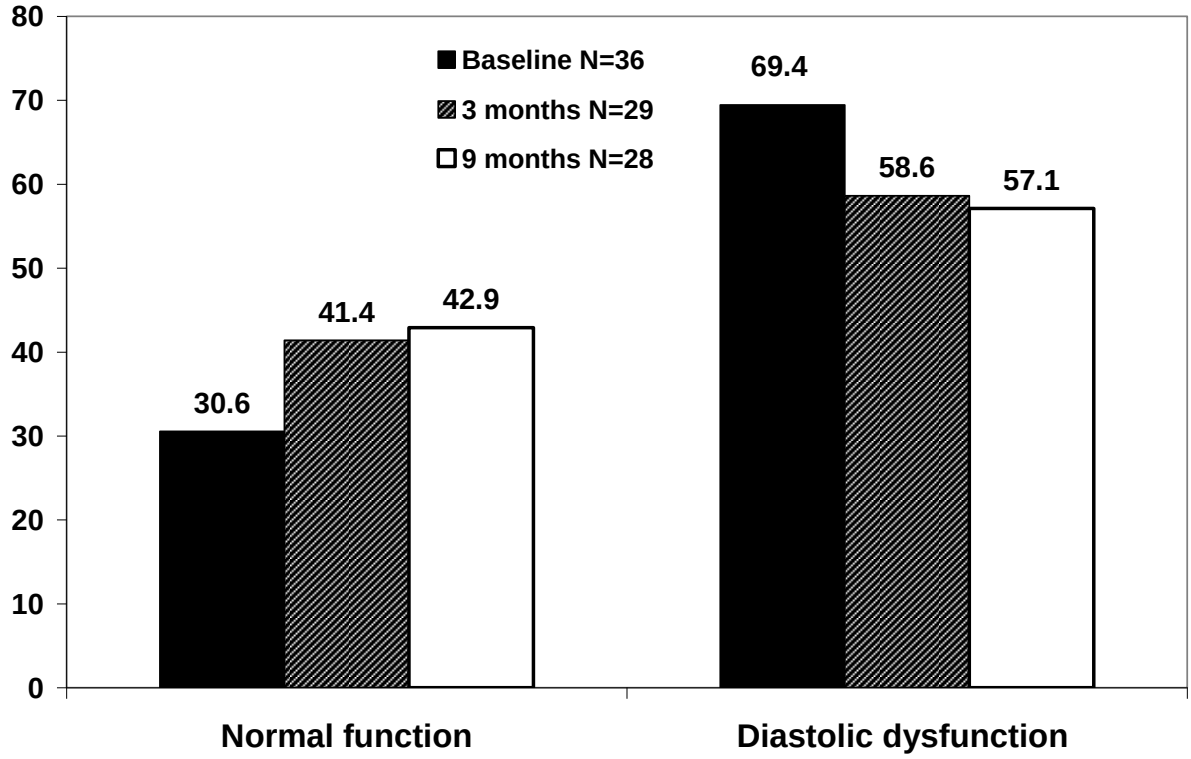
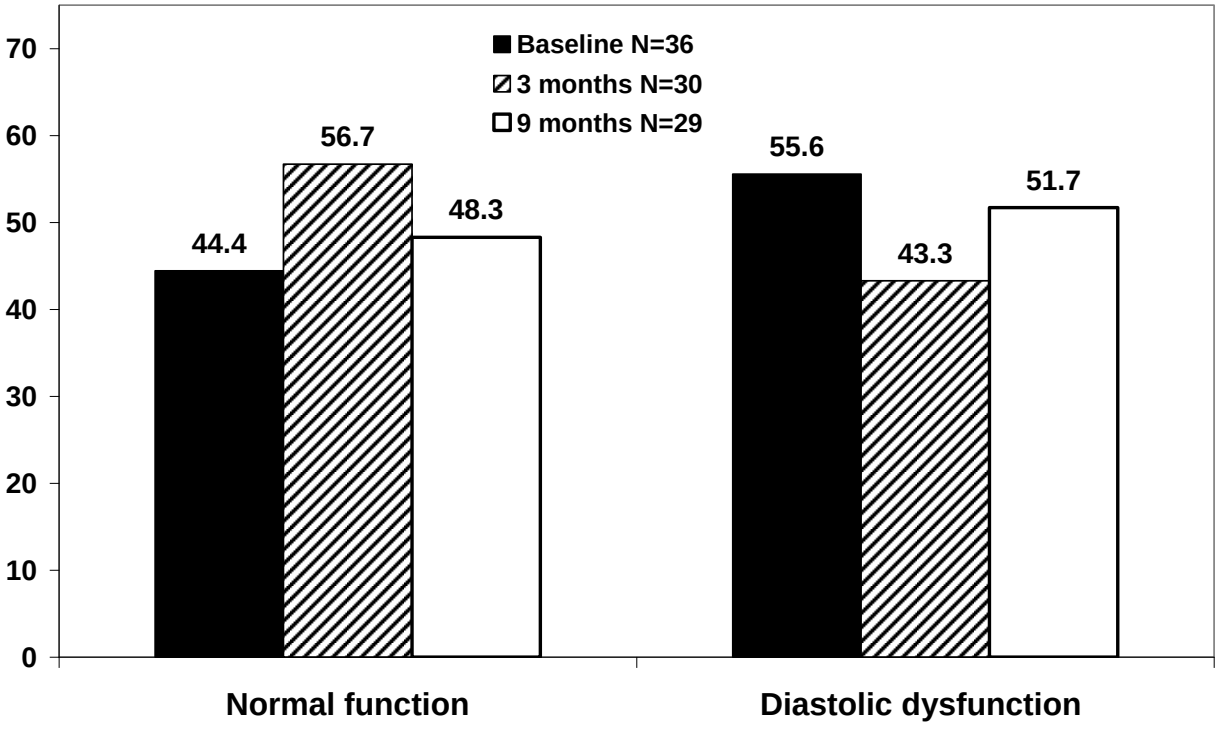



**Figure 12. Percent of patients from the IE group with normal diastolic function and diastolic dysfunction at baseline, 3 months, and 9 months.**



*Quality of life*

As reported in the previous chapter (Chapter 4), data from 3 subjects were excluded from the statistical analysis. Repeated measures Anova analysis found no differences between the groups in MH and PH changes throughout the follow-up period (Table 20). However, only the CE group improved their total score significantly during this time ($p = 0.030$, $eta^2 = 0.162$), resulting in almost a significant difference between the groups ($p = 0.052$). It is important to note that the physical health score and the total score were significantly higher in the IE group (N= 27) compared to the CE group (N = 28) at baseline, and that total score was still significantly higher in the IE group compared to the CE group at 3 months before the follow-up phase, as was revealed by independent T-Test analysis. However, it is also important to refer to the relatively high SD of these scores within the CE group across all time points. Figure 13 illustrates the changes of the total score within and between the groups throughout the 9 months of the study.

Most of the subscales did not differ significantly within or between the groups over this time. Only the domains of role limitations due to physical health and due to emotional problems were different significantly between the groups. These differences occurred due to improved scores within the CE group along with lowered scores within the IE group. However, T-test analysis demonstrated that these scores were significantly higher among IE subjects before the follow-up period compared to the scores within the CE group ($p = 0.006$, and $p = 0.009$, respectively). At 6 months follow-up there were no differences between the groups in these two domains ($p = 0.832$, and $p = 0.884$, respectively).

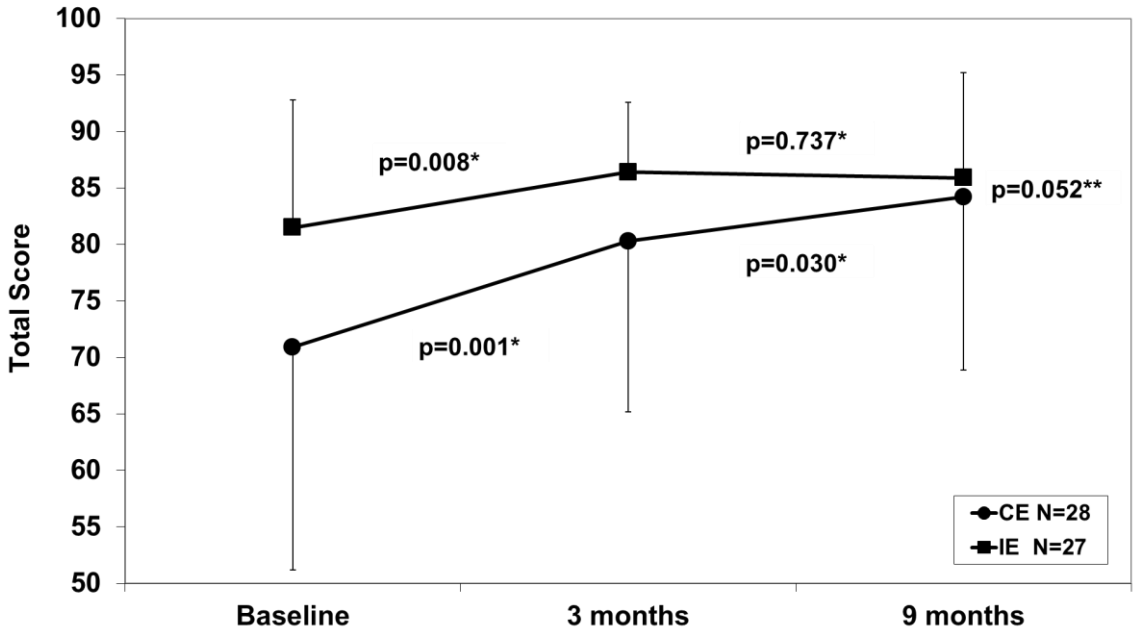
**Table 20 - SF-36 Quality of Life Questionnaire variables**

| | CE | | IE | | P value | Partial Eta$^2$ |
|---|---|---|---|---|---|---|
| | 3 months | 9 months | 3 months | 9 months | | |
| **N** | **28** | **28** | **27** | **27** | | |
| PH score | 78.3 ± 15.7 | 82.3 ± 15.8 | 83.0 ± 7.2 | 82.3 ± 11.1 | 0.086 | 0.055 |
| MH score | 79.6 ± 13.9 | 82.1 ± 14.8 | 83.9 ± 6.2 | 83.1 ± 8.3 | 0.095 | 0.052 |
| Total score | 80.3 ± 15.1 | 84.2 ± 15.3* | 86.4 ± 6.2 | 85.9 ± 9.3 | 0.052 | 0.069 |

Values are means and SD.

* Differences within groups from 3 months to 9 months, p value< 0.05
**PH**: physical health. **MH**: mental health
Patients 44, 69, and 71 were excluded from this analysis due to non-cardiac related personal issues.

**Figure 13. Total score of SF-36 at baseline, 3 months, and 9 months in CE and IE groups**




* p values represent changes within the groups over time

** p values represent differences between the groups from 3 to 9 months

Both groups increased Total score from baseline to 3 months ($p<0.05$) with almost significant differences between them at 9 months ($p>0.05$). Only CE improved total score from 3 to 9 months.

## Discussion

The purpose of this study was to examine the sustained effects of two aerobic exercise prescriptions on cardiorespiratory fitness, clinical parameters and health-related quality of life in cardiac patients. Patients completed 3 months of either moderate-high aerobic IE or moderate aerobic CE at our CR centre and subsequently were followed for 6 months. As is the custom in Israel, at the end of the formal CR program patients chose whether to continue exercising at the CR facility or to leave the program and exercise on their own, but all patients were invited for the follow-up measurements, in which 61 subjects ultimately took part.

*Cardiorespiratory parameters*

Cardiorespiratory parameters were not different between the training groups at 6 months follow-up. Overall, taking into consideration measurements performed before the start of the intervention, both exercise prescriptions improved peak $VO_2$ significantly from baseline to 3 months with no further changes at follow-up. However, compared to baseline levels, only IE subjects were able to maintain higher levels of functional capacity at 9 months, whereas CE subjects presented similar values at baseline and at 9 months. These outcomes were different from a study that reported further improvements during 6 months follow-up by IE participants with significant differences compared the CE subjects (Moholdt *et al.,* 2009).

Another study (by the same author), with a considerably longer duration of follow-up (30 months) demonstrated that values of peak $VO_2$ at the end of the follow-up were similar compared to baseline within IE patients but lower than baseline values within CE subjects (Moholdt *et al.,* 2011). The authors suggested that the differences between the training groups at follow-up were attained partly due to the higher increase in exercise capacity during the intervention, which was not apparent in our study. Moreover, in their study, subjects from the IE group reported better adherence to home exercise compared to their CE peers (Moholdt *et al.,* 2011). In our study, all patients reported similar amount of exercise per week (see Appendix G). These results suggest that interval training might have an advantage over continuous training in maintaining physiological adaptations, even if the same amount of exercise is being performed following 3 months of intervention. Analyses

of patients who completed follow up testing produced similar results with the comparison performed at the end of the intervention except that the difference in the duration of the exercise test (and thus maximal power output) lost significance. It is possible that the 'new' sample size that was used for the follow-up period was underpowered for detecting these differences.

*Blood parameters and CVD risk biomarkers*

Interval training may have some long-term beneficial effects on several blood parameters. This was shown when levels of HDL-C were increased only within the IE group, and with group differences in TG and HbA1c in favour of the IE group. Moreover, other variables including TC, TG, LDL-C, and hs-CRP, were increased within the CE group. This was similar to a trial that revealed a deterioration in TC, LDL-C, TG, and blood glucose in patients exercising using the moderate aerobic continuous method, at 18 months follow-up. It is important to note that in their study different training volumes were used compared to the present study and that the follow-up period was longer than in our study (Hansen *et al.,* 2010). Conversely, our results are contradictory to those of Moholdt *et al.* (2009, 2011) who reported no changes at 6 months follow-up for HDL-C, TG, glucose, LDL-C (Moholdt *et al.,* 2009), and hs-CRP (Moholdt *et al.,* 2011), within or between the training groups. Both the CE and the IE groups in the present study improved HDL-C from baseline to 9 months in 3.3 ± 7.3 mg/dl and 4.2 ± 10.6 mg/dl respectively. Increasing HDL-C levels in 1 mg/dl may reduce cardiovascular risk by 2-3% (Ali, Wonnerth, Huber, and Hojta, 2012). In the current study, blood glucose levels within the CE group were higher than the recommended values and compared to the IE group due to a higher number of diabetic patients in this group. This fact can explain the better outcomes in HbA1c at 9 months within the IE group although it is also possible that interval training can improve glucose metabolism (Tjønna *et al.,* 2008).

It is important to comment for clinical relevance, that most blood lipids at both time points (3 and 9 months) remained within the normal ranges according to the ESC guidelines whether they have changed or not (Steg *et al.,* 2012). However, LDL-C and hs-CRP levels reached values of clinical implication within the CE group after 6 months follow-up. Both variables are considered to be associated with greater cardiovascular and mortality risks when exceed the recommended values of LDL-C

< 70 mg/dl (Ridker *et al.,* 2005; Smith *et al.,* 2006) and hs-CRP < 1 mg/l. In fact it was found that CAD patients reaching hs-CRP values greater than 3 mg/l are at considerably higher risk compared to those with levels smaller than 1 mg/l (Bassuk *et al.,* 2004; Morrow *et al.,* 2006). In this current study, 23% and 23.5% of the CE and the IE subjects respectively had hs-CRP $\geq$ 3 mg/l at 3 months; while 28% and 21% of these subjects correspondingly had values $\geq$ 3 mg/l at 9 months.

Thus, apparently more patients from the CE group that were at moderate risk for CVD at the end of the intervention were considered to be at high risk at 9 months. The hs-CRP responses to different training modalities cannot be explained due to little research with interval training. Hs-CRP has been shown to consistently be predictive of CVD events but it was presumed that it is not modifiable in either primary or secondary prevention (Shlipak, Ix, Bibbins-Domingo, Lin & Whooley, 2008). This present study illustrated that more patients from the CE group exhibited abnormal levels of hs-CRP over 9 months, implying they were exposed to a higher cardiovascular risk (Bassuk *et al.,* 2004). In contrast, at the same time, the IE participants were able to maintain the levels of hs-CRP and blood lipids, and even enhance HDL-C which is an independent risk factor for CAD (Castelli *et al.,* 1986). Thus, our study might suggest that interval training can have a positive effect on CVD risk.

A study that looked at the effect of exercise on hs-CRP in at-risk population, found that cardiorespiratory fitness was inversely related with hs-CRP levels (Huffman *et al.*, 2006). Since our results demonstrated that only IE patients have maintained higher peak $VO_2$ levels at 6 months follow-up compared to baseline, it could be the reason for the maintained lower levels of hs-CRP in this group while the CE group exhibited increased inflammatory levels. CTnT consistently remained low during the follow-up time, which might be suggestive that training in both modalities has long-term positive effects on this prognostic cardiac biomarker.

*Body composition and hemodynamic variables*

CE and IE participants exhibited no differences between them in body composition and hemodynamic variables, which is in agreement with former trials (Hansen *et al.,* 2010; Moholdt *et al.,* 2011). None of the other interval studies have followed these parameters after training; therefore it was difficult to compare the results.

Since most patients were not assisted by a dietitian and since supervision over exercise was diminished or did not exist during the follow-up time, it seems that body composition was unlikely to be favourably changed.

*Echocardiography*

The improvement of the systolic indices including ESV and LVEF within the CE group alone could not be explained, however the changes seem to be rather small (0.9 ± 2.2 ml and 1.2 ± 2.1%, respectively). No changes were found in other systolic parameters during this phase which is in agreement with a previous study (Yu *et al.,* 2004). The sole change in diastolic indices during the follow-up occurred with the increase in MV-A among CE subjects, which was similar to the finding in the study done by Yu *et al.* (2004). They found an increased MV-A in control subjects post AMI and PCI at 8 months follow-up, however, this study was comparing non-exercisers versus the standard training and not interval training. Parameters of mitral annulus velocities in the current study did not change or differ over time. To our knowledge none of the CAD interval training trials have conducted follow-up echocardiography measurements; thus, comparison with past research was not possible and conclusion regarding the long-term effect of interval training on either systolic or diastolic variables could not have been drawn.

In terms of the distribution of diastolic function grading, after what seemed to be an improvement in both training groups during the 3 months of intervention, the results revealed a slight regression in diastolic function within the former IE group during the follow-up period, while there was almost no change in the former CE group. This was in contrast to the study performed by Yu *et al.* (2004) who have presented a further improvement in diastolic function grading at 8 months follow-up. These favourable changes occurred only in the training group who exercised for 60 minutes daily, while the control group had a meaningful reduction in the proportion of patients with a normal pattern and an increase in the number of patients with abnormal LV diastolic function. Therefore, it can be assumed that exercise training should be performed more regularly in order to maintain or further improve in diastolic function.

In summary, only small significant changes were seen in echocardiography parameters including small increases in ESV, LVEF% and MV-A wave within the

CE group, which probably have no clinical relevance. Also, according to the current findings, it seems that normal diastolic function might deteriorate with time, unless exercise is being regularly maintained (Yu *et al.*, 2004). These outcomes seem to be difficult to explain or be supported due to scarce existing research.

*Quality of life*

IE patients started the follow-up period with significantly higher, total score, and some of the subscales, compared to CE subjects. At the end of this phase, these differences between the groups did not exist anymore due to the significant improvements within the CE group from 3 to 9 months. However, it is important to remind the reader that the SD of the QoL scores were higher within the CE group during each time point, which might raise a doubt regarding the certainty of these outcomes. Both groups had bigger improvements during the intervention period compared to the follow-up time; actually the IE group had no change during the follow-up period but the patients had maintained their high scores throughout this time. Consequently, both groups had 'very good' MH and PH scores (according to Shumeli *et al.,* 1998) after 6 months follow-up. Similarly, three previous trials have demonstrated the preservation of improved QoL parameters during follow-up within both training groups (Moholdt *et al.,* 2009; Moholdt *et al.,* 2011) and within IE group (versus controls) (Nilsson, Westheim & Risberg, 2008). Also, Willmer, and Waite (2009) demonstrated improved QoL parameters at 6 months follow-up among cardiac patients who have exercised regularly. Basically, it seems that training group modality has no impact on psychological indices.

To summarize, these data demonstrate that improvements in functional capacity and several CVD risk factors following exercise-based CR are sustained at 6 month follow-up when the exercise consisted of aerobic interval activities. In contrast, when training consisted continuous aerobic exercise, fitness and CVD risk were not different at follow up compared with baseline values. This suggests that an exercise prescription of IE may positively influence the extent to which improvements in functional capacity and CVD risk can be sustained once the formal component of CR has ended. Future work is warranted to explore the interaction between prescribed exercise and long-term benefits training modalities in cardiac rehabilitation.

# Chapter 6

# Comparison of CR-based and non-CR-based patients during the 6 months post intervention

## Summary

While exercise-based CR programs have been found to be extremely beneficial (Lavie *et al.,* 2009), most CR programs are relatively short-term and medium- to long-term effects are not fully known. Thus, the effects of each training modality (CE and IE) were examined 6 months post intervention and this analysis was presented in Chapter 5. However, that analysis does not take into account that 31 out of 72 patients enrolled in the study continued to exercise at our CR centre during this 6 month period. Thus, the purpose of the current chapter is to present further analyses to determine whether or not continuing to exercise at a CR centre has any impact upon outcomes achieved during a 3 month exercise intervention. Although this comparison was not included in the research design, it became apparent that the patients who continued to exercise at the CR centre (CR-based) may have benefitted from regular supervision and monitoring. Thus, it was possible that these persons would have exercised more regularly, and with greater intensity, compared to those patients had chosen to leave the centre (non-CR-based) at the end of the exercise interventions. This led to a *posteriori* hypothesis that CR-based would have better outcomes compared with non-CR based at 6 month follow up.

The results indicate that CR-based patients, who were equally physically active compared to the non-CR-based patients, were able to maintain cardiorespiratory and several cardiac risk factors benefits, while non-CR based experienced a greater deterioration in some of the outcome measurements. While some changes, including the systolic indices, seem rather small and not clinically relevant, it is noteworthy that there was better maintenance of cardiorespiratory fitness among CR-based subjects. This is very important, due to the fact that maximal functional capacity is a crucial factor in cardiac morbidity and mortality. In conclusion, the analysis presented in this chapter, although it was which was not included in the original research design, suggest that supervision and monitoring of exercise in CR-patients in the medium- to long-term may confer some degree of protection

against deterioration of health gains achieved during a 3 month CR-programme . However, more research is needed to establish the optimal structure and length of CR programs.

