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Intensity vs. Duration of Exercise in Producing Cardiovascular Benefits

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INTENSITY VS. DURATION OF EXERCISE IN PRODUCING CARDIOVASCULAR BENEFITS

A Research Paper

Submitted

in Partial Fulfillment

of the Requirements for the Degree

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Katie Lynn Sandbulte

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Table of Contents

Chapter I

INTRODUCTION

It is well known that the obese and overweight population has significantly increased over the last two decades in the United States contributing to a significant increase in adults with cardiovascular disease (CVD), coronary artery disease (CAD), myocardial infarction (MI), and other CV related disease. Physical inactivity was cited as 1 of 9 major contributors to heart disease mortality worldwide in the 2004 INTERHEART study (Carnethon, M.R., 2009); it is also an established risk factor for CVD. There are many benefits to a lifelong commitment to exercise, healthy living, and physical fitness, as well as many well established medical correlations between exercise and CV health, and many studies have shown an inverse relationship between physical activity and CVD risk factors (Duscha, Slentz, Johnson, Houmard, Bensimhon, Knetzger, & Kraus, 2005). It has been proven by previous studies that exercise and physical activity help prevent or reduce all-cause mortality rates in older and younger men and women, and lowers the risk of heart disease, hypertension, cancer, obesity, and type II diabetes as well as reduce the severity of existing heart disease (Haennel and Lemire, 2002). Therefore, due to these benefits, according to Duscha et al., the recommendation of regular exercise to prevent CVD is widely accepted throughout the medical community. Although physical activity is recommended as an important component of a healthy lifestyle, the effects of intensity, duration, and frequency of exercise required to produce sufficient healthy changes in the CV system, reduce CVD risk factors, and protect against coronary heart disease (CHD) and stroke is unclear.

Sports science has established that mode, frequency, duration, and intensity are essential for the extent of the effects of exercise training (Wisloff, Ellingsen & Kemi, 2009). However, as

previously mentioned, it is unknown which of these variables of exercise training is most effective in producing healthful changes in the CV system, as well as provide prevention, treatment, and rehabilitation of CVD risk factors and other CV related diseases. Previous reports, according Duscha et al. (2005), have suggested vigorous physical activity is required to reduce the risk of CVD and all-cause mortality, while other epidemiologic studies suggest a relationship between total energy expenditure, CVD, and all-cause mortality independent of exercise intensity. Along with this idea, many studies suggest that moderate-intensity exercise training is sufficient to produce substantial benefits in the cardiovascular system (Iwasaki, Zhang, Zuckerman & Levine, 2003). The effect of exercise training in patients at highest risk for CV events, according to Iwasaki et al., is manifest early, i.e., within the first few months after MI. Moreover, Iwasaki et al. go on to state that for such patients, exercise training reduces the risk of sudden death but has a limited impact on recurrent MI, suggesting a greater effect on dynamic CV control processes than on slowly developing arteriosclerosis.

There are other studies, however, that suggest high-intensity interval or sprint training is more effective in producing beneficial adaptations in the CV system. Wisloff et al. (2009) define high-intensity aerobic interval training as walking or running intensity at bouts of 85%-90% of peak oxygen uptake (VO_{2peak}) or 90%-95% of peak heart rate, separated by two to three minutes of active recovery at approximately 60%-70% of peak heart rate. According to Wisloff et al., based on results of several other recent studies aerobic interval training at a relatively high-intensity was found to induce larger beneficial effects to the heart compared with exercise training at moderate or low intensity. Wisloff et al. go on to state that many studies suggest that moderate exercise intensity is sufficient to reduce the risk of CVD in women and in older men, but there are some indications that middle-aged men need vigorous exercise to achieve

protection. They also point out that in another study, high exercise intensity was associated with reduced all-cause mortality, a greater reduction in the risk of CHD and CV death, but there was no additional benefit found in this study from increasing the duration or the number of exercise sessions per week. In another study, the authors pointed out that low-cardiorespiratory fitness is a powerful predictor of CHD mortality, and there are meta-analyses that suggest that CHD mortality is lower in highly fit individuals than in moderately fit individuals, and because of this dose-response relationship, it is important that exercise guidelines explain how cardiorespiratory fitness is optimized (O'Donovan, Owen, Bird, Kearney, Nevill, Jones, & Woolf-May, 2005). O'Donovan et al. go on to state that current guidelines suggest that changes in cardiorespiratory fitness are similar in high-intensity interventions and in moderate-intensity intervention of longer duration if the energy cost of exercise is similar. However, those randomized controlled trials that have compared intervention of equal energy cost have concluded that high-intensity training is more effective in improving cardiorespiratory fitness. Therefore, exercise intensity may be a more significant factor than duration in achieving CV benefits.