## Introduction

The option to continue exercising at a CR facility once the supervised exercise component has been completed is standard practice for CR centres in Israel. Therefore, during the 6 month period between the end of the intervention and the follow-up assessments, some patients continued to exercise in the CR facility, whereas others decided to exercise on their own rather than in the CR facility. While there is solid evidence of the advantages of CR programs on physiological and psychological outcomes, less is known about the lasting effects of these programs after they have ended (Willich, Muller-Nordhorn, Kulig, Binting & Gohlke, 2001). Within the few studies that have looked at long term effects of CR programs, variation exists with respect to the duration of the follow-up periods and the outcomes considered. For instance, studies that followed cardiac patients for 2-5 years after completion of a CR plan found favourable reductions in cardiac-related events, CV mortality, days of hospitalizations, and increased survival rates, amongst those patients that continued to exercise in the CR facility when compared to those who did not remain in the program (Giannuzzi,Temporelli & Maggioni, 2005; Panovsky, Kukla, Jancik, Meluzin & Dobsak, 2013; Plus, 2011).

Other investigations with follow-up durations lasting between several months to 5 years, revealed that patients who completed short-term CR programs often experienced deterioration in exercise habits (levels of physical activity) and cardiac risk factors such as blood pressure, and levels of LDL-C and triglycerides over time (Reid, Morrin, pipe, Dafoe & Higginson, 2006; Hansen, 2010). These indications were in contrast to those who continued to exercise in a CR setting, that often showed either maintenance of their previously gained beneftis (Wilmer & Waite, 2009) or even further improvements in those markers including cardiac risk factors and lifestyle habits (exercise, diet, and stress management) (Giannuzzi *et al.,* 2005; Lear, Spinelli, Linden, Brozic & Kiess, 2006).

In the previous chapter (Chapter 5) we examined the long-term effects (after 6 months) of different training types on the primary and secondary outcomes in this thesis. However, the effect of continuing or discontinuing to exercise at a CR facility was not taken into consideration for those analyses. Therefore, the focus of the present chapter is a comparison of outcomes at six months follow up between patients who had stayed in the CR facility (CR-based) and those who had exercised on their own (non-CR-based) during this period. In light of findings presented in Chapter 4 of this thesis, it was determined that the CR-based and the non-CR-based groups would not be further subdivided according to the two training modalities (i.e. CE and IE). Thus, although it was not included in the original design, the primary aim of this secondary analysis was to provide insight into the effectiveness of continuing to monitor exercise in CR-patients following completion of 3 months of supervised exercise. It was hypothesized that CR-based would have greater physiological and psychological benefits compared to non CR-based.

## Methods

All of the data presented in this chapter were retrospectively analysed from that which was collected at the 6 month follow-up (Chapter 5) to the prospective randomized controlled trial. The methods for the measurements have been described in Chapter 3 of this thesis.

## Statistical analysis

For the purposes of this analysis, the sample was divided into two groups (irrespective of training method): patients who continued to exercise at the CR centre (CR-based) and patients who did not (non-CR-based). Repeated measures ANOVA was used to examine differences between the CR-based and non-CR-based subjects during the follow-up period of 6 months. ANCOVA was used when the effect of covariate variables was investigated. When categorical variables were compared chi-square tests were used. For comparisons between the groups at each time point independent T-tests were applied. For each statistical analysis the relevant assumptions were tested, and in any case for a violation, it was treated appropriately and stated in the text. Also, when necessary, exclusions of specific subjects due to extreme outliers were also noted in this chapter.

## Results

The number of subjects who continued to attend the CR centre (CR-based) after the completion of the intervention phase was 31, which represented 43% of the 72 patients who completed the intervention. The remaining 41 subjects (57%) left the CR program immediately or shortly after they had concluded the intervention phase (non-CR-based). In response to informal questions, the most common reasons cited for continuing to exercise in the CR facility included: feeling safe to exercise at the cardiac centre, the need for a structured program, being monitored by the professional staff, and enjoying the company of other participants. Frequent reasons for leaving the program included: feeling safe enough to exercise on their own, saving the time of the trip to the hospital, and being subscribed in a local gym with flexible hours. At 6 months follow up 11 subjects failed to complete the final measurements, all were from the non-CR-based group. Reasons for not showing up for the test are detailed in the flow diagram (Figure 14).

Using questionnaires regarding habits of physical activity, it was found that all CR-based subjects were physically active, while 23 (77%) non-CR-based subjects reported being physically active during the 6 months follow-up, which resulted in significant differences between them. However, in terms of time spent performing physical activity in minutes per week, no differences were found between these groups (Table 21).

Using the number of patients who completed the follow-up measurements (N=61), all characteristics including age, sex, type of cardiac event, and cardiac risk factors were similar between CR-based and non-CR-based at the beginning of this phase (Table 21). Also, blood lipids, body composition, hemodynamic indices, LVEF%, and peak $VO_2$, were not different between CR-based and non-CR-based at 3 months ($p > 0.05$).

**Figure 14. A flow diagram of the number of CR-based and non-Cr-based patients during 6 months follow-up**

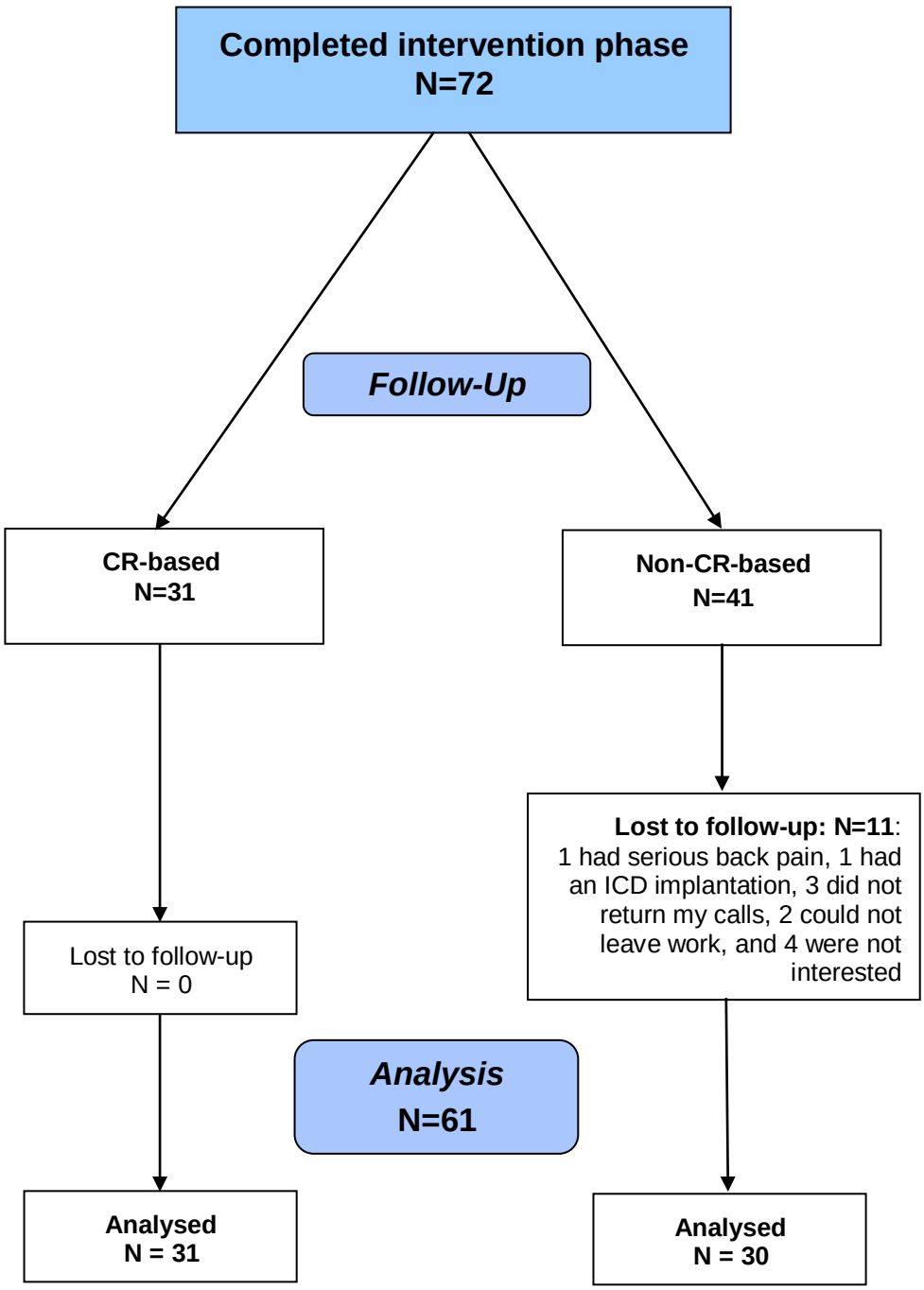


**Table 21. Characteristics of CR-based and Non-CR-based patients at the end of the intervention**

| | CR-based | Non-CR-based | P value |
|---|---|---|---|
| **N** | **31** | **30** | |
| **Personal Characteristics** | | | |
| Age (years) | 58.9 ± 7.0 | 57.3 ± 7.7 | 0.411 |
| Men (%) | 27 (87) | 29 (97) | ----- |
| Women (%) | 4 (13) | 1 (3) | ----- |
| Weight (kg) | 80.8 ± 12.5 | 79.9 ± 9.7 | 0.745 |
| BMI ($kg/m^2$) | 28.2 ± 4.0 | 27.23 ± 3.6 | 0.312 |
| **Coronary disease and risk factors** | | | |
| MI (%) | 22 (71) | 22 (73) | 0.837 |
| CABG (%) | 6 (19) | 6 (20) | 0.949 |
| PCI (%) | 5 (16) | 2 (7) | 0.246 |
| Type 2 DM (%) | 8 (26) | 7 (23) | 0.823 |
| HTN (%) | 12 (39) | 17 (57) | 0.160 |
| Obese, BMI>30 (%) | 12 (39) | 6 (20) | 0.109 |
| Dyslipidemia (%) | 27 (87) | 20 (67) | 0.058 |
| Smoking (current/recent) (%) | 7 (23) | 13 (43) | 0.100 |
| **Physical activity habits** | | | |
| Continued to exercise* (%) | 31 (100) | 23 (77) | 0.004 |
| Physical activity (min/week)** | 175 ± 93 | 134 ± 24 | 0.159 |

Values are presented as mean ± SD or frequencies and percentage (%), as appropriate. **BMI**: body mass index; **MI**: myocardial infarction; **CABG**: coronary artery bypass graft; **PCI**: percutaneous coronary intervention. **DM**: diabetes mellitus; **HTN**: hypertension;

*Cardiorespiratory variables*

At 6 months follow up, peak $VO_2$ was for the CR-based subjects was similar to that post intervention; on the other hand there was a strong trend for a decrease ($p = 0.054$) among non-CR-based subjects. Figure 15 demonstrates similar improvements in peak $VO_2$ among patients from both these groups during the intervention, but different responses for CR-based and non-CR-based patients during the follow-up, resulting in a significant difference between the groups ($p = 0.040$). The differences between the groups remained significant also after controlling for weight, BMI, and body fat percentage. Differences in duration of CPET and maximal output were also significant between these groups, due to a substantial decline among non-CR-based subjects in duration of test ($p = 0.027$, $eta^2 = 0.174$), and in maximal output ($p = 0.013$, $eta^2 = 0.201$). Data is presented in Table 22.

**Table 22. Comparisons of cardiorespiratory parameters between CR-based and non-CR-based from 3 months to 6 months follow-up**

| | CR-based N = 31 | | Non-CR-based N= 30 | | P value between groups | Partial Eta$^2$ |
|---|---|---|---|---|---|---|
| | 3 months | 9 months | 3 months | 9 months | | |
| $VO_2$ peak (ml/kg/min) | 24.7 ± 7.3 | 25.2 ± 7.5 | 25.2 ± 5.7 | 24.0 ± 5.1 | 0.040 | 0.072 |
| Maximal output (watt) | 134.6 ± 33.5 | 136.5 ± 31.2 | 140.4 ± 33.2 | 132.8 ± 28.0* | 0.031 | 0.034 |
| Duration of test (min) | 9.0 ± 2.2 | 9.0 ± 2.0 | 9.4 ± 2.0 | 8.9 ± 1.7* | 0.036 | 0.081 |
| Maximal HR (bpm) | 135.6 ± 17.3 | 134.6 ± 17.3 | 133.1 ± 21.3 | 135.0 ± 20.0 | 0.351 | 0.017 |
| VT/predicted $VO_2$ max (%) | 52.4 ± 13.3 | 55.3 ± 14.4 | 50.5 ± 10.2 | 50.1 ± 10.0 | 0.126 | 0.044 |
| $VO_2$ peak / predicted $VO_2$ max (%) | 88.0 ± 26.3 | 91.4 ± 26.4 | 85.9 ± 18.9 | 81.7 ± 16.5 | 0.747 | 0.002 |
| Maximal RPP (mmHg X BP) | 25565 ± 5665 | 26202 ± 6919 | 257217 ± 5852 | 26454 ± 6200 | 0.925 | 0.000 |

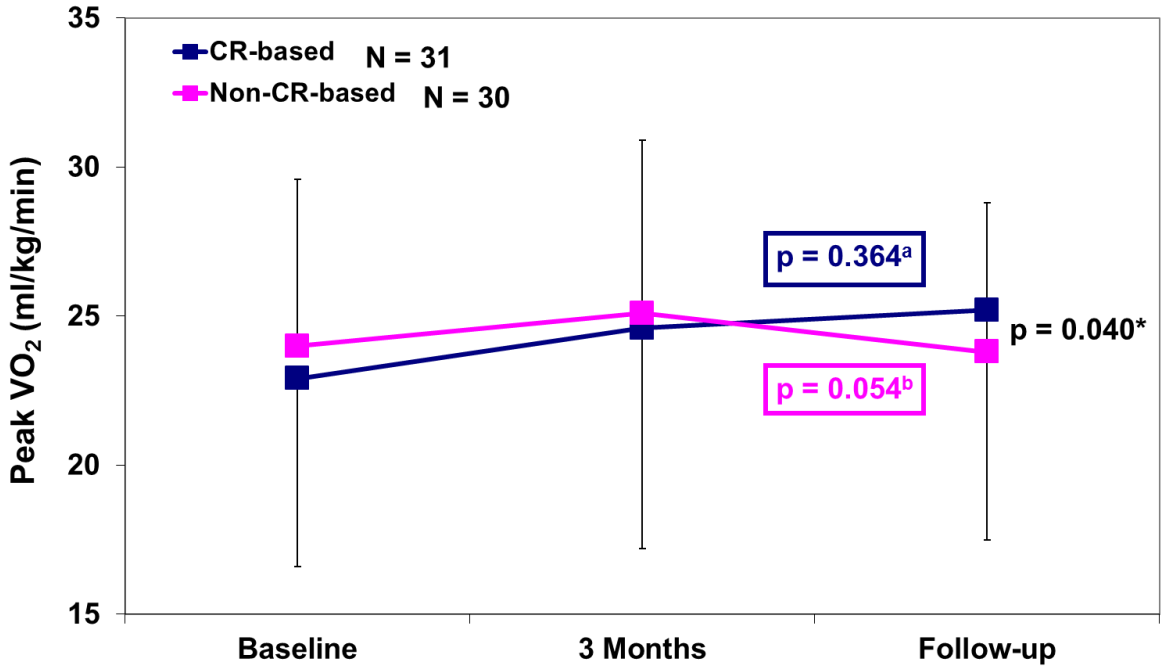
Values are presented as mean ± SD

*****Significant changes within the group over time

P value represents differences between 3 months and 9 months

**HR**: heart rate **; SBP:** systolic blood pressure; **VT**: ventilatory threshold; **VE**: ventilation; **RPP**: rate pressure product; **RER:** respiratory exchange ratio; **RPE:** Rating of perceived exertion

**Figure 15. Differences between CR-based and non-CR-based subjects in peak $VO_2$ from baseline to 9 months.**




* p value < 0.05 represents differences between CR-based and non-CR-based groups from 3 months to 9 months

[a] p value represents changes within CR-based patients from 3 months to 9 months

[b] p value represents changes within non-CR-based patients from 3 months to 9 months

CR-based maintained peak $VO_2$ during follow-up period while non-CR-based had lowered their peak $VO_2$ throughout this time.

*Blood parameters and CVD risk biomarkers*

Total cholesterol, LDL-C, and HDL-C were elevated significantly within the CR-based group at follow-up compared with at the end of the initial exercise intervention; this accounts for a significant difference in the values fro these parameters between the two groups at follow-up. Other blood lipids and cardiovascular biomarkers were not changed (Table 23).

**Table 23. Comparisons of blood lipids and markers between CR-based and non-CR-based from 3 months to 6 months follow-up**

| | CR-based N=31 3 months | CR-based N=31 9 months | Non-CR-based N=30 3 months | Non-CR-based N=30 9 months | P value groups | Partial eta$^2$ |
|---|---|---|---|---|---|---|
| **Blood lipids and markers** | | | | | | |
| TC (ml/dl) | 130.7 ± 22.5 | 139.5 ± 21.9* | 138.0 ± 31.3 | 135.0 ± 18.8 | 0.040 | 0.070 |
| Blood glucose (ml/dl)[a] | 104.3 ± 14.5 | 106.6 ± 15.7 | 101.5 ± 13.7 | 105.6 ± 20.6 | 0.532 | 0.007 |
| HbA1c (%) | 5.78 ± 0.52 | 5.73 ± 0.55 | 5.93 ± 0.63 | 6.03 ± 0.85 | 0.099 | 0.046 |
| TG (ml/dl) | 92.3 ± 43.1 | 91.2 ± 38.1 | 95.7 ± 35.8 | 101.1 ± 35.3 | 0.333 | 0.016 |
| LDL-C (ml/dl) | 63.7 ± 17.0 | 70.3 ± 17.8* | 74.2 ± 26.0 | 69.4 ± 13.4 | 0.023 | 0.086 |
| HDL-C (ml/dl)[b] | 46.7 ± 10.4 | 49.4 ± 12.5* | 43.9 ± 7.8 | 46.3 ± 10.4 | 0.913 | 0.00 |
| HS-CRP (mg/l)[c] | 1.96 ± 1.73 | 2.75 ± 3.25 | 2.02 ± 1.80 | 2.67 ± 2.65 | 0.813 | 0.001 |
| cTnT < 0.014 (ng/ml)** | 29 (93.5) | 29 (93.5) | 29 (96.7) | 30 (100) | ---- | ---- |

* Differences within the group from 3 months to 9 months ($p < 0.05$).

** Values are presented as number of patients and percentage (%).

[a] Patients number 84 and 28 were excluded

[b] Patients number 57, 52 were excluded

[c] Patient number 63 was excluded

**TC**: total cholestrol. **HbA1c**: glycosylated haemoglobin. **TG**: triglycerides. **LDL-C**: low density lipoprotein cholesterol; **HDL-C**: high density lipoprotein cholesterol; **HS-CRP**: high sensitive C-reactive protein; cTnT: Troponin-T

*Body composition and hemodynamic variables*

Values are presented in Table 24. There was a strong trend for differences between the groups in body composition variables that resulted from increased values of BMI and percent of body fat within the non-CR-based group ($p = 0.048$, $p = 0.001$, respectively). In contrast, CR-based participants maintained their body weight parameters during the follow-up period. As has already been indicated, the group differences in body composition did not account ofr the group differences in

peak $VO_2$. There was no effect of post intervention training location (CR based versus non-CR based) on resting HR, SBP, and DBP.

**Table 24. Comparisons of body composition and hemodynamic parameters between CR-based and non-CR-based from 3 months to 6 months follow-up**

| | CR-based 3 months | CR-based 9 months | Non-CR-based 3 months | Non-CR-based 9 months | P value groups | Partial eta$^2$ |
|---|---|---|---|---|---|---|
| | N = 31 | N = 31 | N = 30 | N = 30 | | |
| Weight (Kg) | 81.7 ± 12.4 | 81.5 ± 12.5 | 79.9 ± 9.9 | 81.2 ± 10.2 | 0.056 | 0.065 |
| BMI (Kg/m$^2$) | 28.5 ± 4.0 | 28.5 ± 3.9 | 27.4 ± 3.6 | 27.8 ± 3.7* | 0.059 | 0.063 |
| Percent of body fat (%) | 28.7 ± 9.0 | 28.7 ± 8.8 | 27.2 ± 6.9 | 28.2 ± 7.1* | 0.058 | 0.064 |
| WC (cm) | 99.1 ± 10.2 | 98.9 ± 9.7 | 98.8 ± 7.5 | 99.3 ± 7.9 | 0.254 | 0.024 |
| Resting HR (bpm) | 66.2 ± 9.6 | 64.9 ± 8.8 | 61.2 ± 7.8 | 61.0 ± 8.9 | 0.545 | 0.007 |
| Resting SBP (mmHg) | 116.7 ± 12.6 | 117.0 ± 11.9 | 118.7 ± 10.1 | 120.2 ± 10.8 | 0.591 | 0.005 |
| Resting DBP (mmHg) | 71.2 ± 8.2 | 70.7 ± 7.7 | 73.4 ± 6.1 | 72.4 ± 6.8 | 0.787 | 0.001 |

* Values are means and SD* Within p value< 0.05

**BMI**: body mass index. **WC**: waist circumference. **HR**: heart rate. **SBP**: systolic blood pressure. **DBP**: diastolic blood pressure

*Echocardiography parameters*

Several small changes within the groups and differences between the groups were noticed at 6 months follow-up; these are presented in Table 25. The CR-based group had a small reduction in resting in ESV at follow-up ($p = 0.017$, eta$^2 = 0.193$); in contrast the non-CR-based had an elevated EDV ($p = 0.044$, eta$^2 = 0.159$). Calculated EF was increased within CR-based patients ($p = 0.019$, eta$^2 = 0.187$) whereas SV was increased within non-CR-based patients ($p = 0.025$, eta$^2 = 0.192$). Diastolic indices did not change and continuation of exercise at the CR facility did not seem to affect diastolic function classification according to frequencies and Chi-Square analysis.

**Table 25. Comparisons of echocardiography parameters between CR-based and non-CR-based from 3 months to 6 months follow-up**

| | CR-based | | | Non-CR-based | | | P value groups | Partial Eta$^2$ |
|---|---|---|---|---|---|---|---|---|
| | N | 3 months | 9 months | N | 3 months | 9 months | | |
| LA area ($mm^2$) [a] | 28 | 20.3 ± 3.3 | 20.1 ± 3.5 | 25 | 20.6 ± 4.2 | 19.9 ± 3.9 | 0.528 | 0.007 |
| **Diastolic function** | | | | | | | | |
| MV-E (cm/s), | 28 | 75.2 ± 16.8 | 71.9 ± 12.9 | 25 | 72.6 ± 12.1 | 69.1 ± 15.5 | 0.944 | 0.000 |
| MV-A (cm/s) | 28 | 64.5 ± 11.7 | 68.6 ± 15.4 | 25 | 63.4 ± 14.1 | 65.6 ± 14.1 | 0.477 | 0.010 |
| E/A ratio | 28 | 1.2 ± 0.3 | 1.1 ± 0.3 | 25 | 1.2 ± 0.5 | 1.1 ± 0.3 | 0.654 | 0.004 |
| MV-DT (ms) [a] | 29 | 179.7 ± 40.9 | 176.7 ± 37.5 | 26 | 181.4±40.0 | 173.1±38.1 | 0.701 | 0.003 |
| e' (ms) | 22 | 9.4 ± 1.2 | 9.6 ± 1.2 | 17 | 9.6 ± 1.3 | 9.2 ± 1.4 | 0.126 | 0.062 |
| E/e' [b] | 22 | 8.1 ± 1.8 | 7.7 ± 2.0 | 17 | 7.6 ± 1.1 | 7.8 ± 2.0 | 0.354 | 0.023 |
| **Systolic function** | | | | | | | | |
| EDV (ml) | 28 | 98.2 ± 12.1 | 96.5 ± 13.4 | 25 | 101.0±12.7 | 102.6±12.6 | 0.034 | 0.085 |
| ESV (ml) | 28 | 42.6 ± 10.4 | 41.0 ± 11.0 | 25 | 45.0 ± 11.7 | 45.1 ± 13.1 | 0.055 | 0.039 |
| SV (ml) | 28 | 55.6 ± 10.0 | 55.5 ± 9.6 | 25 | 55.9 ± 9.0 | 57.5 ± 8.3 | 0.158 | 0.001 |
| LVEF(%) | 28 | 56.7 ± 8.2 | 57.9 ± 8.4 | 25 | 55.7 ± 8.1 | 56.6 ± 8.1 | 0.673 | 0.004 |

Values are means and SD.

Patient number 29 was excluded from all echo analaysis

* Significant within the group over time ($p < 0.05$)

[a] Patient number 10 was excluded

[b] Patient number 44 was excluded

**MV-E**: early diastolic mitral inflow velocity. **MV-A**: late diastolic mitral inflow velocity. **MV-DT**: mitral valve deceleration time. **e'**: average of septal and lateral e'. **EDV**: end diastolic volume. **ESV**: end systolic volume. **LVEF**: left ventricular ejection fraction.

*Quality of life*

Table 26 represents QOL values at 6 month follow-up. Apart of an improvement in total score of SF-36 among non-CR-based patients (time effect: p = 0.046, $eta^2$ =0.135), no other changes or differences were seen in these variables.

**Table 26. Comparisons of SF-36 Quality of Life Questionnaire variables between CR-based and non-CR-based from 3 months to 6 months follow-up**

| | CR-based | | Non-CR-based | | P value | Partial $Eta^2$ |
|---|---|---|---|---|---|---|
| | 3 months | 9 months | 3 months | 9 months | | |
| **N** | **26** | **26** | **29** | **29** | | |
| PH score | 80.9 ± 13.8 | 81.8 ± 14.6 | 80.0 ± 12.3 | 83.2 ± 11.3 | 0.378 | 0.015 |
| MH score | 81.3 ± 12.3 | 81.4 ± 13.5 | 81.9 ± 10.7 | 84.0 ± 9.4 | 0.274 | 0.023 |
| Total score | 83.0 ± 13.4 | 84.0 ± 14.2 | 83.2 ± 11.8 | 86.2 ± 9.9* | 0.344 | 0.017 |

Values are means and SD.

* Differences within groups from 3 months to 9 months, p value< 0.05

**PH**: physical health. **MH**: mental health

Patients 69, 71 and 74 were excluded from this analysis due to non-cardiac related personal issues.

## Discussion

As is the custom in Israel, at the end of the formal CR program the patients enrolled into this study chose whether to continue exercising at the CR facility or to leave the program and exercise on their own. At six month follow-up the number of patients that had chosen to continue exercising at the centre was approximately equal to the number of those who chose not to stay. This enabled an additional, opportunistic, comparison of data, the aim of which was to determine whether or not continuing to exercise in the environment of our CR facility had any impact upon the outcomes achieved after the initial training period. Given that only relatively few differences were found between interval and continuous training methods, the CR-based and the non-CR-based groups were not further subdivided according to the two training modalities (i.e. CE and IE).

We acknowledge that this chapter represents a secondary analysis, which was not part of the original research design. However, the data indicates that more than half of the CR-based subjects complied with the minimum recommendation of 150 minutes of exercise per week, whereas two thirds of non-CR-based did not. Consequently, CR-based performed 40 minutes more of exercise per week compared with non-CR-based; this represents a 30 % difference in weekly exercise duration between the two groups.

Peak $VO_2$ and other fitness indices from CPET (maximal load and duration of test) were maintained in the CR-based group, whereas there was a decline in the patients who did not attend the CR centre after cessation of the intervention. Due to the findings that non-CR-based patients also demonstrated elevated BMI and body fat percentage (though changes were small), maximal functional capacity was analyzed, controlling for body composition variables. Following this analysis, peak $VO_2$ was still significantly higher in the CR-based group, thus implying that the difference in peak $VO_2$ was not driven by the weight gain in the non-CR-based group. This preservation of peak $VO_2$ in CR-based exercisers is notable, since maximal functional capacity is considered to be a strong prognostic factor in cardiac patients. Furthermore, the lack of changes in elevated BMI and body fat percentage implies that continuing to exercise at the CR facility had a positive effect on body composition. Previous studies by Giannuzzi *et al.* (2005) and Willmer and Waite (2009) also suggest that sustaining exercise after completion of a CR program results in favorable body weight and BMI. Taken together, our findings suggest that, at the end of an initial 3-month CR intervention, patients who decide to continue exercise at a CR facility are more likely to retain any improvements in peak $VO_2$, functional capacity, and body composition, which were achieved as a result of the initial exercise training, than those who did not stay. These beneficial effects may be attributed to greater adherence to the recommendation for total exercise per week, as well as features of exercising within CR facility environment (e.g. supervision and monitoring, motivation, social interaction).

It is important to note that in many follow-up studies, rather than examine functional capacity over time, the outcome has been related to CV events, CV morbidity and mortality (Giannuzzi et al., 2005;; Panovski *et al.,* 2013; Pluss *et al*., 2011). On the

other hand, a small number of studies have investigated changes in CVD risk during follow-up. For example, studies by Hansen *et al.* (2010) and Willich *et al.* (2001), both report worsening of several risk factors, including elevated blood lipids and blood pressure. In their report, Hansen *et al.* (2010) observed that the deterioration in the beneficial outcomes of their CR programme may be attributed, at least in part, to poor compliance with the exercise recommendations provided at the end of the intervention. In the present study, some changes were observed at 6 month follow - up within the CR-based group. In particular, levels of LDL-C, HDL-C, and consequently TC, were elevated compared with at the end of the intervention, although the values were within recommended levels. These rises cannot be easily explained, although several pharmacological changes occurred during the follow-up period within both groups (with no differences between them). Otherwise relatively few differences in cardiac risk factors were observed between the two groups. It is worth noting that another study, Lear *et al*., (2006) observed beneficial changes in cardiac risk factors following a CR program were preserved by continuation of exercise which is partly in agreement with the changes in this study.

Assessment of resting cardiac function at 6 month follow-up revealed several systolic changes in both groups. However all of the changes were small and do not seem to be clinically significant. There was no evidence of any alterations in diastolic parameters at follow up in either group. On the other hand, in a study performed by Yu *et al.* (2004), diastolic function was reported to be improved at 8 months follow-up in patients that had continued to exercise for 60 minutes daily. In the same study, the number of patients with abnormal LV diastolic function was increased in a non-exercisers control group (Yu *et al.* 2004). Therefore, it was assumed that exercise training should be performed more regularly in order to maintain or further improve diastolic function. It is not entirely clear why the follow-up findings presented in this chapter differ from these of Yu *et al.* (2004), though it might be attributed to the rather large number of subjects that participated in that study (n = 269) and to the fact that exercise was performed every day for 60 minutes.

Assessment of QOL using the SF-36 indicated that PH and MH were not affected by continuing to exercise in a CR facility. It is noteworthy that there was a small improvement (4%) in the total score amongst the non-CR-based subjects. This

seems counterintuitive, inasmuch as the group who were outperformed on functional outcomes, appeared to experience a greater improvement in QOL. However, it is possible that one of the reasons that led these patients to leave the CR program and exercise on their own, was better self-assurance compared to those who had stayed, and this may be reflected in the total score at follow-up.

In summary, while previous studies established that maintaining a structured exercise program following a short-term CR plan improves survival rates (Panovski *et al.,* 2013), and reduces CVD events and hospitalizations (Giannuzzi et al., 2005; Pluss *et al*., 2011), in this current analysis it seems that continuing to exercise in a CR setting can help maintain beneficial changes in cardiorespiratory fitness, functional capacity and cardiac risk factors improvements, or at least prevent their deterioration after ending a CR program. Since this was an unplanned analysis, it might be that a well-planned follow-up intervention with randomized group allocations would yield better results. Professionals in CR facilities should try to optimize the programs in terms of interventions and durations for getting the best outcomes for cardiac patients.

# Chapter 7

# Predictors of fitness improvements in cardiac patients receiving outpatient, centre-based CR

## Summary

There is a great variation in clinical parameters and the level of fitness of patients entering exercise-based CR. The aim of this chapter was to determine if certain parameters can explain the change in $VO_2$ peak . Thus, it might be possible to identify several parameters most likely to predict improvement in cardiorespiratory fitness following exercise-based CR. A single-sample (N = 72) design was used to retrospectively analyze cardiorespiratory fitness, clinical parameters, and quality of life data. Peak $VO_2$, duration of exercise test, maximal output, and VT parameters improved significantly during the intervention. In addition, $VO_2$, RPE and HR at some submaximal levels were lowered suggesting possible improvements in exercise tolerance and increased work efficiency.

Small but significant reductions in weight and BMI were observed with time. However, it was the BF% that was found to be one of the predictors for peak $VO_2$ change in a multiple regression analysis. These results might indicate that CR programs are helpful in improving body composition which in turn can be effective for gaining favorable cardiovascular outcomes. Only two changes in blood analysis were detected, including a small reduction in HbA1c (0.13% of change), and a 12% reduction in the cardiac marker cTnT, which has not been thoroughly explored in the past.

Further analysis of cardiac systolic and diastolic function revealed no changes in diastolic parameters, though the proportion of patients with diastolic dysfunction was reduced and the proportion of those with normal diastolic function was elevated. The systolic indices of LVEF and SV demonstrated small changes, which cannot be determined as clinically significant. However, LVEF was found to be one of the contributors to the change in peak $VO_2$. QoL parameters were found to be improved significantly following training. Moreover, the total score was also

included in the regression analysis, implying that better psychological status can contribute to better training practice and therefore increased $VO_2$ peak outcome

Multivariate regression analysis revealed that 38.5% ($R^2$) and 32.5% (adjusted $R^2$) of the variance in change on peak $VO_2$ with training can be explained by 6 variables. In conclusion, whilst many factors may contribute to fitness gains following exercise-based CR, this study identifies the best determinants as baseline values for adiposity (BF%), left ventricular function (LVEF), psychological state (QoL total score), peak $VO_2$, and RPP during maximal exercise testing, along with the number of exercise sessions completed. CR programs may benefit from incorporation of nutritional and psychological interventions for elevating the prospect of patients to improve their CRP fitness. Additionally, patients with lower fitness level, LVEF, mental state or RPP, along with obese patients should be targeted for special attention and motivation through

## Introduction

There is considerable variability in clinical parameters and fitness levels of patients entering CR programs. Factors influencing baseline fitness include gender, age (Woo, Derleth, Stratton & Levy, 2006), obesity (Fletcher *et al.,* 2013), LV cardiac function (Witte, Nikitin, De Silva, Cleland & Clark*,* 2004), and psychological state (Lavie *et al.,*2009). Furthermore, whilst it is widely recognized that exercise-based CR improves fitness and clinical parameters, there is considerable variation in the fitness improvements. Prior fitness is known to strongly influence improvements in $VO_2$ peak (Lavie & Milani, 1994). Therefore, it seems reasonable to investigate which factors predict improvement in fitness capacity. Given that the improvement in fitness was not dependent upon the training type, it was possible to perform a single sample, retrospective analysis of the data with the main objective of investigating which parameters predict improvement in fitness

It has been reported that maximal (and submaximal) functional capacity can be improved with CR programs (Feuerstadt *et al.,* 2007; Lavie *et al.*, 2009; Onishi *et al.,* 2010; Stahle *et al.,* 1999). As stated in the general introduction, CR programs have also been found to be beneficial in improving cardiac risk factors including body composition, blood lipids (Franklin *et al.,* 2002; Onishi *et al.,* 2010),

hemodynamic factors (Franklin *et al.,* 2002), and QoL indices (Dugmore *et al.,* 1999). However, in most cases these parameters have been examined separately in different studies that have used various methodologies. The methodology of this current study made it possible to explore all of the relevant parameters in one standard real-life setting CR program, and to compare their changes between baseline and after 3 months of training. Subsequent to the examination of the effect of 3 months of training on cardiorespiratory parameters, cardiac risk factors, LV function, and QoL parameters, a regression analysis was performed.

Knowing that peak $VO_2$ is a major predictor of cardiac morbidity and mortality (Dorn *et al.,* 1999; Kavanagh *et al.,* 2002), it seemed important to identify the variables that most influence its improvement following training. Using multiple regression analysis, several variables have been found to be the best contributors to the variance of the change in maximal functional capacity after training for 3 months. For the purpose of this analysis, factors that were theoretically and logically considered to be related to cardiorespiratory changes were examined. For example, the contribution of hemodynamic variables was tested, since they comprise of the central factors of the $VO_2$ max formula (the Fick equation, Chapter 1). The peripheral variables (a-$vO_2$ difference) were not tested since they were not measured in this study. The hemodynamic variables, resting and maximal HR and blood pressure, and the consequent RPP were entered to the regression analysis in order to look for possible relationships with the dependent variable (e.g. $VO_2$ peak change).

Another exercise capacity limiting factor is obesity (Fletcher *et al.,* 2013); *it is* known that people with a greater body mass will have lower maximal functional capacity (Lavie & Milani, 1996) therefore body composition indices were tested in this analysis including BMI, WC, and BF%. Furthermore, echocardiography parameters have been looked at during the regression analysis. Based on past research, normal systolic function was rarely examined or found to be related to exercise performance, while some researchers have demonstrated an association between diastolic function and exercise capacity (Otto *et al.,* 2011; Yu *et al.,* 2004). However, since systolic function (e.g. LVEF) is widely considered as an important clinical parameter, it was decided to inspect both systolic and diastolic functions in this current analysis. Also, it was established before that psychological wellbeing

has meaningful relationship with functional capacity (Müller-Nordhorn *et al.,* 2004; Oldridge *et al.,* 1991), thus QoL indices from the SF-36 questionnaire were inspected in the regressions analysis as well.

As has been mentioned before, higher training intensities can increase functional capacity (Tanasescu *et al.,* 2002). Thus, variables reflecting intensity levels including METS, loads (in watts), and HR during exercise were also considered in the analysis as possible predictors. After entering the various parameters into the linear multiple regression, the strongest variables which resulted in the highest coefficient and were associated with the dependent variable were included in the final regression analysis.

Therefore, the purpose of this chapter was to explore the relationship between selected parameters capable of predicting fitness improvements during the prospective RCT reported in Chapter 3. It was postulated that it will be possible to explain some of the variance in $VO_2$ peak change, to a certain extent, using several factors and characteristics that were examined in this research. Due to the understanding that maximal functional capacity has an important prognostic value in CAD population, and that every positive change in this parameter can be meaningful, it seemed important to evaluate which specific individual parameters can have an effect on the change in peak $VO_2$ and to what extent. Consequently, these findings could assist professionals in CR programs with targeting specific factors and features that can be helpful in increasing cardiorespiratory fitness and thus prognosis.

## Methods

Methodology of training, monitoring, and outcome measurements are elaborated in chapter 4. All subjects have been exercising aerobically in a 12-week CR program. Regardless of training modality, all patients have been training according to the standard recommendations of exercise-based CR programs, which include moderate-high intensity levels, corresponding to the range of 50-85% Peak $VO_2$, and RPE of 11-16 on a 6-20 Borg scale. Outcome measurements were obtained at baseline and 3 months for all subjects as one group, including maximal and submaximal cardiorespiratory variables, blood lipids, hemodynamic parameters, body composition indices, QoL measurements, and systolic and diastolic function.

Additionally, a multiple linear regression analysis was performed to investigate predictors of changes in peak $VO_2$. Relevant characteristics and variables were tested in the prediction analysis. Variables that were found to be associated with the dependent variable or contributing to the other factors were included in the analysis, while variables that seemed to have no contribution to the dependent and the regressor variables were excluded.

## Statistical analysis

Dependent T-test comparisons were performed between baseline and 3 months. Effects size (d) was calculated by using the Cohen's d equation:

$$d = \overline{X}/SD$$

where $\overline{X}$ represents the mean difference between baseline and 3 months, and SD represents the difference SD. Additionally, a multiple enter method linear regression analysis was conducted. A multiple regression analysis is commonly used for two purposes. The first one is to predict values of the dependent variable using multiple independent variables. The second one is to determine how much of the variation in the dependent variable can be explained by the independent variables. Besides the overall fit of the model, this analysis can also demonstrate the unique relative contribution of each of the predictors to the total variance explained. Furthermore, in this model of analysis, all the independent variables are entered into the equation at the same time, for eliminating any hierarchical effect of the predictor variables on the dependent variable. The relevant assumptions were tested for each analysis and reported when violations were found. Outliers were reported and removed when appropriate.

## Results

### Participants

A total of 72 patients were included in the analysis. The mean age was 58.4 ± 7.4 yrs, sixty seven men (93.1%) and 5 women (6.9%). Forty seven (67%) patients were post MI, 14 (19%) patients were post CABG, and 11 patients (15%) had

undergone PCI. There were 17 (24%) patients with diabetes, 37 (51%) subjects had high blood pressure, 56 patients (78%) had dyslipidemia, and 26 (36%) patients were current smokers or have recently stopped smoking. Ninety percent of the patients were taking beta blocker medications, for slowing down the heart rate, and 97% of the patients have been taking statins for lowering cholesterol levels. Also, 47% of the patients reported being inactive in the past few years while the remaining 53% reported being physically active on a regular basis. Data is presented in Table 27. No major cardiac events occurred during the intervention, as was reported in chapter 4 and Appendix D.

**Outcome measurements**

*Cardiorespiratory variables*

Peak $VO_2$ values ranged between 11.0 ml/kg/min and 36.2 ml/kg/min (mean 23.0 ± 5.7) at baseline and between 13.0 ml/kg/min and 43.5 ml/kg/min (mean 24.5 ± 6.1) after training. Therefore, $VO_2$ peak improved by 6.0 ± 10.2% from baseline to 3 months, $t(71) = 4.857$, $p < 0.001$. Other variables that were statistically significant with time included maximal output (7.4 ± 9.4%) and duration of the test (6.9 ± 11.4%) ($p < 0.001$ for both). Also, %VT of predicted $VO_2$ max and %VT of maximal output were improved in 12.3 ± 20.7% and 12.1 ± 22.0% respectively ($p < 0.001$ for both variables) (Table 28). Additionally, several submaximal variables were changed over time as presented in Table 29 and Figure 16 (A-C). RPE was reduced at 60 and 90 watt with values over time ($p < 0.05$). $VO_2$ and HR were reduced during levels of 120 watts (among patients who were able to reach these levels during the CPET) ($p = 0.047$, $d = 0.4$; and $p = 0.022$, $d = 0.5$, respectively).

**Table 27. General Characteristics of all subjects**

| | All patients N= 72 |
|---|---|
| **Subject Characteristics** | |
| Age (years) | 58.4 ± 7.4 |
| Men | 67 (93) |
| Weight (Kg) | 81.8 ± 12.1 |
| BMI (Kg/m$^2$) | 28.3 ± 4.0 |
| **Coronary Disease and Risk Factors** | |
| MI | 47 (65) |
| CABG | 14 (19) |
| PCI | 11 (15) |
| Type 2 DM | 17 (24) |
| HTN | 37 (51) |
| Overweight, BMI>25 | 54 (75) |
| Obese, BMI>30 | 23 (32) |
| Dyslipidemia | 56 (78) |
| Smoking (current/recent) | 26 (36) |
| Lack of physical activity | 34 (47) |
| **Cardiac Medications** | |
| Beta blockers | 65 (90) |
| Statins | 71 (97) |

Values are presented as mean ± SD or frequencies and percentage (%), as appropriate.