Endurance training has also been shown to produce significant improvements in maximal oxygen uptake (VO_2max), weight, body fat, waist circumference, and insulin resistance. Left ventricular (LV) structural adaptation in response to aerobic endurance exercise training (EET) has been well characterized by increased in LV chamber dimensions, wall thickness, and mass in individuals who participate in EET (Baggish, Yared, Wang, Weiner, Hutter, Picard, & Wood, 2008). Baggish et al. go on to state that several reports demonstrate that EET results in enhanced LV diastolic function. EET has also been shown to cause eccentric LV hypertrophy and improved cardiac compliance in previous male bed rest models (Dorfman, Levine, Tillery, Peshock, Hastings, Schneider, Macias, Biolo, & Hargens, 2007). It has also been shown to

improve CVD risk factors such as hypertension, cholesterol levels, and resting and active heart rate (HR), as well as reduce manifestation of CAD by increasing coronary blood flow by increasing the diameter of the coronary arteries (Haskell, Sims, Myll, Bortz, Frederick, St. Goar, & Alderman, 1993). Symptoms of CHF have also been found to be improved as a result of regular exercise and endurance exercise training. CHF is often characterized by a reduced ability to perform aerobic exercise and tends to cause early fatigue, but endurance exercise training has been found to improve endothelial function and coronary perfusion, decrease peripheral resistance, and induce cardiac and skeletal muscle cell remodeling, leading to increased oxygen uptake, substrate oxidation, and resistance to fatigue in patients with CHF (Ventura-Clapier, Mattauer, & Bigar, 2006). Finally, according to Iwasaki et al. (2003) endurance training can also decrease CV mortality, sudden cardiac death, and even reduce the possibility of recurrent MI.

Despite the significant findings from various studies that demonstrate the CV benefits that exercise can produce in both healthy individuals and those with high CVD risk or CAD and CHF, it remains unclear whether intensity or duration of exercise is correlated with greater CV benefits. Thus, the purpose of this review of literature is to determine whether high-intensity exercise or endurance-type exercise (i.e., intensity vs. duration) produces greater CV adaptations in both healthy individuals and those suffering from a CVD.

Chapter II

REVIEW OF LITERATURE

High-Intensity Exercise Training

It is well known that engaging in regular physical activity, or exercise, is associated with many health benefits. Exercise, specifically, has been known to prevent occurrences of cardiac events; reduce the incidence of stroke, hypertension, type 2 diabetes mellitus, colon and breast cancers, obesity, depression, and anxiety, and delay mortality (Armstrong, L., Balady, G.J., Berry, M.J., Davis, S.E., Davy, B.M., Davy, K.P, 2006). In fact, in recent years there has been a growing consensus that exercise has beneficial effects in patients with CVD, even for those with severely impaired cardiac function (Wisloff, Stoylen, Loennechen, Bruvold, Rognmo, Haram, et al., 2007). Recent clinical and epidemiological studies however, suggest that beneficial effects of regular physical exercise may depend on intensity or amount of work performed during training (Kemi, Haram, Loennechen, Osnes, Skomedal, Wisloff, & Ellingsen, 2005), and according to Wisloff et al. (2009) mode, frequency, duration, and intensity are essential for the extent of the effects of exercise training.

Many studies suggest that moderate-intensity exercise is sufficient to reduce the risk of CVD and the CDC and American College of Sports Medicine recommend that adults engage in at least 30 minutes of moderate physical activity most days and preferably on all days (CDC, 2007). However, according to Wisloff et al. (2009) there are some indications that middle-aged men need vigorous exercise to achieve protection. To support this notion Wisloff et al. found evidence from other clinical studies that suggests high-intensity exercise induces greater aerobic and CV adaptations in comparison to low and moderate-intensity exercise, and that a link exists between high-intensity exercise and CV adaptations. In a separate clinical study by Wisloff et al.

(2007) the authors state that several lines of evidence suggest greater aerobic and CV adaptations after high-intensity exercise than with low and moderate levels in patients with CAD, CHF, or left ventricular (LV) dysfunction function and in healthy subjects. In fact, Wisloff et al. go on to state that aerobic interval training (AIT) involving 90% of VO_{2peak} has been shown to rescue impaired cardiomyocyte contractility attenuate myocardial hypertrophy, and reduce myocardial expression of atrial natriuretic peptide in a rat model of postinfarction heart failure.

In several studies improvements in Vo_2max and VO_{2peak} were found to be intensity dependent. One study reviewed by Wisloff et al. (2009) found that high-intensity aerobic interval training at 90%-95% of maximal heart rate increased Vo_2max by 18% and LV mass by 12% and increased LV contractility during exercise by 13% in previously untrained female subjects, while in male subjects improvements in Vo_2max and stroke volume were intensity dependent, with the highest response in those who trained with the highest exercise intensity (90%-95% of HR_{max}) when compared with the effect of performing at lower exercise intensities but longer duration, as well as moderate-intensity training. Wisloff et al. also performed their own clinical study in which the results showed that Vo_{2peak} increased more with high-intensity interval training than moderate continuous training at 70% of peak heart rate (46% vs. 14%). In a separate study done by Wisloff et al. (2007), after 12 weeks of training, Vo_{2peak} increased 46% and 14% in the AIT and MCT (moderate continuous training) groups. The AIT group in this study also improved work economy as demonstrated by 15% reduced oxygen cost, and 8-bpm lower heart rate, and 59% lower blood lactate at a given submaximal walking speed. Kemi et al. (2005) found in their study that Vo_{2max} increased by 71% in the high aerobic training group and 28% in the moderate training group, whereas maximal aerobic running velocity increased by 112% and 38% in the high (HIGH) and moderate (MOD) trained groups. However in a different