**BMI**: body mass index; **MI**: myocardial infarction; **CABG**: coronary artery bypass graft; **PCI**: percutaneuous coronary intervention. **DM**: diabetes mellitus; **HTN**: hypertension

**Table 28. Cardiorespiratory parameters at baseline and 3 months.**

| Parameter | Baseline | 3 months | P value | Effect size (d) |
|---|---|---|---|---|
| $VO_2$ peak (ml/kg/min) | 23.0 ± 5.7 | 24.5 ± 6.1 | 0.000 | 0.572 |
| Maximal work load, watt | 130.8 ± 28.8 | 140.5 ± 32.6 | 0.000 | 0.537 |
| HR recovery difference at 1 min (bpm) | 23.5 ± 10.1 | 26.4 ± 17.2 | 0.143 | 0.154 |
| VT/predicted $VO_2$ max (%) | 45.5 ± 12.2 | 51.1 ± 12.2 | 0.000 | 0.464 |
| Work load at VT (watt) | 64.3 ± 17.3 | 72.1 ± 21.1 | 0.000 | 0.537 |
| $VO_2$ peak/predicted $VO_2$ max (%) | 70.3 ± 33.7 | 73.1 ± 36.7 | 0.057 | 0.254 |
| RPP (mm/Hg X bpm) | 24297 ± 6617 | 25653 ± 6339 | 0.075 | 0.262 |
| Duration of test (min) | 8.7 ± 2.2 | 9.3 ± 2.4 | 0.000 | 0.524 |

Values are presented as mean ± SD

P value represents differences between baseline and 3 months

**HR**: heart rate. **VT**: ventilatory threshold. **VE**: ventilation. **RPP**: rate pressure product.

**Table 29. CPET submaximal variables at different load levels (watts)**

| Parameter | N | Baseline | 3 months | P value | Effect size (d) |
|---|---|---|---|---|---|
| HR at 60 watts (bpm) | 61 | 93.5 ± 11.2 | 92.5 ± 13.7 | 0.436 | 0.100 |
| HR at 90 watts (bpm) | 60 | 109.1 ± 12.9 | 106.7 ± 16.4 | 0.084 | 0.227 |
| HR at 120 watts (bpm) | 24 | 121.1 ± 15.0 | 116.2 ± 14.2 | 0.022 | 0.500 |
| $VO_2$ at 60 watts (ml/kg/min) | 59 | 12.5 ± 2.5 | 12.6 ± 2.5 | 0.784 | 0.036 |
| $VO_2$ at 90 watts (ml/kg/min) | 58 | 16.8 ± 3.4 | 17.1 ± 3.2 | 0.376 | 0.117 |
| $VO_2$ at 120 watts (ml/kg/min) | 23 | 22.4 ± 4.1 | 21.4 ± 3.3 | 0.047 | 0.440 |
| RPE at 60 watts | 61 | 12.3 ± 1.6 | 11.7 ± 1.7 | 0.000 | 0.498 |
| RPE at 90 watts | 60 | 14.3 ± 1.6 | 13.8 ± 1.5 | 0.001 | 0.470 |
| RPE at 120 watts | 24 | 15.0 ± 1.2 | 14.7 ± 1.3 | 0.174 | 0.286 |

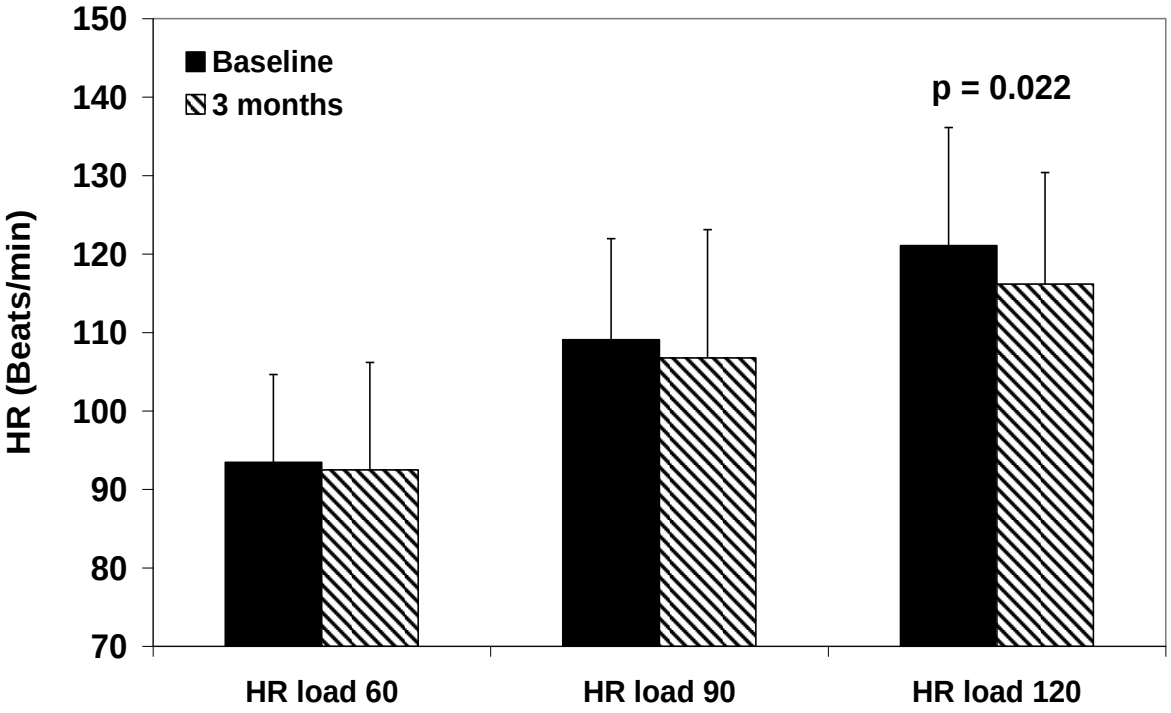
Values are presented as mean ± SD

P value represents differences between baseline and 3 months

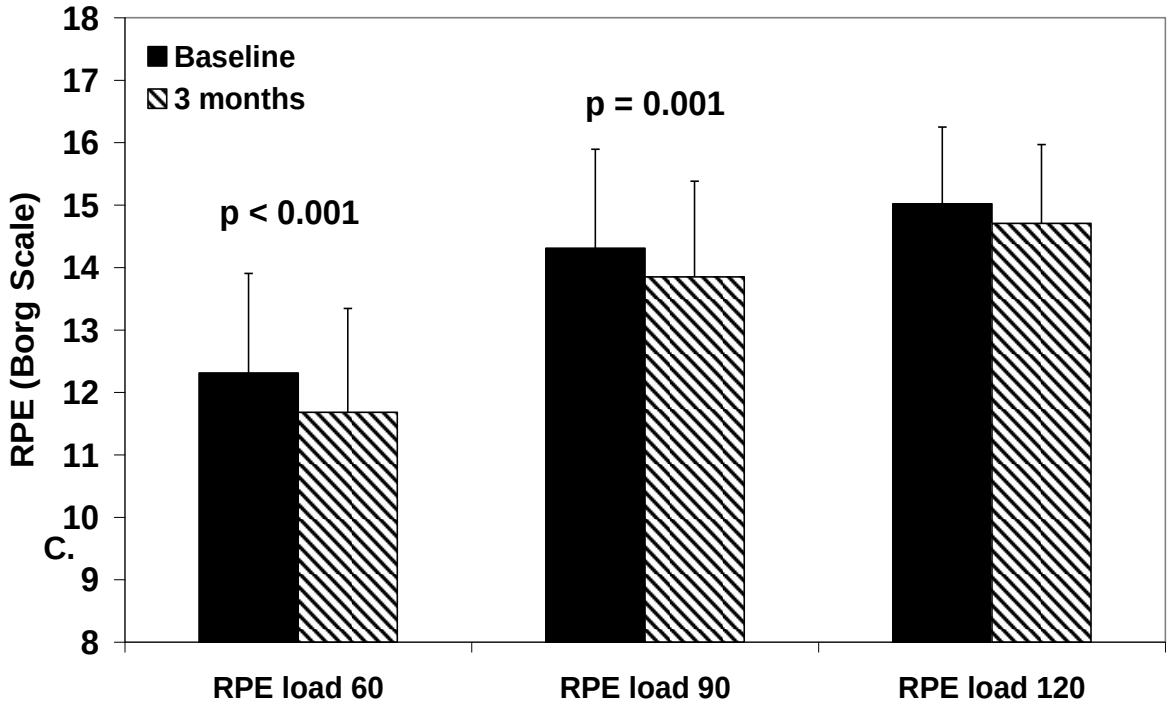
**HR:** heart rate; **RPE:** rating of perceived exertion

**Figure 16. CPET submaximal changes from baseline to 3 months**

**A. Submaximal HR**

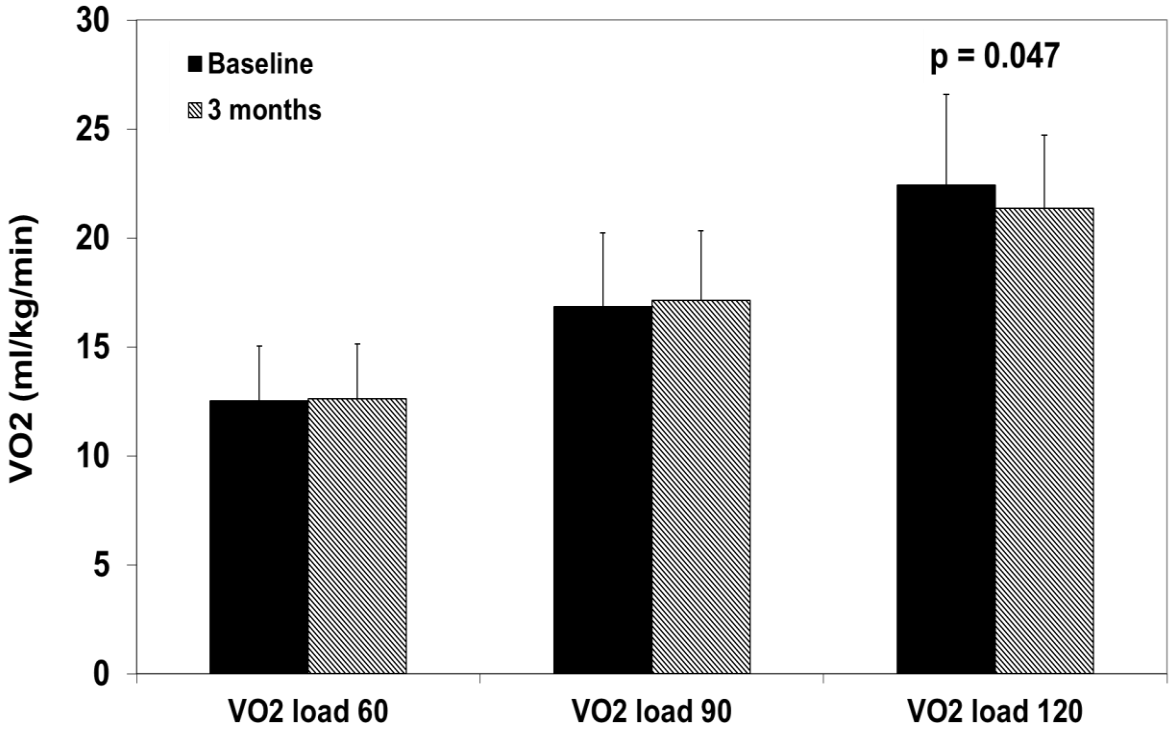



**B. Submaximal RPE**




C.

**C. Submaximal $VO_2$**




Data is presents as means and SD

**A.** Exercise HR was significantly lower at 120 Watts during the CPET at 3 months compared to baseline.

**B.** RPE was significantly lower at 60 and 90 Watts during the CPET at 3 months compared to baseline**.**

**C**. Submaximal $VO_2$ was significantly lower at 120 Watts during the CPET at 3 months compared to baseline

*Blood chemistry, hemodynamic variables, and body composition*

Table 30 features all relevant data. None of the blood parameters have changed except for the glucose metabolism marker, the HbA1c, which was lowered by 0.13% ($p = 0.001$, effect size (d) = 0.421). The cardiac marker cTnT decreased by 12%, ($p < 0.001$), while the inflammatory marker, hs-CRP did not change. Weight, BMI, BF%, and resting HR decreased significantly from baseline to 3 months (-0.9%, $p = 0.023$; -0.7%, $p = 0.018$; and -2.7%, $p = 0.014$, respectively), although changes in means seem rather small. When splitting the group into obese and non-obese subjects (with a cutoff of BMI $\geq$ 30 kg/m$^2$), it was found that obese patients had significantly lower values of $VO_2$ peak before and after the intervention (20.3 ± 5.7 ml/kg/min and 21.3 ± 5.0 ml/kg/min, respectively) compared to non-obese patients (24.3 ± 5.3 ml/kg/min and 26.0 ± 6.1 ml/kg/min, respectively). Thus, obese patients were able to improve their peak $VO_2$ by 4.9% while non-obese demonstrated a 7.0% increase. Also, training intensities on the treadmills (as were calculated in METS) were significantly improved over time within both obese and non-obese subjects, however, improvements were statistically higher among the non-obese compared to the obese subjects (increased by 15.3% and 5.8% respectively, $p = 0.010$).

**Table 30. Secondary parameters at baseline and 3 months.**

| | Baseline | 3 months | P value | Effect size (d) |
|---|---|---|---|---|
| **Blood Chemistry and Markers** | | | | |
| TC (ml/dl) | 133.6 ± 31.2 | 135.5 ± 25.7 | 0.542 | 0.072 |
| Blood glucose (ml/dl) | 107.3 ± 17.4 | 105.1 ± 18.3 | 0.117 | 0.153 |
| HbA1c (%) | 6.01 ± 0.6 | 5.88 ± 0.57 | 0.001 | 0.421 |
| TG (ml/dl) | 95.9 ± 35.5 | 96.6 ± 39.2 | 0.856 | 0.078 |
| LDL-C (ml/dl) | 69.6 ± 26.5 | 70.3 ± 21.9 | 0.805 | 0.024 |
| HDL-C (ml/dl) | 44.8 ± 10.9 | 45.9 ± 11.7 | 0.154 | 0.170 |
| HS-CRP (mg/l) | 2.4 ± 2.9 | 2.1+2.1 | 0.256 | 0.138 |
| CTnT < 0.014 (ng/ml)* | 58 (84) | 69 (96) | 0.000 | 0.276 |
| **Body composition and Hemodynamic Variables** | | | | |
| Weight (Kg) | 81.8 ± 12.1 | 81.1 ± 11.4 | 0.023 | 0.275 |
| BMI ($Kg/m^2$) | 28.3 ± 4.0 | 28.1 ± 3.9 | 0.018 | 0.255 |
| WC (cm) | 100.0 ± 10.1 | 99.4 ± 9.2 | 0.083 | 0.207 |
| BF (%) | 28.2 ± 7.7 | 27.9 ± 7.4 | 0.013 | 0.195 |
| Resting HR (bpm) | 66.3 ± 9.3 | 64.5 ± 9.5 | 0.014 | 0.298 |
| Resting SBP (mmHg) | 119.5 ± 11.6 | 118.8 ± 12.3 | 0.523 | 0.076 |
| Resting DBP (mmHg) | 72.4 ± 7.6 | 72 ± 8.6 | 0.809 | 0.035 |
| **Quality of life SF-36 questionnaire** | | | | |
| PH score | 71.9 ± 17.5 | 78.2 ± 14.5 | 0.000 | 0.673 |
| MH score | 72.2 ± 18.7 | 78.4 ± 14.9 | 0.000 | 0.566 |
| Total score | 73.6 ± 17.8 | 80.5 ± 14.6 | 0.000 | 0.745 |

Values are presented as mean ± SD

* Values are number of patients and percentage (%). Chi-square analysis was performed

**TC**: total cholesterol. **HbA1c**: glycosylated hemoglobin. **TG**: triglycerides. **LDL-C**: low density lipoprotein cholesterol. **HDL-C**: high density lipoprotein cholesterol. **HS-CRP**: high sensitive C-reactive protein; **CTnT**: troponin-T; **BMI**: body mass index**; WC:** waist circumference; **BF:** body fat; **HR**: heart rate; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure; **PH**: physical health; **MH**: mental health.

*Echocardiography*

Table 31 presents echocardiography data. There were very small changes in LVEF and SV. Diastolic echocardiography parameters were not changed during the intervention. LA area was abnormal (> 20 $mm^2$) among 53%, and 57% of the patients at baseline and 3 months, respectively. Diastolic function distribution is presented in Figure 17. While the percentage of subjects with normal diastolic function was increased after the intervention (from 37.5% to 45.1%), the percentage of those with diastolic dysfunction (including impaired relaxation, pseudonormal relaxation, and restrictive pattern) was decreased (from 62.5% to 54.9%). However, two patients (3%) that were classified at baseline as having impaired relaxation became restrictive during the study.

Looking at cardiorespiratory fitness among patients with normal and abnormal diastolic function, repeated measures mixed ANOVA revealed no significant difference between them in peak $VO_2$ change; in fact, they all improved their fitness levels significantly over time. However, looking at baseline and 3 months separately, it was obvious that patients with normal diastolic function, had significantly higher values of peak $VO_2$ and percent of predicted $VO_2$ max, compared with patients with diastolic dysfunction. For these analysis an Independent T-test was used for each time point; however it is important to note, that group numbers (n) were different and that equal variances were not assumed (Figure 18).

**Table 31. Echocardiography variables**

| | Baseline | 3 months | P value | Effect size (d) |
|---|---|---|---|---|
| LA area ($mm^2$) [a] | 20.2 ± 4.2 | 20.4 ± 4.2 | 0.482 | 0.085 |
| **Diastolic function** | | | | |
| MV-E (cm/s) [a] | 71.6 ± 12.4 | 73.3 ± 14.5 | 0.332 | 0.119 |
| MV-A (cm/s) [a] | 66.3 ± 15.5 | 65.7 ± 13.7 | 0.660 | 0.053 |
| E/A ratio [a] | 1.2 ± 0.5 | 1.2 ± 0.4 | 0.791 | 0.032 |
| MV-DT (ms)[b] | 178.1 ± 32.1 | 183 ± 43.4 | 0.257 | 0.138 |
| e' (ms) [c] | 9.4 ± 1.5 | 9.3 ± 1.4 | 0.797 | 0.035 |
| E/e' [c] | 7.8 ± 1.9 | 8.1 ± 1.8 | 0.246 | 0.163 |
| **Systolic function** | | | | |
| EDV (ml) [a] | 97.3 ± 14.0 | 98.4 ± 13.7 | 0.142 | 0.179 |
| ESV (ml) [a] | 43.3 ± 11.5 | 43.0 ± 11.7 | 0.523 | 0.078 |
| SV (ml) [a] | 54.0 ± 9.5 | 55.7 ± 9.3 | 0.012 | 0.310 |
| Calculated LVEF(%)[a] | 55.7 ± 8.0 | 56.7 ± 7.9 | 0.027 | 0.271 |

Values are means and SD.

P value represents changes from baseline to 3 months.

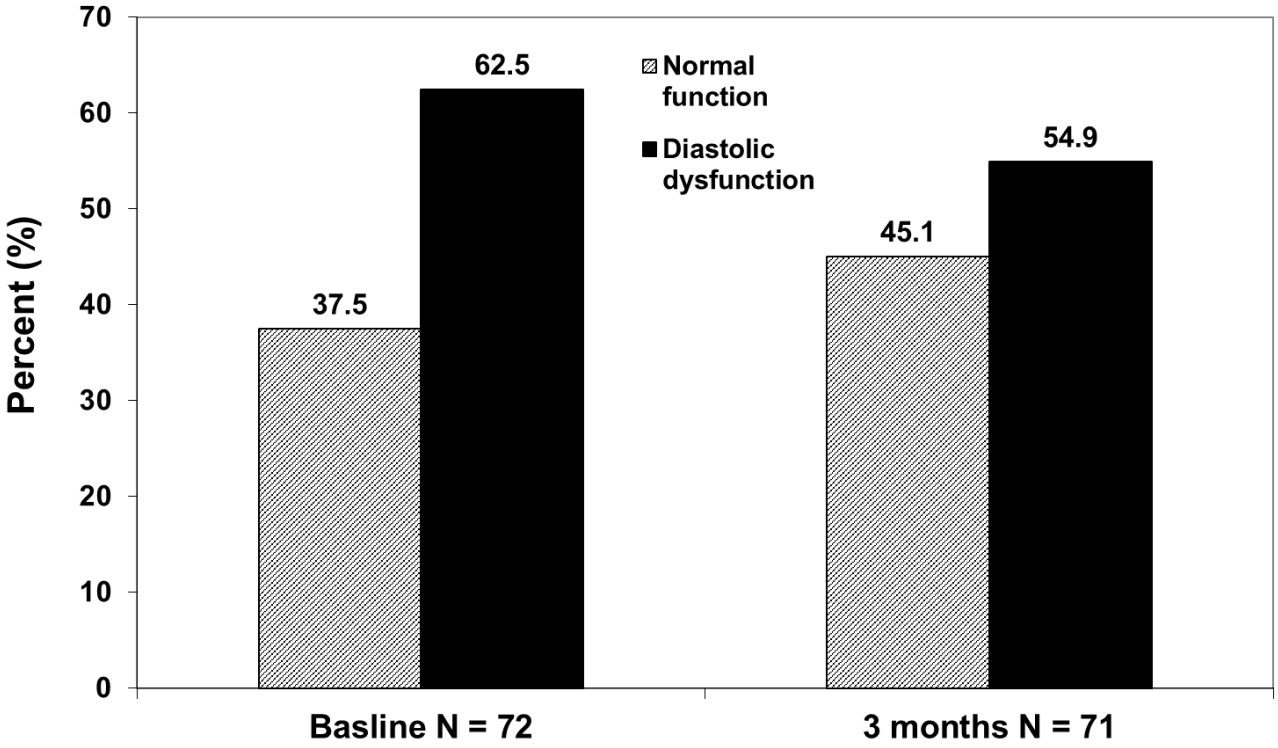
[a] Patients 29 and 35 were excluded

[b] Patient number 44 was excluded

[c] Patient number 10 was excluded

**LA:** left atria; **MV-E**: early diastolic mitral inflow velocity; **MV-A**: late diastolic mitral inflow velocity; **MV-DT**: mitral valve deceleration time; **e'**: average of septal and lateral e'; **EDV**: end diastolic volume; **ESV**: end systolic volume; **SV:** stroke volume; **LVEF**: left ventricular ejection fraction

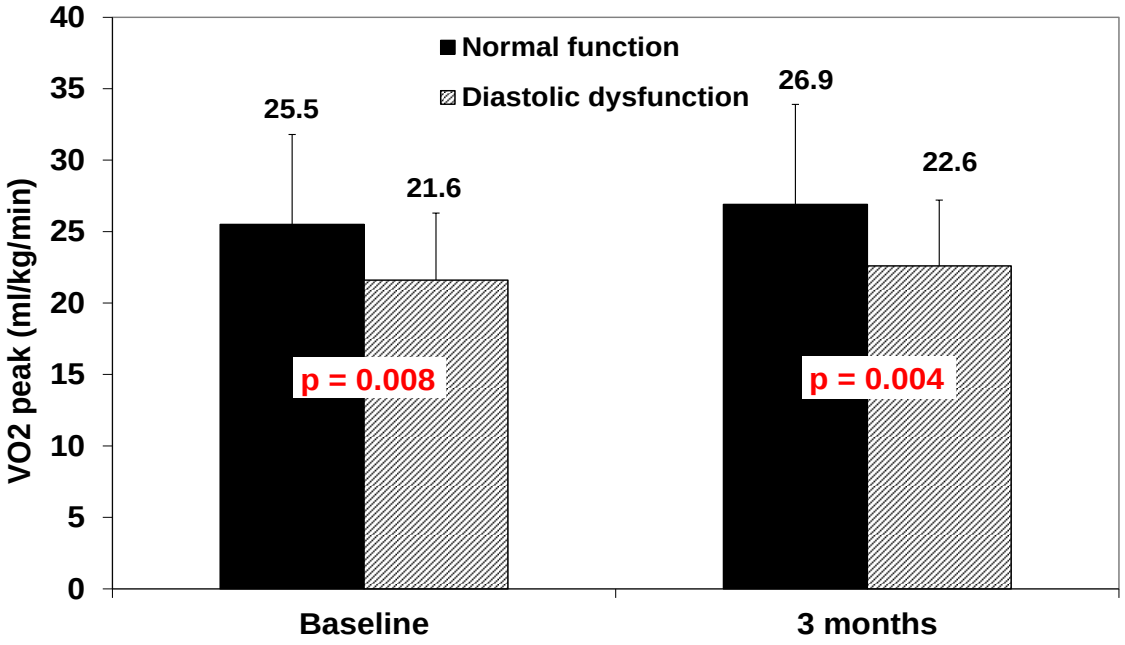
**Figure 17. Diastolic function classification before and after training**



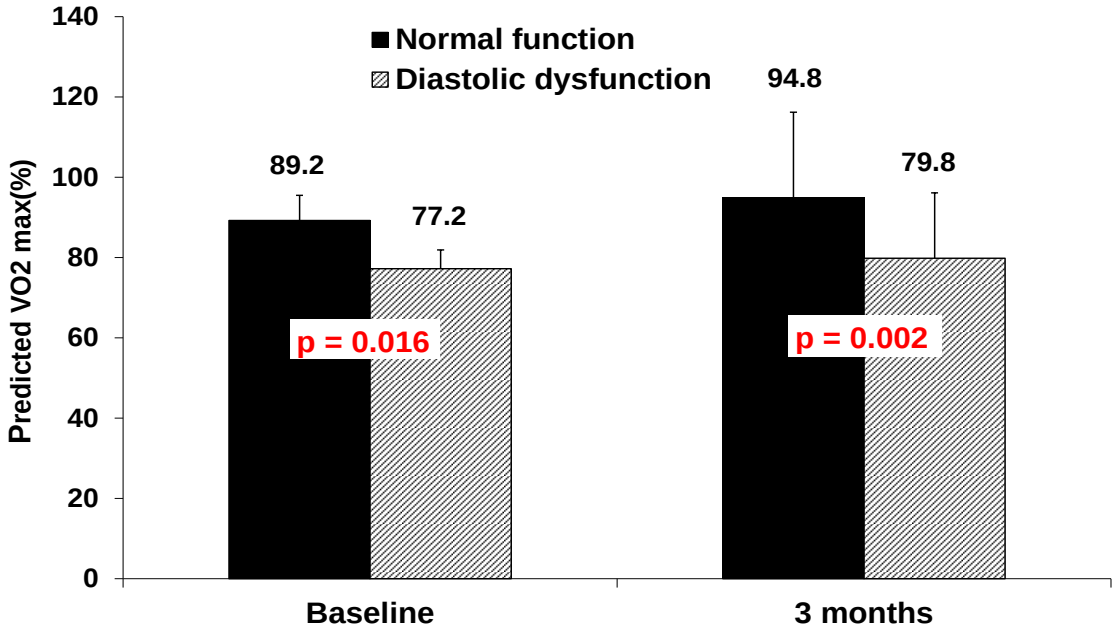

Data is presented in percentage

**Figure 18. $VO_2$ peak and percent of predicted $VO_2$ max among patients with normal diastolic function versus patients with diastolic dysfunction**

**A. Peak $VO_2$ at baseline and 3 months**




**B. Percent of predicted $VO_2$ max at baseline and 3 months**




A. P values represent differences in peak $VO_2$ between patients with normal function and diastolic dysfunction at baseline and at 3 months

B. P values represent differences in percent of predicted $VO_2$ max between patients with normal function and diastolic dysfunction at baseline and at 3 months

*Quality of Life*

All scores of quality of life SF-36 questionnaire improved significantly from baseline to 3 months (Table 30). The PH score increased by 8.8% ($p < 0.001$, 95% CI, 4.0 to 8.8, $d = 0.673$); the MH score increased by 8.6% ($p < 0.001$, 95% CI, 3.8 to 8.8, $d = 0.566$); and the TS score was improved by 9.9% during the intervention ($p < 0.001$, 95% CI, 4.8 to 9.3, $d = 0.745$). Six of the 8 subscales in the questionnaire including physical functioning, role physical, role emotional, social functioning, vitality, and bodily pain, were elicited after training ($p < 0.05$). Mental health and general health perception did not change over time.

**Regression analysis results**

Using the data as one retrospective sample enabled us to perform a regression analysis in order to find the parameters that can explain the variance of the peak $VO_2$ change. Selection of variables was performed after considering all relevant variables that theoretically could have been contributing to the prediction model. Only the strong variables were ultimately left in the model. These parameters included peak $VO_2$ at baseline, baseline BF%, baseline maximal rate pressure product (RPP), baseline SF-36 QoL total score, baseline LVEF and number of sessions. These variables were found to significantly predict peak $VO_2$ improvement, $F(6, 66) = 6.254, p < 0.001$ and accounted for 38.5% of the variance of its change in this study ($R^2$) and 32.3% of the variance in the population (adjusted $R^2$). Data is presented in Table 32.

**Table 32. Enter Method regression analysis of change in peak $VO_2$ from baseline to 3 months**

| Variable | Unstanderdized Coefficient (B) | Std. Error | Standardized Coefficient (β) | p value | Zero order | Partial |
|---|---|---|---|---|---|---|
| Change in $VO_2$ peak | 7.205 | 3.992 | | 0.076 | | |
| $VO_2$ peak* | -0.157 | 0.061 | -0.353 | 0.013 | -0.022 | -0.314 |
| BF%* | -0.109 | 0.040 | -0.333 | 0.008 | -0.202 | -0.336 |
| Maximal RPP* | 0.000 | 0.000 | 0.287 | 0.020 | 0.282 | 0.295 |
| SF-36 Total score* | 0.039 | 0.015 | 0.285 | 0.009 | 0.273 | 0.327 |
| LVEF%* | -0.056 | 0.030 | 0.197 | 0.067 | 0.231 | 0.234 |
| Number of sessions | -0.366 | 0.126 | -0.304 | 0.005 | -0.348 | -0.350 |

$R^2$ = 0.385, Adjusted $R^2$ = 0.323

*Baseline parameters

**BF%:** body fat percentage. **RPP:** rate pressure product. **LVEF:** left ventricular ejection fraction.

## Discussion

This chapter presents secondary analyses of cardiorespiratory fitness, clinical parameters, and quality of life data from patients enrolled in the prospective RCT reported in Chapter 3. The two intervention groups were combined into a single sample and retrospective analyses were undertaken. The aim of the analyses was to determine the extent of change in cardiorespiratory fitness, clinical outcomes, and quality of life, following 12 weeks of supervised exercise in our centre. Furthermore, multivariate regression analysis was used to examine which baseline parameters had most influence on the change in the primary outcome (i.e. peak $VO_2$)

*Cardiorespiratory parameters*

Even though this study shows significant improvements in peak $VO_2$, it is usually expected to see larger increments than the 6% change shown here (Lavie *et al.,* 2009). However, such improvements have been seen before; for example, Onishi *et al*. (2010) reported significant increases of 3.6% in peak $VO_2$ after 6 months of training in a CR program. Another study demonstrated a 6.5% improvement in

peak $VO_2$ after 3 months of training among patients after an acute MI (Fontes-Carvalho *et al.,* 2015). One explanation of the relatively small increase in maximal oxygen consumption may be related to the fact that baseline $VO_2$ peak was relatively high (Seki *et al.,* 2008). Another explanation can be associated to the drug therapy. Ninety-seven percent of the subjects were taking statins for lowering blood cholesterol, and 90% of the subjects were taking beta blockers agents that can affect the cardiorespiratory response. Mikus *et al.* (2013) have found that statin therapy attenuates improvements in peak $VO_2$ by impairing increases in skeletal muscle mitochondrial content and function. Also, some researchers found that beta blockers can cause to a reduced effect of submaximal exercise due to lower abilities to increase intensity levels; Therefore, maximal exercise capacity can be impaired as well (Tesch *et al.,* 1983; Wolfel *et al.,* 1986).

However, it was also shown that patients receiving β1-selective blockade (such as the patients in the present study) can demonstrate higher intensity levels and greater degree of functional capacity compared to patients receiving non-selective beta blockade (Tesch, 1985). These patients can reach similar training intensities compared to other cardiac patients who are not receiving beta-blocker treatment (Eston & Connolly, 1986). Thus, the impact of these medications on our subjects is not clear. Other possible explanations for the relatively modest improvement in fitness, including the 4-week adjustment period and intensity of exercise, were addressed in Chapter 4.

The reduced values of submaximal RPE, $VO_2$ and HR during specific load levels in the second CPET may signify physiological adaptations and improved efficiency of the aerobic system. These changes have been reported elsewhere following CR exercise programs (Franklin *et al.,* 2002; Stahle *et al.,* 1999; Wenger, 2008). Decreased submaximal $VO_2$ and HR might reduce the myocardial oxygen demand during activities of daily living (Leon *et al.,* AHA, 2005), though these were only lowered at 120 watts. The reduction in $VO_2$ and HR at higher load of the exercise test can imply for physiological improvements following training. The fact that RPE was reduced during the lower levels of the exercise test (60 and 90 watts) might suggest that exercise tolerance was improved with time. However, since RPE is a subjective tool, it may be that reduced levels of reported RPE occurred due to improved self-confidence and feel of security of the subjects during the second

exercise test, rather than due to improved aerobic functioning. Other improved cardiorespiratory parameters that were measured during the CPET included maximal output, duration of test, VT/predicted $VO_2$ max, and work load at VT. These favorable changes signify the enhanced tolerance that may contribute to the performance of daily activities which are accomplished in submaximal levels of effort (Milani *et al.,* 2006; Warburton *et al*., 2004).

*Blood chemistry, body composition, and hemodynamic variables*

None of the blood lipids were changed during the training period. Studies show various findings depending on baseline levels and drug therapy. For instance, when baseline LDL-C levels were higher than recommended values (LDL-C > 100 mg/dl) among 55% of the patients, significant reductions were observed after 3 months of training (Magalhaes *et al.,* 2013). In the present study only 7% of the patients had LDL-C > 100 mg/dl and there was no change with training. Similar findings were seen with TC and TG in the same study compared to the present one (Magalhaes *et al.,* 2013). Regardless, most researchers agreed that changes in blood lipids during CR programs are highly dependent on baseline levels and drug therapy (Stahle *et al.,* 1999) which is prescribed individually according to risk stratification and disease etiology (Stone *et al.,* 2013).

In terms of glucose metabolism, HbA1c decreased slightly, reaching lower values than 6%, as recommended by the AHA (Smith *et al.,* 2011). This small reduction of 0.13%, which might suggest an improvement in glucose intolerance, has not been proven to be clinical relevant (Stratton *et al.,* 2000). The cardiac marker cTnT appeared to be over the reference value of 0.014 ng/ml among 16% of the subjects at baseline and among 4% of the patients after 3 months, proposing a better prognosis for MI (Zhelev *et al.,* 2015). Based on previous findings suggesting that cardiac troponin concentrations are inversely related to the level of physical fitness (deFilippi *et al.,* 2012), it was postulated that cTnT is a modifiable parameter, which can be reduced by exercise training. However, the majority of studies examined the effect of an acute training session on cTnT and one study looked at the effect of resistance training only (Linden *et al.,* 2015). Therefore, comparison of the present results from our study was not possible for drawing conclusive conclusions.

Parameters of body composition including body weight, BMI, and BF% decreased with training, though changes were rather small (≤ 1% for each parameter). Lavie and Milani (1996) also reported modest reductions in BMI following a CR program. Furthermore, in this current cohort, obese participants reached 1.36 less METS compared to their non-obese counterparts (BMI < 30 kg/m$^2$). Comparable to these outcomes, others found that patients with higher BMI had lower maximal and submaximal functional capacity (Grewal *et al.,* 2009; Lavie & Milani, 1996). Additionally, regression analysis demonstrated that BF% significantly contributed to the change in peak $VO_2$ (beta = -0.333, p = 0.008), suggesting that lower BF% can assist in a greater change in $VO_2$ peak during training. Lavie *et al.* (2009) reported that better improvements in exercise capacity occurred among patients who have lost more weight. These results may lead to the conclusion that obesity is a limiting and important factor in exercise performance that should be addressed in CR facilities. In conclusion, emphasizing the need for weight reduction interventions in these programs could not only lower the incidence of this risk factor, but also can help improve cardiovascular outcomes (Leon *et al.,* 2005).

The only hemodynamic change was seen in RHR, which was also observed in previous trials following a CR program (Franklin *et al.,* 2002), although the change was rather small and probably not clinically significant (Wilmore *et al.,* 2001). The importance of decreasing RHR levels for CVD is still not clear, though studies show lower incidence of mortality among CAD patients with beta-blockers which seem to be associated with reduced resting HR. Also, decreased RHR has been associated with the prevention of exercise-induced angina and ischemia (Fox *et al.,* 2007). Consequently, the clinical implication of the present reduction in RHR is not obvious. The lack of changes in resting BP could be attributed to the extensive use of drug therapy, or to the normotensive values of our patients throughout the study (Kessler *et al.,* 2012).

*Echocardiography parameters*

LVEF and SV slightly increased statistically but the changes do not seem to be clinically significant (van Wolferen *et al.,* 2011). Despite the small changes in systolic parameters, regression analysis demonstrated that baseline LVEF was a contributor to the change in peak $VO_2$, and was independently correlated with this parameter (r = 0.231, p = 0.030). This observation suggests that higher systolic

function can predict a bigger improvement in aerobic performance. Most of the studies that examined the associations between LVEF and aerobic capacity included heart failure patients with reduced values of LVEF. These studies mainly aimed for predicting long-term cardiac morbidity and mortality rather than predicting functional capacity. These researchers concluded that patients with reduced exercise capacity along with lower LVEF had the highest risk for cardiac and total mortality compared to trained patients with higher or normal LVEF (Dutcher, Kahn, Grines & Franklin, 2007; Specchia *et al.,* 1996).

The lack of changes in diastolic indices is supported by others (Fontes-Carvalho *et al.,* 2015). Even though no significant changes were observed in diastolic indices in the current trial, it was shown that following a CR program, the proportion of patients with diastolic dysfunction decreased from 62.5% to 54.9%, whereas more patients exhibited normal diastolic function. This was in agreement with a previous research (Wuthiwaropas *et al.,* 2013). Moreover, peak $VO_2$ and percent of predicted $VO_2$ max were significantly higher within patients with normal diastolic function compared to those with diastolic dysfunction, both at baseline and post training. Increased peak $Vo_2$ was associated with improved LV diastolic function among adult hypertensive patients in a previous study (Stewart, Ouyang, Bacher, Lima & Shapiro, 2006). It is assumed that abnormal filling rates of the left ventricle inhibit SV from increasing with the progression of exercise intensity, thus impairing exercise tolerance (Amundsen *et al.,* 2008). However, the mechanisms are not fully clear (Sakate *et al.,* 2001), and it is still not obvious whether exercise training can change diastolic function in CAD patients (Yu *et al.,* 2004). Nonetheless, according to our findings, it seems that exercise may have a positive influence on patients with diastolic dysfunction that could prevent the worsening of their disease, and therefore it is important to encourage these patients to participate in such programs.

*Quality of life*

SF-36 QoL scores were improved during the 3 months of training. These favorable changes are mostly in agreement with previous trials (Dugmore *et al.,* 1999; Yu *et al.,* 2004). Moreover, regression analysis revealed significant positive associations between the total QoL score and change in peak $VO_2$, suggesting that the better perception of their health would be, the greater the change in peak $VO_2$ could

occur with training. Similar associations between QoL and exercise tolerance were found in previous studies (Müller-Nordhorn *et al.,* 2004; Oldridge *et al.,* 1991). In a study published by Lavie *et al.* (2009), it was shown that any improvement in maximal exercise capacity was associated with an equivalent decrease in level of depression. On the other hand, cardiac patients who did not improve their functional capacity have continued to suffer from a high prevalence of depression. Most studies looked at the change in QoL indices following a CR program rather than the contribution of psychological and mental status for CRP fitness. Therefore, this current study demonstrates the need for psychological interventions for increasing the probability of larger improvements in maximal aerobic performance.

*Regression analysis variables*

Maximal $O_2$ consumption is considered to be an important prognostic factor, with a significant value for every change (Feuerstadt *et al.,* 2007; Kavanagh *et al., 2002;* Myers *et al., 2002*; Vanhees, Fagard, Thijs, Staessen & Amery, 1994*).* Given that, it seems important to find the parameters that most influence maximal $VO_2$ improvement. After demonstrating an $R^2$ value of 38.5% and an adjusted $R^2$ of 32.3%, it can be assumed that the independent factors in the analysis can explain almost 40% of the change in peak $VO_2$ in this present sample and 32% in the comparable population. It also means that the regressor values are strongly correlated with the dependent variable according to the Cohen's effect size (0.323). The variables that predicted the change in peak $VO_2$ following training included $VO_2$ peak at baseline, baseline BF%, baseline maximal RPP, baseline total score of SF-36 QoL questionnaire, LVEF at baseline, and number of sessions during the intervention. Past research found other predictors for gains in exercise including age (Marchionni *et al.,* 2003), gender (Sandercock, Hurtado & Cardoso*.,* 2013), and intensity levels (O'Donovan *et al.,* 2005*;* Tanasescu *et al.,* 2002; Uddin *et al.,* 2015). However, in this present study these parameters were not found to be contributing to the dependent factor. Another study demonstrated that $VO_2$ max responses were predicted up to 50% by genomic factors (Bouchard *et al.,* 2011), which might explain partly the additional variance of peak $VO_2$ change.

Peak $VO_2$ at baseline was strongly and negatively correlated with the change in peak $VO_2$, suggesting that the lower the initial cardiorespiratory level, the larger the change would be with training, which is supported by Lavie and Milani (1994). Also,

researchers reported that peak $VO_2$ following training and the change in its value, were independent predictors of CVD mortality in patients with CAD (Vanhees, Fagard, Thijs & Amery, 1995). Consequently, baseline peak $VO_2$ seems to be an important factor in predicting exercise performance enhancement and thus prognosis of CVD mortality.

Out of the hemodynamic parameters, resting and maximal HR and blood pressure were excluded from this analysis as possible predictors, due to weak relationships with the dependent variable (e.g. $VO_2$ peak change). However, it was found that the maximal RPP during baseline CPET can be considered as a strong predictor. RPP, which is the product of maximal HR and maximal systolic blood pressure, is known to be an indirect indicator of the myocardial oxygen uptake. Supposedly a linear relationship exists between myocardial $O_2$ uptake and coronary blood flow. Thus, when blood flow increases during exercise, so does RPP, provided there is no significant obstructive CAD (Fletcher *et al.,* 2001). Therefore, it can be assumed that when adequate coronary blood flow exists, high exercise capacity can be reached. Not many studies looked at maximal RPP in association with exercise capacity; most studies have looked at resting or submaximal RPP reductions as an indication of improvement of the myocardial demand during rest or at any given submaximal effort. A study performed by Fornitano and Godoy (2006) reported that patients who reached higher levels of RPP during exercise had the lowest occurrence of significant coronary obstructions, suggesting they have better cardiac function during exercise. According to that study and to the present finding in this current study, it might be assumed that RPP, separately or jointly with maximal aerobic capacity, can play an important role in the prognosis of CAD patients.

Another factor that was found to be a predictor of change in cardiorespiratory fitness is the number of exercise sessions during the 3 months of intervention. However, this factor was found to be a negative predictor, meaning that the fewer the number of sessions, the higher the change in peak $VO_2$ would be, which could not be easily explained by us. The range of number of session was between 18 to 26 sessions, while most of the patients (57%) participated in 22-24 sessions, 17% participated in 18-21 sessions, and 26% subjects participated in 25-26 sessions. Though this association might seem odd, it is possible that patients who were

absent from several sessions due to sickness or holidays, participated in more exercise sessions than the others, in order to compensate for their skipped classes. The fact that they did not perform these sessions continuously might have resulted in a smaller change in peak $VO_2$. Thus, it could be that the number of sessions is not really a determinant negative factor (as supported by Sandercock *et al.,* 2013), but that maintaining a strict exercise program routine is important for better results.

The other predictors, including BF%, total score of SF-36 QoL questionnaire, and LVEF, were explained above. Intensity parameters including exercise METS, training loads, and HR during exercise were not included in the final analysis. As intensity issues were explained in Chapter 4, they could possibly explain the lack of contribution to the dependent variable in the current analysis. In summary, the results of the regression analysis indicate that 6 variables seem to be explaining almost 40% of the change in peak $VO_2$ in this cohort, and 32% of the change in the population of CAD patients. Although one might argue that it is common sense, the data supports that lean people who are unfit, in a good psychological state, with no evidence of current obstructions in their coronary vessels, and with a good LVEF, might have a better prospect in improving their cardiorespiratory fitness within 12 weeks of training. Also it seems that adherence to the training routine is important for better outcomes. Since BF% and QoL status are both manageable factors, it is important to highlight nutritional and psychological interventions as inseparable elements of a CR plan. According to this data, CR professionals can now target specific patients and encourage them to commit to a 12-week moderate intensity exercise program for the purpose of improving their cardiorespiratory factors, and thus their prognosis.

# Chapter 8

# General Discussion

## Background

Cardiac rehabilitation programs have targeted several important goals for cardiac patients going through secondary prevention, including: enhancing exercise tolerance, optimizing cardiac risk factors counting glucose metabolism and lipid profile, blood pressure, and body weight; and also improving the emotional status following a cardiac event (Wenger, 2008). While most CR research has proven that rehabilitation programs are substantially beneficial in achieving these goals (Dugmore *et al.*, 1999; Lavie *et al.,* 2009; Onishi *et al.,* 2010), different exercise methodologies have been explored in recent years.

The most widespread traditional training method used in rehabilitation programs is moderate continuous aerobic exercise, which encourages the patients to reach 40-85% of their HRR or peak $VO_2$, according to their risk stratification and physical fitness level (Fletcher *et al.,* 2001). Within this wide range of intensity levels of exercise, it was found that exercise performed near or at the upper limit (i.e. high intensity) elicits higher improvements in peak $VO_2$ and other cardiovascular outcomes compared to exercise performed below or at the mid-range (i.e. low-moderate intensity) (Haskell *et al.,* 2007; Tanasescu *et al.,* 2002). However, high intensity exercise might be more difficult to perform for long durations compared to low-moderate intensity exercise (Conraads *et al.,* 2015). Therefore, some researchers suggested that using interval training in CR programs may result in better improvements in maximal aerobic capacity, risk factor status, and psychological well-being because it involves the use of high and moderate intensity levels interchangeably (Moholdt *et al.,* 2012; Munk *et al.,* 2009; Rognmo *et al.,* 2004). The rationale for interval training in CAD patients relies on the idea that the patient has resting periods in between high intensity bouts which makes it possible for him to exercise at higher intensities (Ito, Mizoguchi & Saeki, 2016).

It was suggested that high intensity interval training can increase mitochondrial oxidative capacity, increase cardiac efficiency by lowering the myocardial oxygen demand, and improve the ability to catabolize carbohydrates over fats, all of which

result in improved aerobic capacity (Hafstad *et al.,* 2011) which is substantially associated with better cardiovascular prognosis (Kavanagh *et al.,* 2002; Keteyian *et al.,* 2008). However, although high intensity interval training has been reported to be more effective, there is a concern about patient safety (for reviews see, Ito, Mizoguchi & Saeki, 2016). Therefore, in this current study, only moderate-high intensity levels were used rather than high intensity. Also, to reduce the risk it was suggested that cardiac patients should be carefully selected and evaluated for ischemia prior to engaging in interval training, as was practiced in this current study (Ito, Mizoguchi & Saeki, 2016). Consequently, it was our intention to compare the standard exercise regimen in our centre to a modified version of high-intensity interval training for the purpose of finding which would be the more effective training method that should be recommended in cardiac secondary prevention programs. We hypothesized that 12 weeks of interval training will result in greater improvements in peak $VO_2$ and possibly in other measured outcomes compared to the continuous exercise.

## Summary of results

Eighty-four CAD patients were initially recruited for this study, 72 of them completed 12 weeks of either moderate-high interval or moderate continuous training. Following 6 months, 61 subjects concluded the follow-up measurements. Following training maximal functional capacity determined at CPET (duration and peak power) was increased by a greater amount in the interval trained patients, but $VO_2$ peak was not different between the two training groups. Furthermore, several submaximal exercise variables including $VO_2$, HR, and RPE were significantly improved within the IE group following the intervention. As was suggested elsewhere, these outcomes might be indicative of improved exercise tolerance and daily functioning (Warburton *et al*., 2004). Furthermore, following 6 months follow-up peak $VO_2$ remained significantly elevated compared to baseline levels only within the IE group.

While no differences were found between the groups in peak $VO_2$ with training, each training group demonstrated ~6.0% (~1.5 ± 5.9 ml/kg/min) enhancement in $VO_2$ peak. Though these improvements are considered to be small compared to other studies, it has been established that every 1 ml/kg/min increase in peak $VO_2$ can attribute to improve prognosis by approximately 15% (Keteyian, *et al*., 2008).

Thus, the change in this present study can be considered clinically important, and it seems reasonable to assume that this change is sufficient to reduce all-cause or cardiovascular-specific mortality by 15%.

Given that blood lipids were closely regulated by medications, and given the normality of most blood variables at the beginning of the study, the lack of changes in blood lipids was expected. Despite the fact that no effects on blood lipids were seen during the intervention, as was also demonstrated by others (Moholdt *et al.,* 2009; Munk *et al.,* 2009), several blood lipids and hs-CRP were negatively increased only by the CE group during the 6 months follow-up, while a positive increase occurred in HDL-C in the former IE group.

Compared with other parameters, relatively little is known about potential changes in echocardiographic indices following interval training in CR settings. It seems that the intensity and duration of CR programs necessary for improving LV function have not been evaluated sufficiently and that 3 months are not sufficient enough for inducing systolic changes (Panovsky *et al.,* 2011). While no effect of training modality was observed on LV systolic or diastolic function, it seemed that diastolic function can be related to exercise capacity. This was observed when $VO_2$ peak and percent of predicted $VO_2$ max were particularly higher among patients with normal diastolic function compared to those with diastolic abnormality (with no dependence on exercise group). Grewal *et al. (*2009) and Yu *et al. (*2004) found moderate to strong correlations between diastolic and exercise indices. These findings highlight the importance of identifying patients with diastolic impairments for the purpose of helping them to increase exercise capacity. More than 50% of our patients presented with some level of diastolic dysfunction.

Regardless of training method, QoL scores were increased throughout the intervention in both groups. Since QoL improvement is one of the main goals of CR programs (Lavie & Milani 1995), the finding that all patients were able to improve their scores reaching at least ‘very good’ scores and preserve them during the follow-up, is very important for this study. Due to the lack of research involving QoL assessments following interval training in CR programs, it was difficult to foresee certain effects before the study. Hence, in order to examine the effect of interval training on QoL status, more interval studies should involve health related QoL assessments.

Even though no differences were found in peak $VO_2$ between training modalities, the results suggest that continuing to exercise in a CR setting, irrespective of training mode, may help maintain peak $VO_2$ and other cardiac related risk factors, while some of these outcome measurements were worsened among patients who did not exercise in the CR center after 3 months of intervention. It has been proven that a long term adherence to an exercise regimen in a CR setting, is very beneficial in improving and maintaining hemodynamic, and metabolic parameters (Gayda, Brun, Juneau, Levesque & Nigam, 2008). Also, a one-sample analysis demonstrated that during the intervention, a clinically significant enhancement in maximal aerobic capacity was observed for all patients together. Consequently, a question arose regarding the factors which are responsible for these improvements in $VO_2$ peak. A multiple linear regression analysis was performed for the purpose of explaining the variability of $VO_2$ peak change following training and thus for professionals in CR centers who will be able to aim their attention to specific features within their patients. The change in peak $VO_2$ after 12 weeks of training, regardless of exercise method, was found to be partially (~39%%) explained by several variables, including lower BF%, lower peak $VO_2$, increased LVEF, and higher QoL assessment. Consequently, it can be assumed that targeting patients with these specific characteristics could play an important role in determining the magnitude of change in their maximal functional capacity and their prognosis.

## Strengths and limitations

All previous interval studies have used different methodologies and exercise protocols. The protocol used in this study was based on protocols from these studies and on past experience with cardiac patients in Asaf Harofe Medical Centre. Thus, it was our objective to design the most appropriate protocol for this study. There are some strengths in this study that are important to point out. While most interval studies recruited few subjects and mostly heart failure patients, this current research used a relatively large sample size and included patients following MI, PCI, or CABG, which represent the majority of the cardiac population that attends CR centers. Furthermore, during this study it was repeatedly emphasized that the methodology and protocol were adapted to real-life circumstances, rather than being performed as lab-based designs. For example: the 4-week adjustment period was administered for the purpose of allowing the patients to get familiar with

exercise instruments and with being physically active after their cardiac event. Also, maintaining real-life conditions involved carrying out the exercise sessions at the patient's choice of time during the week, in heterogeneous groups, with the same professional staff members and exercise guidance, which were available for the other patients who were not participating in the research. Unfortunately, some of these strengths might also be considered as limitations.

As opposed to previous trials, this present study recruited a relatively higher number of CAD patients. These patients were randomized after baseline measurements, eliminating bias through these tests. Most of the clinical staff (except for the exercise physiologist and the trainers) was blinded for group allocation. It seems that randomization and blinding were not reported adequately in past research (Cornish, Broadbent & Cheema, 2010; Elliot *et al.,* 2015). The strongest feature of this research was that is seems to be the first study of its kind that looked at wide ranging outcomes including almost all of the parameters that were defined as the target outcomes of CR programs. These outcomes encompassed cardiorespiratory, body composition, hemodynamic, blood lipids, glucose metabolism, hs-CRP, systolic and diastolic function, and QoL variables, during two different phases (intervention and 6 months follow-up); thus making it a unique comprehensive and relevant research.

To summarize the strengths of this trial, it tries to overcome the limitations that were mentioned by Cornish, Broadbent & Cheema (2010) in their systemic review, who reported numerous lack of assessments including cardiovascular risk factors, past and current physical activity, blindness of assessor, symptoms and hospitalizations, randomization procedures, safety issues, compliance and adherence to exercise, dietary and psychological interventions, and usually the use of small sample sizes.

Although it is considered to be an advantage in this study, we acknowledge the fact that the 4-week run-in period that was administered for gradual adjustment, might have reduced the potential outcomes within or between the groups. It is more than likely that during that time patients were able to improve their cardiorespiratory fitness and consequently have greater enhances in peak $VO_2$ by the end of the intervention. It is also possible that if the intervention had started in the beginning of the CR program, interval training could have had a greater impact on the

measured outcomes. However, as mentioned before, it seems that interval training is not appropriate for new CAD and/or sedentary patients (Mittleman *et al.,* 1993), and that it was important for us to practice safety in real-world settings. Another limitation was the fact that only 5 women completed our study. Although it was our intention to recruit an equal number of men and women, we were able to recruit only 7 women, of which 2 had left during the study. The remaining 5 females were equally (as possible) distributed between the groups. The low number of recruited women resulted from a fairly low number of women arriving to the CR facility. There are some possible explanations including the assumptions that fewer women are referred to CR programs following a cardiac event, women are busier with routine household tasks, and some women feel uncomfortable exercising with a majority of men. Nonetheless, more women should be included in interval studies for the purpose of generalization for the CAD population (Currie *et al.,* 2013).

Another limitation is related to the exercise prescription, specifically in the IE group, which resulted in insufficient intensity levels during high-intensity bouts compared to what was prescribed by the exercise physiologist, though reported RPE was generally appropriate. It is possible that the intended exercise intensity was not achieved because of reliance on peak $VO_2$ from the CPET at baseline (Iellamo *et al.* 2013; Tschentscher, Eichinger, Egger, Droese, Schonfelder*, et al.,* 2016), or due to insecurity of the patients. Nevertheless, our finding is consistent with that of Tschentscher *et al.* (2016), who suggested that the small gap in exercise intensities between the groups was one of the causes for the lack of differences in maximal functional capacity.

In any case, it appears that more individual supervision is necessary in order for reaching higher intensity levels, which might not be possible where group exercise is being performed (Nillson *et al.,* 2008a*).* Lastly, during the 6 months follow-up approximately half of the patients from each group continued to exercise in the CR program, while the others have left. Consequently, the analysis of the follow-up period did not distinguish between patients who were still training in the CR facility and those who were not, in affiliation to their training modality (CE or IE). This kind of analysis would have been more appropriate if larger sub groups were involved. However, our data suggest that patients who continue to exercise in the CR-setting may retain some of the adaptations achieved during the prescribed CR-

programme. However, further studies are required to determine the effect of the training method (e.g. interval vs. continuous) on outcomes of CR-based compared to non-CR-based patients during a follow-up time.

## Practical implications and conclusions

A very important, and as yet unresolved, question regarding exercise prescription in a CR center, is which patients are most likely to benefit from interval training and which are not? Due to the relatively small number of these studies, small sample sizes and numerous protocols, this question is yet to be answered. Even the most updated interval studies in CAD patients are still heterogeneous and controversial. For instance, two recent studies, both recruited a small number of subjects (N=28, N=19) (Kim, Choi & Lim, 2015; Currie, Bailey, Jung, McKelvie & MacDonald, 2015), and each found different results. Kim, Choi & Lim (2015) reported that high intensity interval training is more effective than moderate continuous training for improving $VO_2$ peak in acute myocardial infarction patients with drug-eluting stent.

On the other hand, Currie et al., (2015), demonstrated significant but similar improvements in peak $VO_2$ following interval and continuous training among patients post MI, PCI, or CABG. As was the case in the current study, exercise training was initiated 5-6 months following the cardiac event, and this lead the authors to suggest that they might have found greater fitness gains had training been initiated earlier (Currie *et al.,* 2015). Due to the diverse methodologies in the literature, and the difficulty in defining the optimal interval training protocol, it has been suggested that interval training should be tailored to each patient according to their medical history and functional state, even if it is prescribed during different phases of the CR program (Guiraud *et al.,* 2011; Ito, Mizoguchi & Saeki, 2016).

Advocates of interval training argue that this type of training could be an effective tool for improving adherence and motivation to exercise (Guiraud *et al.,* 2011; Ito, Mizoguchi & Saeki, 2016); however, in the current study, adherence rates were similarly high in both training groups. Furthermore, it was previously reported that patients stated being 'less bored' and more motivated while using this training modality (Bartlet *et al.,* 2011; Keteyian *et al.,* 2014). In this present study, although only moderate-high intensity levels were prescribed, not all patients in the IE group tolerated this method equally well. Some subjects claimed that 'it was too hard', 'it

made me feel exhausted for the rest of the day', 'changing intensity every 2 minutes was too confusing', etc; while others pointed out several positive views of the training method including: 'time was passing by faster', 'I enjoyed working out harder', 'I will use only interval training from now on', etc. Unfortunately, the subjects' personal views in this study were not routinely recorded, thus could not have been analyzed properly.

However, on the basis of the anecdotal comments, we are inclined to agree with Guiraud *et al.* (2011) that interval training should not be incorporated for all patients at the same time of the rehabilitation process, and it is not necessarily suitable for all CAD patients. It could be argued that if a patient feels anxiety, unfit, or insecure about interval exercise, the exercise prescription should be' personalized' in terms of intensity, duration of bouts, and frequency and durations of exercise sessions; the prescription can be updated and upgraded to coincide with improvements and increased self-efficacy of the patient (Ito, Mizoguchi & Saeki, 2016).

While trying to identify the patients that will benefit the most from interval training, no specific characterizations were found in terms of age, body composition, hemodynamic, type of a cardiac event, cardiac risk factors, LV function, or QoL assessment. However, while no conclusive decisions have been made regarding the best candidates for interval training, it was found that some patients will be able to benefit more from an exercise regimen in CR programs regardless of their training modality. Apparently, patients who are less fit will be able to improve their maximal functional capacity more than patients who are more fit, which is important information for both the trainer and the patient. Also, it may be important to encourage obese patients to refer to nutritional guidance since lean persons will be able to reach greater cardiovascular achievements. Likewise, patients who present with lowered psychological status should be referred to psychological counselling for improving their QoL and therefore reaching better changes in maximal aerobic capacity. Lastly, though systolic function has not been proven to be changed with exercise, it is important to motivate patients with reduced systolic function to commit to the exercise program for the chance they will improve their LVEF% and thus their functional capacity.

To summarize the benefits of interval training over the continuous training, it seems that interval training can be more effective and useful in CR programs as was seen

in some Meta- Analysis (Elliot *et al.,* 2015; Pattyn *et al.,* 2014), though our study shows dominance of interval training only in some of the outcome measurements, not including the main one (peak $VO_2$). It has been also recognized that long-term cardiovascular morbidity and mortality, which are important factors in evaluating exercise effectiveness, have not been assessed in the past (Elliot *et al.,* 2015) or in this current trial. Additionally, these 2 newer Meta-analyses (Elliot *et al.,* 2015; Pattyn *et al.,* 2014) and a recent review (Ito, Mizoguchi & Saeki, 2016) identified almost the same limitations that were reported by Cornish, Broadbent & Cheema (2010), including inconsistent and heterogeneous interventions, small sample sizes, and limited information regarding randomization, blinding of assessors, and caloric calculations.

In the future, additional comprehensive long-term research, including bigger cohorts, is needed for the purpose of finding the ultimate training protocol and for establishing the target CAD population that will benefit the most from interval training. Our study may have important implications on CR programs, proposing that interval training may have some superior favorable outcomes in terms of performing daily activities for a longer time with less exertion, and preserving cardiorespiratory fitness and perhaps several cardiac risk factors for at least 6 months. However, it is possible that the existing standard continuous training is also adequate for resulting in higher maximal aerobic capacity and improving QoL status. Nevertheless, regardless of training modality Lavie et al. (2013) emphasized the need for greater efforts in promoting exercise in CAD patients, preferably through CR programs. We also know that long-term adherence to physical activity is very important for maintaining health achievements (Gayda *et al.,* 2008; Hansen *et al.*, 2010; Willich *et al.*, 2001), thus longer CR programs than the standard ones may be more appropriate. Lastly, professionals in secondary CR facilities should be able to identify those patients who need more attention in order to enhance their cardiorespiratory fitness and thus improve their cardiovascular and overall prognosis.

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# Appendix A

# SF-36 Quality of Life Questionnaire Form

Subject's number: ____ Name: _____ ID: _____ Date: _____

**THE MOS 36 ITEM SHORT (SF36) SURVEY**

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

| | |
|---|---|
| Excellent | 1 |
| Very good | 2 |
| Good | 3 |
| Fair | 4 |
| Poor | 5 |

2. **Compared to one year ago**, how would your rate your health in general **now**?

| | |
|---|---|
| Much better now than one year ago | 1 |
| Somewhat better now than one year ago | 2 |
| About the same | 3 |
| Somewhat worse now than one year ago | 4 |
| Much worse now than one year ago | 5 |

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much? **(Circle One Number on Each Line)**

| | Yes, Limited a Lot | Yes, Limited a Little | No, Not limited at All |
|---|---|---|---|
| 3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports | [1] | [2] | [3] |
| 4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | [1] | [2] | [3] |

| | | | |
|---|---|---|---|
| 5. Lifting or carrying groceries | [1] | [2] | [3] |
| 6. Climbing **several** flights of stairs | [1] | [2] | [3] |
| 7. Climbing **one** flight of stairs | [1] | [2] | [3] |
| 8. Bending, kneeling, or stooping | [1] | [2] | [3] |
| 9. Walking **more than a mile** | [1] | [2] | [3] |
| 10. Walking **several blocks** | [1] | [2] | [3] |
| 11. Walking **one block** | [1] | [2] | [3] |
| 12. Bathing or dressing yourself | [1] | [2] | [3] |

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**? **(Circle One Number on Each Line)**

| | Yes | No |
|---|---|---|
| 13. Cut down the amount of time you spent on work or other activities | 1 | 2 |
| 14. **Accomplished less** than you would like | 1 | 2 |
| 15. Were limited in the **kind** of work or other activities | 1 | 2 |
| 16. Had **difficulty** performing the work or other activities (for example, it took extra effort) | 1 | 2 |

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)? **(Circle One Number on Each Line)**

| | Yes | No |
|---|---|---|
| 17. Cut down the **amount of time** you spent on work or other activities | 1 | 2 |
| 18. **Accomplished less** than you would like | 1 | 2 |
| 19. Didn't do work or other activities as **carefully** as usual | 1 | 2 |

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? **(Circle One Number)**

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

21. How much **bodily** pain have you had during the **past 4 weeks**?

**(Circle One Number)**

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)? **(Circle One Number)**

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks** .**(Circle One Number on Each Line)**

| All of the Time | Most of the Time | A Good Bit of the Time | Some of the Time | A Little of the Time | None of the Time |
|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| 23. Did you feel full of pep? | 1 | 2 | 3 | 4 | 5 | 6 |
| 24. Have you been a very nervous person? | 1 | 2 | 3 | 4 | 5 | 6 |
| 25. Have you felt so down in the dumps that nothing could cheer you up? | 1 | 2 | 3 | 4 | 5 | 6 |
| 26. Have you felt calm and peaceful? | 1 | 2 | 3 | 4 | 5 | 6 |
| 27. Did you have a lot of energy? | 1 | 2 | 3 | 4 | 5 | 6 |
| 28. Have you felt downhearted and blue? | 1 | 2 | 3 | 4 | 5 | 6 |
| 29. Did you feel worn out? | 1 | 2 | 3 | 4 | 5 | 6 |
| 30. Have you been a happy person? | 1 | 2 | 3 | 4 | 5 | 6 |
| 31. Did you feel tired? | 1 | 2 | 3 | 4 | 5 | 6 |

32. During the **past 4 weeks,** how much of the time has your**physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)? **(Circle One Number)**

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

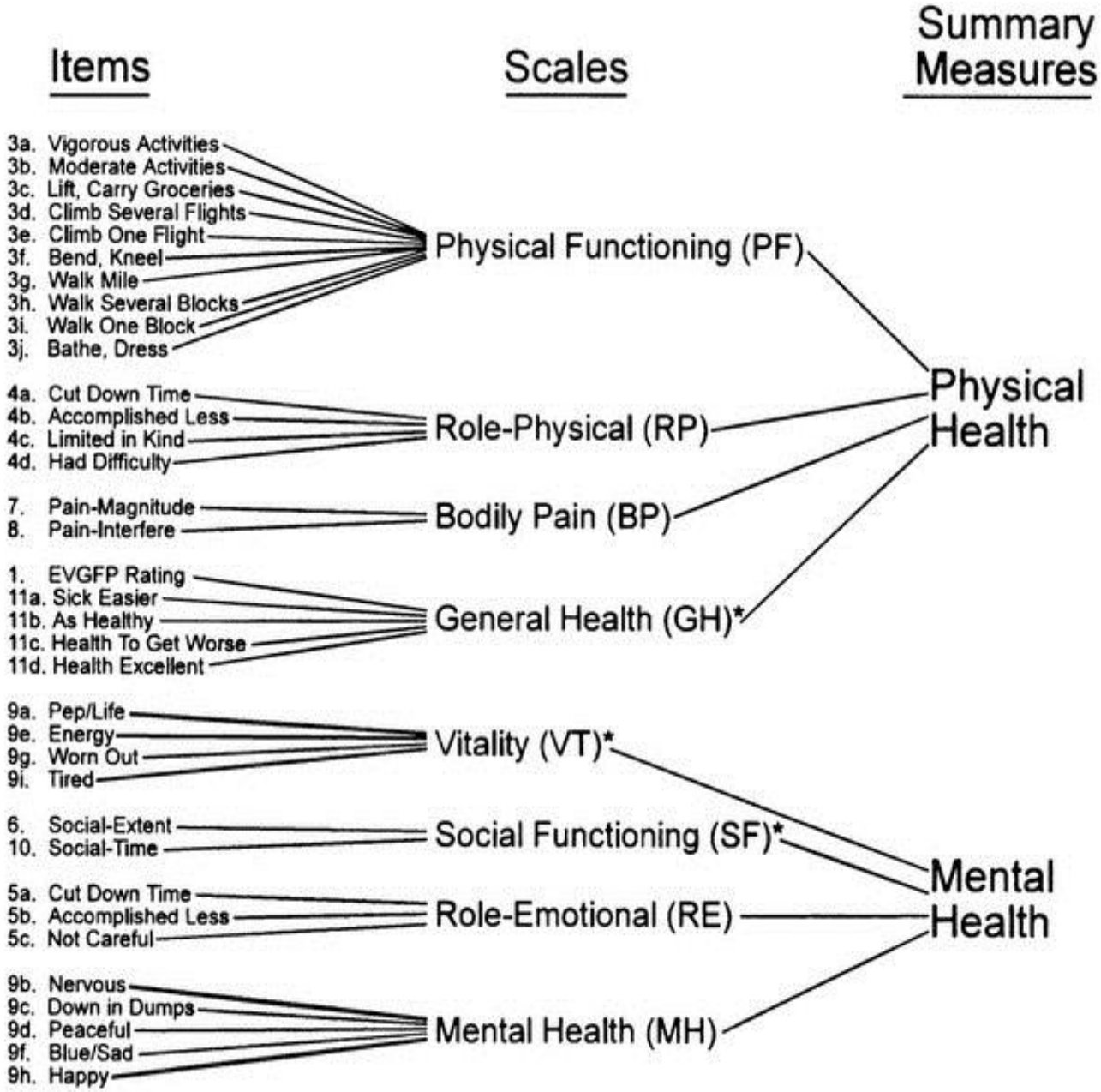
None of the time 5

How TRUE or FALSE is <u>each</u> of the following statements for you. **(Circle One Number on Each Line)**

| | Definitely True | Mostly True | Don't Know | Mostly False | Definitely False |
|---|---|---|---|---|---|
| 33. I seem to get sick a little easier than other people | 1 | 2 | 3 | 4 | 5 |

| | | | | | |
|---|---|---|---|---|---|
| 34. I am as healthy as anybody I know | 1 | 2 | 3 | 4 | 5 |
| 35. I expect my health to get worse | 1 | 2 | 3 | 4 | 5 |
| 36. My health is excellent | 1 | 2 | 3 | 4 | 5 |

**Figure 19. SF-36 Measurement Model**




(Ware, 2000)

# Appendix B

# Examples of CE and IE Training

# IE Training Form

**Diagnosis:** _____

**Name:** _____ **Comments:** _____ **THR:** _____/_____

| Date | RHR | Resting BP | Exercise BP | BP post exercise | HR post exercise |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## Treadmill (18 min)

| Time | RPE | Speed | Incline | METS | HR | RPE | Calories |
|---|---|---|---|---|---|---|---|
| | 2 min 11-13 | | | | | | |
| | 2 min 14-16 | | | | | | |
| | 2 min 11-13 | | | | | | |
| | 2 min 14-16 | | | | | | |
| | 2 min 11-13 | | | | | | |
| | 2 min 14-16 | | | | | | |
| | 2 min 11-13 | | | | | | |
| | 2 min 14-16 | | | | | | |

## Stationary bike / Rowing machine / Elliptical / Arm ergometer (10 min)

| Instrument | Time | RPE | Difficulty level | RPM / SPM | Mets / Watts | HR | RPE | Calories |
|---|---|---|---|---|---|---|---|---|
| | | 2 min 11-13 | | | | | | |
| | | 2 min 14-16 | | | | | | |
| | | 2 min 11-13 | | | | | | |
| | | 2 min 14-16 | | | | | | |
| | | 2 min 11-13 | | | | | | |
| | | 2 min 14-16 | | | | | | |
| | | 2 min 11-13 | | | | | | |
| | | 2 min 14-16 | | | | | | |

## Stationary bike / Rowing machine / Elliptical / Arm ergometer (10 min)

| Instrument | Time | RPE | Difficulty level | RPM / SPM | Mets / Watts | HR | RPE | Calories |
|---|---|---|---|---|---|---|---|---|
| | | 2 min 11-13 | | | | | | |
| | | 2 min 14-16 | | | | | | |
| | | 2 min 11-13 | | | | | | |
| | | 2 min 14-16 | | | | | | |
| | | 2 min 11-13 | | | | | | |
| | | 2 min 14-16 | | | | | | |
| | | 2 min 11-13 | | | | | | |
| | | 2 min 14-16 | | | | | | |

Date of appointment with the exercise physiologist: _____

# CE Training Form

**Diagnosis:** _____

**Name:** _____ **Comments:** _____ **THR:** _____/_____

| Date | RHR | Resting BP | Exercise BP | BP post exercise | HR post exercise |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## Treadmill (21 min)

| Time | Speed | Incline | METS | HR | RPE | Calories |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

## Stationary bike / Rowing machine / Elliptical / Arm ergometer (10 min)

| Instrument | Time | Difficulty level | RPM / SPM | Mets / Watts | HR | RPE | Calories |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

## Stationary bike / Rowing machine / Elliptical / Arm ergometer (10 min)

| Instrument | Time | Difficulty level | RPM / SPM | Mets / Watts | HR | RPE | Calories |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

Date of appointment with the exercise physiologist: _____

# Appendix C

# Energy expenditure calculation

Different durations of exercise sessions for each group were set in order to reach equal total work (Rognmo *et al.,* 2004; Wisloff *et al.,* 2007). Taking the average $VO_2$ peak that had been reported in previous similar trials (approximately 24 ml/kg/min) (Kavanagh *et al.,* 2002; Moholdt *et al.,* 2009; Munk *et al.,* 2009), we could estimate the $VO_2$ consumption during exercise for each group. Accordingly, an estimation of energy expenditure during each session was calculated as follows (Rognmo *et al.,* 2004).

***Prescribed % of $VO_2$ peak X the average $VO_2$ peak reported (24ml/kg/min) X duration of exercise session (minutes)***

*The calculation for one exercise session for the CE group:*

| |
|---|
| 55% X 24 ml/kg/min X 41 minutes = **541.2 ml/kg** |

*The calculation for one exercise session for the IE group:*

Low intensity bouts:

50% X 24 ml/kg/min x 22 minutes = **264 ml/kg**

High intensity bouts:

72.5% X 24 ml/kg/min X 16 minutes **= 278.4 ml/kg**

| |
|---|
| Low + high intensity: 264 + 278.4 = **542.4 ml/kg** |

In order to reach equal energy expenditure between the groups (541.2 and 542.4) duration of exercise sessions should be 41 minutes in the CE group and 38 minutes in the IE group. Caloric expenditure during each exercise instrument was recorded in order to calculate total caloric expenditure in each exercise session for each patient. In the end, total calories were compared between the groups to verify equality.

# Appendix D

# Symptoms, cardiac events, and hospitalizations

**Three months of intervention**

Patients were asked to report of any symptoms that occurred either during exercise or at rest both at the CR center and outside the hospital. None of the reported symptoms had occurred during or within 3 hours after exercise. Data is presented in Table 33.

*Symptoms*

Shortness of breath (SOB): During the 3 months of intervention 5 patients (14.3%) from the CE group and 4 patients (11.4%) from the IE group reported SOB; overall 12.9% of the patients reported SOB. There were no differences between the groups ($X^2 = 0.721$). Chest pain (CP): During the intervention period 4 patients (11.4%) from the CE group and 4 patients (11.4%) from the IE group experienced CP, overall 11.4% of the patients suffered from CP. There were no statistical differences between the groups ($X^2 = 1.000$).

*Cardiac events*

None of the patients experienced a cardiac related event. There were two episodes of vasovagal responses during the CPET; no further treatment was needed after these patients had recovered with the assistance of the medical staff. Two different patients (one from each group, one male and one female) had undergone an angiography in which no significant narrowing was found and no intervention was needed. Both patients were released from the hospital with recommendations for continuing conservative treatment, exercise, medications and lifestyle modifications.

*Hospitalizations*

Four patients from each group (5.7% of the patients) were admitted to the hospital due to cardiac suspicions during the 3 months of intervention. Two of them (one from each group) were released after a couple of days of observation without any

treatment being required. The other two patients had undergone a PTCA with no significant findings as was mentioned above.

**Table 33. Cardiac symptoms, events, and hospitalizations during the intervention**

| | CE | IE | $X^2$ |
|---|---|---|---|
| SOB | 5 (14.3) | 4 (11.4) | 0.721 |
| CP | 4 (11.4) | 4 (11.4) | 1.000 |
| Cardiac events | 0 (0) | 0 (0) | 1.000 |
| Hospitalizations | 2 (5.7) | 2 (5.7) | 1.000 |

Values are number of patients (percentage)
**SOB**: shortness of breath. **CP**: chest pain

### Six months follow-up

Data regarding manifestation of symptoms or occurrence of cardiac events and subsequent hospitalizations was collected during the follow-up in both continuers and non-continuers. All patients were asked to report changes in their medical status throughout this time. Only 2 patients, both from the IE group (6.7%) reported feeling SOB during the follow-up phase. One subjects from the CE group (3%) and 4 from the IE group (13.3%) experienced CP during 6 months of follow-up. The three patients from the IE group were consequently admitted to the hospital, of which 2 of them demonstrated re-stenosis in a PCI. As a result, they were implanted with drug eluting stents and returned to normal activity within 2 weeks. The third patient was hospitalized and underwent a PTCA, in which no significant narrowing was found and he was released the following day. None of the reported symptoms had been manifested during exercise. A couple of these subjects had not been training at the CR during the follow-up, while the other 4 patients, including those who were hospitalized due to CP, were had continued to exercise in the CR throughout this time.

## Conclusions

It is important to note that due to the underpowered sample size and short duration of follow-up specifically for these outcomes, it is not reasonable to draw decisive conclusions for CAD patients. It is possible to affirm with cautious that exercise training (both interval and continuous equally) seems to be safe since no adverse cardiac events occurred during the intervention similarly to previous reports (Keteyian *et al.,* 2014; Moholdt *et al.,* 2009; Warburton *et al.,* 2004). A study examining the risk for cardiovascular events during moderate and high intensity exercise reported that one patient from the moderate intensity exercise group had died as a result of a cardiac arrest during exercise (a total of 129,456 exercise hours), and two non-fatal events (not MI) took place within the high intensity interval training group (a total of 46,364 exercise hours) (Rognmo *et al.,* 2012). Similarly to our singular event, Munk *et al.* (2009) described one adverse event of orthostatic collapse that had happened during an interval training session. In our study one patient almost collapsed immediately after the exercise test, however he recovered rather quickly. Also, in their study the researchers reported fewer admissions for CP and re-catherizations in the exercise group compared to non-exercising patients (Munk *et al.,* 2009). In the present study the frequencies of symptoms, cardiac events, and hospitalizations were low and similar between the groups with no comparison to non-exercisers. More studies involving interval training should be performed for establishing safety.

# Appendix E

# Calculated intensity levels during exercise

Intensity parameters are presented in Table 34 and Figure 20. This data includes: RPE, metabolic equivalents (METS), training workloads (watts), estimated caloric expenditure, and percent of heart rate reserve (HRR), during exercise. Furthermore, Training Impulse (TRIMP) was calculated in order to quantify training load (Banister, 1991). The TRIMP takes into account the intensity of exercise by calculating the heart rate reserve (HRR) and the duration of exercise. Values relating to the IE group are presented twice: once representing the lower intensity bouts and once representing the higher bouts of intensity. Repeated measures ANOVA tests were used to examine differences between the groups and changes of intensity parameters within each group during the 3 months of intervention.

**RPE**

During their activity on each instrument patients were asked to subjectively grade their level of effort according to the Borg scale (from 6 to 20). Overall, RPE was higher significantly in the IE group in average ($p = 0.013$)

*CE group:* The mean RPE during the first month was 12.4 ± 1.1 in average, and 12.2 ± 0.6 during the third month. Anova comparison did not reveal significant changes throughout this time.

*IE group:* In the lower intensity training mean RPE of all three months was evaluated as 11.7 ± 1.4 with no statistical changes over time. In the higher intensity of exercise RPE was 14.4 ± 0.3 during the first month increasing significantly to 14.9 ± 1.1 during the second month of training, and decreasing non-significantly during the third month to 14.7 ±0.5.

**METS**

Mets were recorded during exercise on the treadmill. The average METS did not differ between the groups over time ($p = 0.363$).

*CE group:* The average METS in the CE group increased from 5.2 ± 1.3 to 5.7 ± 1.6 and 5.8 ± 1.4 from the first month to the last month of the intervention

respectively. Pairwise comparisons showed that the change in METS over time was significant only between the first and the second months ($p = 0.003$).

*IE group:* While exercising in the low bouts, patients increased their METS significantly from the first to the second month of exercise ($p = 0.003$), however it did not change any further. During bouts of higher intensities METS also increased significantly over time throughout each month of training ($p < 0.001$, partial $eta^2 = 0.453$).

The mean METS of this group (low and high bouts intervals together) increased from 5.1 ± 1.3 to 5.9 ± 1.8 throughout the training period, which was significant over time across all 3 months of intervention ($p < 0.001$). Additionally, training METS were found to be positively and strongly related to maximal exercise capacity including $VO_2$ peak and duration of exercise test ($r = 0.651$, $p < 0.001$; $r = 0.668$, $p < 0.001$, respectively).

**Workload levels in watts**

Workloads were recorded in watts while using the stationary bike, the elliptical machine and the rowing machine. ANOVA analysis had proven that both groups had similar changes in exercise workloads ($p = 0.721$).

*CE group:* The CE group increased their workloads from 69.2 ± 27.9 to 77.9 ± 31.7 during the three months of training. Post-Hoc analysis detected significant differences in watts only between the first and the second months ($p = 0.019$).

*IE group:* In the low levels of exercise the workloads increased significantly during the first 2 months ($p = 0.003$), while during the last month of training there is a significant decrease in work output ($p = 0.002$). In the higher bouts workload increased substantially throughout all 3 months of training ($p < 0.001$). Overall the workload in this group was improved during the first 2 months of training.

**Calorie expenditure**

Absolute caloric expenditure was calculated using the sum of calories expended on each exercise instrument. Since personal information was not entered into the machines, these calories represented the absolute level of energy that was expended rather than the relative energy. This value of calories assisted in

estimating the amount of total work that was performed during each training session.

*CE group:* The mean calorie expenditure in the CE group increased from 296.9 ± 51.8 to 331.4 ± 64.9 during the three months of intervention. The change in the calorie expenditure was significant over time ($p < 0.05$), after adjusting for the violation of the Mauchly's test of Sphericity. Also, Post-Hoc analysis showed significant differences in the calorie expenditure between the first and the second months ($p = 0.035$), and between the second and the third months ($p = 0.048$).

*IE group:* In the IE group the mean calorie expenditure increased from 305.3 ± 58.1 to 336.8 ± 81.3 which was significant over time. The change in energy expenditure was noticeable between the first and second months ($p = 0.009$) but not between the second and the third months ($p = 0.413$).

*Differences between the groups:* There were no significant differences between the groups in calorie expenditure as they were compared with independent T-tests during the first month ($p = 0.517$), the second month ($p = 0.406$), and the third month ($p = 0.761$) of intervention.

**Percent of heart rate reserve (HRR)**

Exercise intensity was prescribed using RPE levels and percent of HRR based on the Karvonen formula (Karvonen, Kentala & Mustala, 1957). The purpose of this current analysis was to see if the subjects had reached the intended exercise intensities according to HR. The analysis revealed no significant differences between the groups in the mean of HR during exercise as a portion of HRR ($p = 0.144$).

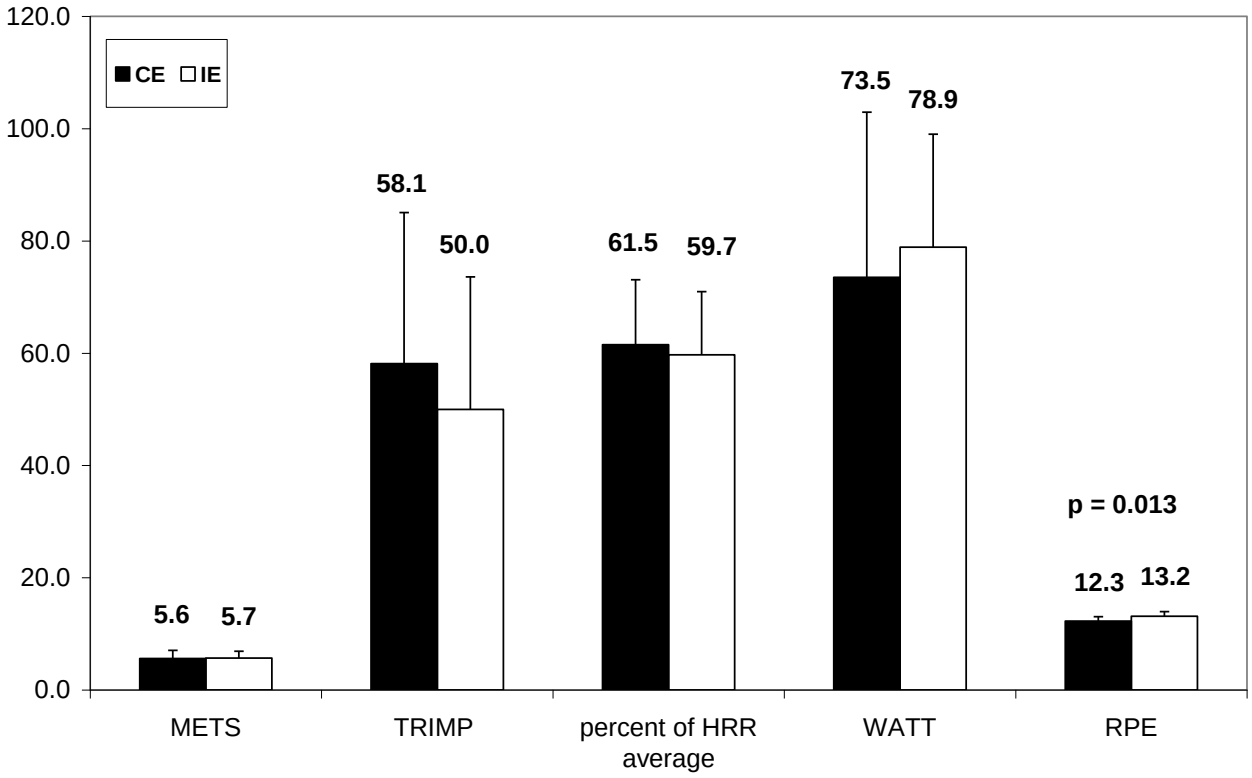
*CE group:* The patients in the CE group have reached 58.3 ± 11.6% of their HRR during exercise in their first month of training and 64.7 ± 10.2% during the third month of training. Post-Hoc analysis discovered significant increases across all intervention period ($p \leq 0.001$) with a mean of 61.5% of HRR.

*IE group:* The mean percent HR of HRR in the lower intensity levels was 53.4 ± 8.1% while it had reached 71.7 ± 11.7 in the higher intensity bouts. No changes in the HRR% were found over time training in the low bouts ($p = 0.126$) whereas a significant increase in HRR% was observed during each month of higher interval training ($p < 0.001$).

### Training Impulse (TRIMP)

Four subjects were excluded from this analysis, 2 from each group. The couple of subjects from the IE group had reached very low heart rates during their training, reaching only 41% HRR and 38% HRR, resulting in extremely low values of TRIMP. The other 2 patients had reached low maximal heart rates during both maximal exercise tests, while during their training sessions they exercised with higher heart rates, hence leading to extremely high values of TRIMP. No group differences were revealed. TRIMP was increased significantly during each month of training in the CE group ($p < 0.001$), while it was almost significant within the IE group ($p = 0.066$).

**Figure 20. Exercise intensity parameters of CE and IE groups**




Values are presented as means ± SD

P values represent differences between the groups, $p < 0.05$

**Table 34. Intensity parameters during each month of the intervention**

| | | CE | | IE | | | |
|---|---|---|---|---|---|---|---|
| | | **RPE 12-14** | **P value within** | **RPE 11-13** | **P value within** | **RPE 14-16** | **P value within** |
| RPE | 1st month | 12.4 ± 1.1 | | 11.4 ± 0.5 | | 14.4 ± 0.3 | |
| | 2nd month | 12.2 ± 0.6 | 0.286* | 12.0 ± 2.3 | 0.196* | 14.9 ± 1.1 | 0.037*a |
| | 3rd month | 12.2 ± 0.6 | | 11.6 ± 0.7 | | 14.7 ± 0.5 | |
| METS | 1st month | 5.3 ± 1.3 | | 4.0 ± 0.7 | | 6.4 ± 1.3 | |
| | 2nd month | 5.7 ± 1.6 | 0.000a | 4.2 ± 0.9 | 0.001a | 7.2 ± 1.8 | 0.000*ab |
| | 3rd month | 5.8 ± 1.4 | | 4.3 ± 0.9 | | 7.5 ± 2.1 | |
| Watts | 1st month | 69.2 ± 27.9 | | 59.8 ± 11.8 | | 87.5 ± 20.8 | |
| | 2nd month | 75.6 ± 29.1 | 0.005a | 69.0 ± 16.3 | 0.000ab | 96.6 ± 29.8 | 0.000*ab |
| | 3rd month | 77.9 ± 31.7 | | 64.7 ± 13.5 | | 100.4 ± 32.2 | |
| TRIMP** | 1st month | 52.7 ± 23.1 | | 20.2 ± 9.2 | | 26.2 ± 16.0 | |
| | 2nd month | 58.9 ± 29.7 | 0.000*ab | 20.4 ± 8.2 | 0.653 | 28.0 ± 16.0 | 0.007*ab |
| | 3rd month | 62.8 ± 27.4 | | 20.9 ± 6.9 | | 30.4 ± 16.1 | |
| Calories | 1st month | 296.9 ± 51.8 | | 305.3 ± 58.1 | | Calories were calculated for both intensities together | |
| | 2nd month | 310.0 ± 57.6 | 0.001ab | 322.7 ± 71.1 | 0.047*a | | |
| | 3rd month | 331.4 ± 64.9 | | 336.8 ± 81.3 | | | |
| Percent of HRR | 1st month | 58.3 ± 11.6 | | 52.4 ± 9.8 | | 68.6 ± 12.3 | |
| | 2nd month | 61.5 ± 12.3 | 0.000 ab | 53.2 ± 8.9 | 0.126* | 71.16 ± 11.4 | 0.000*ab |
| | 3rd month | 64.7 ± 10.2 | | 54.4 ± 7.6 | | 74.0 ± 11.4 | |

Values are presented as mean ± SD

P values represent differences within each group between the first and the third months

*Sphericity assumption of homogeneity was violated. Significant levels were taken from Greenhouse-Geisser

a. Significant differences between the first month and the second month in the Post-Hoc test.

b. Significant differences between the second month and the third month in the Post-Hoc test

**Although some extreme values exist in the TRIMP data, not due to high intensity exercise but due to very low maximal HR during the CPET, excluding these patients (28,32, 39, and 74) did not change the statistical outcomes.

# Appendix F

# Drug therapy

### Beta-blockers agents

In the CE group 83.3% of the patients had no change in their beta-blockers usage. Dosages were increased in 3 of the patients (8.3%) while other 3 of the patients (8.3%) had their dosages decreased. In the IE group 89.9% of the patients had no change in their beta-blockers usage. Dosages were decreased in 4 of the patients (11.1%) while none of the patients had their dosages increased. Overall, there were no differences in the beta-blockers usage between the groups after the intervention, p = 0.201.

During the 6-months follow-up, most subjects did not have any modifications in their drug therapy. One participant from each exercise group had their beta-blocker dosage increased while 3 patients from the IE and one from the CE had their dosages reduced. Chi- square anlaysis showed no differences between the groups in drug usage ($x^2 = 0.679$).

### Cholesterol lowering agents (Statins)

In the CE group 60.0% of the patients had no change in their statins treatment compared to 68.6% in the IE group. Dosages were augmented in 2 patients (5.7%) from the CE group and 4 patients (11.4%) from the IE group; conversely, 12 subjects from the CE group (34.2%) and 7 subjects from the IE group (20.0%) had their dosages reduced. In general, there were no differences in the statins management between the groups post intervention, $x^2 = 0.337$.

Only one patient from the cohort of the follow-up was not taking statins. However, 3 subjects from the CE group and 6 from the IE groups were taking reduced dosages of cholestrol lowering medications. None of the subjects had their quantities increased during that time. These changes were not significant between the groups ($x^2 = 0.339$).

**Anti - hypertensive drugs**

Even though only 39 (51%) of the patients had been diagnosed as hypertensive (usually before their cardiac event), 49 (68%) of the patients were prescribed with anti hypertensive agents. Out of the 49 subjects, 78% from the CE and 58% from the IE group had been taking these drugs, with no differences between them ($x^2$ = 0.077). Also, there were no differences between the groups in the various types of these agents including angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), and calcium channel blockers (CCB).

During the follow-up, one patient from the IE group increased the ACE inhibitor dosage. Two other patients from the same group and one subject from the CE group had stopped taking their anti-hypertensive drugs, resulting in a significant difference between the groups with more subjects medicated from the CE group (75%) compared to the IE group (53%) ($x^2$ = 0.050).

As seen throughout the 3 months of intervention and the follow-up period, BP did not change or differ over time and between the groups. In average both training groups had normal systolic and diastolic BP values through the study. Even patients who were taking anti-hypertensive drugs had similar and normal values of BP (below 120/80 mm/Hg) (Fletcher *et al.,* 2013) compared to patients who had not been taking these medications.

# Appendix G

# Professional consultations and

# Additional physical activity

## Professional consultations

### Three months of intervention

All patients were offered a consultation meeting with a dietitian and a psychologist. Overall 23 patients met with the dietitian, 8 patients were from the CE group (22.2%) and 15 patients from the IE group (42.7%). The psychologist had consulted ten patients including 7 subjects from the CE group (19.4%) and 3 subjects from the IE group (8.3%). No differences were found between the groups in consultations neither with the dietitian ($X^2 = 0.077$) nor with the psychologist ($X^2 = 0.173$), although the number of patients who consulted the dietitian tended to be higher in the IE group (Table 35).

**Table 35. Dietitian and psychological consultations during the intervention**

| | CE | IE | $X^2$ |
|---|---|---|---|
| Dietitian consultations | 8 (22.2) | 15 (42.7) | 0.077 |
| Psychologist consultations | 7 (19.4) | 3 (8.3) | 0.173 |

*Nutritional guidance effects on body composition and blood parameters*

Most of the body composition parameters including weight, BMI, and waist circumference, did not change over time or differed between patients who have consulted the nutritionist and those who haven't. However, subjects that met with the nutritionist had a higher body fat percentage at baseline (30.9 ± 7.8%) compared to those who did not wish to consult the nutritionist (27.0 ± 7.3%), ($p = 0.046$). Post 3 months of exercise (and nutritionist) intervention these differences

were maintained ($p = 0.033$) with no changes in body fat percentage within patients whether or not they have consulted the nutritionist. No differences in body composition variables including body weight, BMI, and BF% were found between CE and IE groups, regardless of being assisted by nutritional guidance or not. However, only IE patients reduced their WC significantly (by less than 1.0 cm) with a trend for a higher rate of nutritional assistance.

Patients guided by the nutritionist had similar blood lipid profile, glucose metabolism profile, and CVD biomarkers compared to those who were not assisted by the nutritionist, before and after the intervention ($p > 0.05$). HbA1c was significantly improved with time within the IE group ($p = 0.002$), with no differences between subjects who have received guidance from the nutritionist and those who have not ($p = 0.760$).

*Psychologist consultations and QOL parameters*

Patients who asked or referred to meet with the psychologist had lower MH and total scores in the SF-36 QOL questionnaire at baseline (58.4 ± 24.9 and 63.6 ± 26.3, respectively) compared to patients who did not seek the psychologist's help (75.2 ± 15.3 and 75.5 ± 14.8, respectively). However, since the assumption of equal variances was violated in this analysis, the differences between these two groups were not significant. Anova analysis had demonstrated that only the subjects who were not consulting the psychologist during the intervention phase improved their QOL scores significantly post treatment ($p < 0.001$). Consequently, these patients had higher MH and total scores (81.4 ± 10.7 and 82.8 ± 11.8, respectively) compared to the participants who were assisted by the psychologist (64.6 ± 19.5 and 70.2 ± 20.2 respectively) at 3 months. However after adjusting for the violation of equal variances, only MH scores remained significant between these two subgroups, $t(64) = 2.541$, $p < 0.05$.

**Six months Follow-up**

Both the dietitian and the psychologist were available for the subjects who were continuing in the CR facility through the follow-up time. None of the patients have requested to meet with the psychologist. Ten patients (33%) had consultations with the nutritionist at the CR center, 4 from the CE and 6 from the IE group. Those who have left the CR program were recommended to monitor their weight and maintain

healthy eating habits, and in some cases they were advised to seek for nutritional guidance in their community. Four of the subjects who hav left (1 from the CE and 3 from the IE group) reported meeting with a nutritoinist during the follow-up period. Overall, the 14 patients that were assisted by a nutritionist had higher values of BMI, WC and body fat perecntage compared to the others, before and after the follow-up ($p < 0.05$). However, over this time there were no changes in body compostion parameters within or between patietnts who have met a nutritionist ($p > 0.05$). Since the number of patients consulting a nutritionist was low in each exercise group, there was no point in a statistical analysis between them. Also, no effect of nutirtional guidance was observed on blood parameters and biomarkkers during the follow-up phase.

## Additional physical activity

### Three months of intervention

The amount of physical activity performed outside the CR program was quantified in 'minutes of aerobic exercise performed per week'. During and after the intervention 27 participants from the CE group were aerobically active; nine of the patients were engaging in a physical activity for equal or more than 180 minutes a week while the others exercised for shorter durations. The amount of physical activity in the IE group was similar, as 20 of the subjects were exercising routinely and 7 of them had been training for at least 180 minutes every week (p value between the groups = 0.083). Resistance training was reported by only 19 patients (26%), 8 were from the CE group and 11 from the IE group with no differences between them. No correlations were found between minutes a week spent on resistance training and cardiorespiratory variables and $VO_2$ peak specifically ($r = 0.120$, $p = 0.323$).

### Six months follow-up

Most subjects (88.5%) were physically active during the follow-up period, some in the CR setting and others were active on their own, either in a gym or outside. But, even though there was a considerable difference in the number of subjects who reported to be exercising between continuers (100%) and non-continuers (76%) ($X^2 = 0.003$), there was no difference between them in the amount of exercise performed in minutes per week ($p = 0.223$). Looking at the recommended physical

activity by the AHA (Fletcher *et al.,* 2013), 53% of the continuers and 38% of the non-continuers, reported performing at least 150 minutes per week of moderate aerobic exercise, with no differences between them ($p = 0.234$) or between the exercise groups.

# Appendix H

# Quality control and reliability

## Blood lab

All blood variables were analyzed using the Cobas advanced integrated system for diagnostic clinical chemistry testing, which is a random and continuous selective automated analyzer. Cobas technology is used for classical chemistry, electrolytes, specific proteins, therapeutic drug monitoring, drugs of abuse, and thyroid hormone testing. It provides with random sample access, innovative robotics and an advance user interface, using windows NT, optimize time management and streamline work flow.

Quality assurance is based on reference control materials and calibrants, as well as repeatability, reproducibility within Run and between Run, stability, evaluation of uncertainty, biological variation, imprecision, bias and pool samples stability, thus assuring on a daily basis the evaluation of patients results. Unless all 3 Levels of Internal Quality Control are within limits, no results are released to patients and the overall acceptance of the biochemistry report is also based on the information related to the patients. The instrument performs the validity of a test automatically. In this appendix, information regarding quality control and reliability is being provided for all blood parameters in Table 36.

**Table 36. Precision and coefficients of variation of blood variables**

| Blood parameter | Precision | CV for repeatability | CV for intermediate precision |
|---|---|---|---|
| **Blood glucose** | Precision was determined using human samples and control in an internal protocol with repeatability and intermediate precision using 3 aliquots per run,1 runs per day and 21 days. | 0.5% - 0.8% | 1.1% - 1.3% |
| **HbA1C** | Precision was determined using blood samples and controls in an internal protocol. Intermediate precision was measured with 3 lots of HbA1c test using 4 different EDTA whole blood samples at the medical decision points and 2 control solutions over 21 days with 2 series each, samples randomized, duplicate measurements per series and specimen. Repeatability was tested with whole blood samples in series of 21 measurements per specimen. | 1.5% - 2.5% | 1.0% - 2.8% |
| **Cholesterol panel** | Precision was determined using controls in CLSI EP5-A2 protocol. Whole blood samples were measured using a modified CLSI protocol in 5 series of 4 replicates in one day. | TC: 1.6% - 1.9%<br>TG: 1.1% - 2.0%<br>HDL: 2.4% - 3.5% | TC: 1.6% - 2.2%<br>TG: 1.1% - 3.7%<br>HDL-C: 2.7% - 3.6% |
| **HS-CRP** | Precision was determined using human samples and controls in an internal protocol with repeatability (n=21) and intermediate precision using 3 aliquots per run, 1 run per day for 21 days. | 0.4% - 1.6% | 1.3% - 8.4% |
| **Troponin - T** | Precision was determined using Elecsys reagents, samples controls in a protocol (EPs-A2) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplication each for 21 days (n=84). | 0.9% - 3.7% | 1.5% - 4.0% |

## Reliability of echocardiography sonographers

For the purpose of showing consistency between the 2 sonographers and within themselves, the sonographers examined 10 cardiac patients, using the same inclusion and exclusion criteria. The echocardiograms were performed on two different occasions with the same machine (the Vivid 9 scanner). During the first examination one sonographer performed the first echocardiogram, followed immediately by the second sonographer who was not exposed to the images taken previously by his colleague. Approximately one week after the initial echocardiograms, the sonographers repeated their examinations on the same patient. To prevent bias of data acquisition, the sonographers were not allowed to be present during each other's echocardiograms or to discuss the results. Sonographers obtained all echocardiography variables that were included in this thesis (Gottdiener et al., 2002).

**Reliability analysis**

Using SPSS 20 analysis pack, inter and intra-observer repeatability was calculated for each variable and determined by: 1.Pearson's Correlation. 2. Two-ways mixed effect intra class correlation coefficient, using an absolute agreement definition, for determining consistency between two measurements or between two observers. The intra-class value of agreement was interpreted as follows: good >0.7, optimal >0.8, and excellent >0.9 (Altman, 1991). Confidence interval of 95% was also calculated and reported. 3. Bland – Altman plots for limits of agreement was performed for 3 major parameters: EF%, E/A, and E/e', within and between observers. Limits of agreement were calculated as: (mean of difference) ± 2(SD of the difference) (Giavarina, 2015).

## Results:

Ten patients, ages 36 – 55, were assessed within a period of 7-10 days between the two measurements. Intra reliability data of Pearson's correlation, intra class correlation, and levels of agreement are presented in Table 37. The same data for inter reliability is presented in Table 38.

**Table 37. Intra observer correlations and intra-class correlation coefficients**

| | Mean difference | SD of the difference | CC | ICC | 95% CI | P value | Level of agreement* |
|---|---|---|---|---|---|---|---|
| **Observer A** | | | | | | | |
| LA | 0.25 | 2.20 | 0.606 | 0.771 | 0.025-0.944 | 0.024 | -4.06-4.56 |
| EDV | 5.10 | 5.28 | 0.781 | 0.817 | 0.183-0.956 | 0.003 | -5.25-15.45 |
| ESV | 0.60 | 3.44 | 0.942 | 0.903 | -0.030-0.982 | 0.000 | -6.14-7.34 |
| EF% | 0.70 | 5.37 | 0.794 | 0.892 | 0.562-0.973 | 0.002 | -9.84-11.24 |
| MV-E | -0.02 | 0.07 | 0.854 | 0.920 | 0.691-0.980 | 0.001 | -0.16-0.13 |
| MV-A | 0.02 | 0.12 | 0.876 | 0.925 | 0.698-0.981 | 0.000 | -0.22-0.25 |
| E/A | -0.10 | 0.27 | 0.856 | 0.879 | 0.547-0.969 | 0.002 | -0.64-0.43 |
| MV-DT | -5.70 | 39.79 | 0.208 | 0.582 | -0.683-0.896 | 0.105 | -83.7-72.3 |
| e' | 0.00 | 0.01 | 0.894 | 0.947 | 0.784-0.987 | 0.000 | -0.03-0.03 |
| E/e' | -0.08 | 1.11 | 0.834 | 0.917 | 0.660-0.980 | 0.001 | -2.26-2.09 |
| **Observer B** | | | | | | | |
| LA | 0.00 | 1.78 | 0.768 | 0.872 | 0.463-0.968 | 0.004 | -3.49-3.49 |
| EDV | 3.30 | 6.82 | 0.849 | 0.892 | 0.515-0.974 | 0.000 | -10.06-16.66 |
| ESV | -0.10 | 3.78 | 0.846 | 0.882 | 0.544-0.970 | 0.001 | -7.52-7.32 |
| EF% | 0.30 | 5.17 | 0.846 | 0.894 | 0.558-0.974 | 0.002 | -9.82-10.42 |
| MV-E | -0.02 | 0.08 | 0.774 | 0.870 | 0.480-.968 | 0.003 | -0.18-0.15 |
| MV-A | -0.04 | 0.11 | 0.867 | 0.899 | 0.618-0.975 | 0.001 | -0.26-0.19 |
| E/A | -0.01 | 0.28 | 0.750 | 0.857 | 0.397-0.965 | 0.005 | -0.56-0.54 |
| MV-DT | -0.20 | 38.22 | 0.532 | 0.692 | -0.381-0.926 | 0.057 | -75.11-74.71 |
| e' | 0.00 | 0.01 | 0.961 | 0.980 | 0.925-0.995 | 0.000 | -0.02-0.01 |
| E/e' | 0.60 | 1.21 | 0.870 | 0.933 | 0.725-0.983 | 0.000 | -2.30-2.42 |

**CC:** correlation coefficient; **ICC**: intra class correlation coefficient; **CI**: confidence interval

*Level of agreement was calculated as (mean of difference) ± 2(SD of the difference).

**LA:** left atria area; **EDV**: end diastolic volume; **ESV**: end systolic volume; **LVEF**: left ventricular ejection fraction**; MV-E**: early diastolic mitral inflow velocity; **MV-A**: late diastolic mitral inflow velocity; **MV-DT**: mitral valve deceleration time; **e'**: average of septal and lateral e'.

**Table 38. Inter observer correlations and intra-class correlation coefficients**

| | Mean difference | SD of the difference | CC | ICC | 95% CI | P value | Level of agreement* |
|---|---|---|---|---|---|---|---|
| **Test 1** | | | | | | | |
| LA | -0.17 | 1.98 | 0.723 | 0.850 | 0.374-0.963 | 0.006 | -4.06-3.72 |
| EDV | -1.30 | 3.72 | 0.900 | 0.894 | 0.534-0.974 | 0.000 | -10.86-8.26 |
| ESV | -1.50 | 3.44 | 0.942 | 0.903 | -0.030-0.982 | 0.000 | -8.79-5.79 |
| EF% | 3.10 | 4.89 | 0.851 | 0.890 | 0.532-0.973 | 0.001 | -6.48-12.68 |
| MV-E | 0.02 | 0.11 | 0.611 | 0.769 | 0.056-0.943 | 0.023 | -0.20-0.24 |
| MV-A | 0.03 | 0.09 | 0.893 | 0.931 | 0.739-0.983 | 0.000 | -0.14-0.20 |
| E/A | -0.00 | 0.14 | 0.910 | 0.957 | 0.825-0.989 | 0.000 | -0.28-0.28 |
| MV-DT | 48.40 | 43.92 | 0.367 | 0.709 | -0.036-0.925 | 0.018 | -37.68-134.5 |
| e' | 0.00 | 0.01 | 0.921 | 0.948 | 0.771-0.987 | 0.000 | -0.02-0.03 |
| E/e' | -0.42 | 1.23 | 0.854 | 0.908 | 0.655-0.977 | 0.001 | -2.92-2.09 |
| **Test 2** | | | | | | | |
| LA | -0.420 | 1.79 | 0.673 | 0.812 | 0.234-0.953 | 0.012 | -3.94-3.10 |
| EDV | -3.10 | 5.52 | 0.887 | 0.925 | 0.676-0.982 | 0.000 | -13.93-7.73 |
| ESV | -2.20 | 5.81 | 0.865 | 0.860 | 0.090-0.970 | 0.000 | -13.58-9.18 |
| EF% | 2.70 | 4.03 | 0.899 | 0.901 | 0.555-0.976 | 0.000 | -5.20-10.60 |
| MV-E | 0.02 | 0.09 | 0.765 | 0.855 | 0.436-0.964 | 0.005 | -0.15-0.20 |
| MV-A | -0.02 | 0.12 | 0.865 | 0.929 | 0.720-0.982 | 0.001 | -0.26-0.22 |
| E/A | 0.09 | 0.22 | 0.897 | 0.937 | 0.760-0.984 | 0.000 | -0.34-0.52 |
| MV-DT | 53.90 | 48.00 | 0.165 | 0.713 | 0.001-0.926 | 0.027 | -40.15-147.9 |
| e' | 0.00 | 0.01 | 0.847 | 0.916 | 0.684-0.979 | 0.001 | -0.02-0.03 |
| E/e' | -0.27 | 1.20 | 0.676 | 0.793 | 0.184-0.937 | 0.033 | -2.63-2.08 |

**CC:** correlation coefficient; **ICC**: intra class correlation coefficient; **CI**: confidence interval

*Level of agreement was calculated as (mean of difference) ± 2(SD of the difference).

**LA:** left atria area; **EDV**: end diastolic volume; **ESV**: end systolic volume; **LVEF**: left ventricular ejection fraction**; MV-E**: early diastolic mitral inflow velocity; **MV-A**: late diastolic mitral inflow velocity; **MV-DT**: mitral valve deceleration time; **e'**: average of septal and lateral e'.

Intra-observer reliability (Table 37).

According to Pearson's correlation coefficients, almost all variables were positively and strongly correlated with each other within both observers, ranging from r = 0.606 to r = 0.961. Only MV-DT was not strongly correlated within the observers (r = 0.532 and r = 0.208). Intra class correlation coefficients were mostly optimal (0.8-0.9) and excellent (>0.9) except for LA measurements within Observer A (which were good) and MV-DT measurements within both observers (≤ good, p > 0.05).

Inter-observer reliability (Table 38)

Pearson's correlation coefficients were positively and strongly correlated in almost all variables between the observers during each examination time, ranging from r = 0.611 to r = 0.942. Only MV-DT was not strongly correlated at both times (r = 0.367 and r = 0.165). Intra class correlation coefficients were mostly optimal (0.8-0.9) and excellent (>0.9) except for MV-E and MV-DT during the first measurements, and MV-DT and E/e' during the second measurements (all were good, between 0.7-0.8).

## Discussion

Based on the results, Pearson's correlations revealed strong relationships between the tests and the sonographers. However, since Pearson's correlations can only represent relationships between one variable and another, rather than differences or agreement between variables, the intra class analysis was also used for assessing agreement. The intra class outcomes demonstrated high reliability within the tests and between the observers. Mean of differences of most variables were close to zero during both measurements, implying good consistencies between observers and between both echocardiograms (Giavarina, 2015). Mean of differences of MV-DT were acceptable when it was compared within each observer, but they were high between the observers during each echocardiography examination, suggesting differences between the sonographers.

Overall, the results show that the sonographers who participated in this study are reliable in examining systolic and diastolic function while obtaining these specific variables on the Vivid 9 scanner.