study comparing the effects of sprint interval training (SIT) and endurance training (ET) on certain CV adaptations to exercise, training increased Vo_{2peak}, but there were no differences found between groups (Rakobowchuk, Tanguay, Burgomaster, Howarth, Gibala, & MacDonald, 2008). Rakobowchuk et al. also found that training reduced steady-state exercising HR and improved Wingate peak power but with no differences found between the SIT and ET groups. However, the increases in Vo_{2peak} of ~10% in this study show the effectiveness of both ET and SIT training. The results of the study by Duscha et al. (2005), comparing the effects of exercise training amount and intensity on peak oxygen consumption and cardiovascular benefits, showed that absolute and relative peak Vo_2 were significantly improved in all the training groups in this study. However, the significant difference in values of absolute and relative peak Vo_2 between the different training groups in this study revealed that improvements were greater in the low-amount, high-intensity (LAHI) and high-amount, high-intensity (HAHI) groups, with the HAHI group improvements being greater than the low-amount, moderate-intensity (LAMI) and LAHI groups. O'Donovan et al. (2005) also found similar results in their study in which after the 24 weeks clinical trial, Vo_2max increased by 0.38 ± 0.14 l/min in the moderate-intensity group and by 0.55 ± 0.27 l/min in the high-intensity group, and when expressed relative to body weight, Vo_2max increased by 4.85 ± 2.10 $ml \cdot kg^{-1} \cdot min^{-1}$ in the moderate-intensity group and by 7.14 ± 3.74 $ml \cdot kg^{-1} \cdot min^{-1}$ in the high-intensity group, which shows that Vo_2max responds differently to moderate- and high-intensity exercise. Finally, in a study performed on cancer patients undergoing chemotherapy, the results of a multimodal high-intensity exercise intervention were found to reduce physical fatigue, and significantly improve physiological outcomes such as aerobic capacity and muscular strength in the cancer patients who were the subjects of this study (Adamsen, Quist, Andersen, Moller, Herrstedt, Kronborg et al., 2009). These improvements in

the patients' self-reported vitality and physical functioning, according to Adamsen et al., were probably attributable to the high intensity component of the training program in this trial, since a connection has been found to exist between high intensity training and vitality in healthy athletes. After reviewing the results from several studies, it appears that a link exists between Vo_2max and exercise intensity because Vo_2max has been shown to improve more profoundly when using high-intensity aerobic exercise training in comparison to low- or moderate-intensity training.

High-intensity aerobic training, in comparison to moderate-intensity continuous exercise or endurance training has also been found to more greatly improve cardiomyocyte hypertrophy, contractility, and calcium (Ca^{2+}) handling. Wisloff et al. (2009) and several other studies found that high-intensity aerobic training improves cardiomyocyte contraction by increasing the extent and the rates with which it shortens during systole and relaxes during diastole and by improving its ability to generate force, independent of neurohormonal influences. The degree of this improvement appears to depend on exercise intensity. According to Wisloff et al. the effects of high-intensity aerobic exercise training on cardiomyocyte contractility are twice that of moderate exercise intensity. They found that regular high-intensity aerobic exercise at 85%-90% of Vo_2max has been shown to improve the maximal extent of shortening in unloaded cardiomyocytes during electrical field stimulation by 40%-50%, whereas contraction and relaxation rates improved by 20%-40%, and the maximal power output in the cardiomyocyte increased by 60% after exercise training. Kemi et al. (2005) found similar results in their study in which myocyte contractile function during electrical stimulation at physiological frequencies improved about twice as much in HIGH as in MOD training. Kemi et al. also found that cell

fractional shortening increased by 45% in HIGH compared to sedentary, and by 26% when compared to MOD, but only 23% in MOD.

High-intensity aerobic exercise not only improves cardiomyocyte contractile functioning, it has also been found to improve cardiomyocyte Ca^{2+} handling. According to Wisloff et al (2009), the cardiomyocyte Ca^{2+} handling process controls cardiomyocyte contractility, and several aspects of it have been found to be susceptible to change by exercise training. Furthermore, they go on to point out that the "similar" changes of Ca^{2+} transients and contraction-relaxation velocities suggest an interdependent relationship, indicating that the changes in rate of Ca^{2+} cycling are associated with the changes in contraction-relaxation rates of the cardiomyocyte after exercise training and detraining. In the study by Kemi et al. (2005) from the conditioning induced parallel reductions in time-course of cell shortening and Ca^{2+} transient, both during contraction and relaxation, HIGH decreased time to 50% and peak contraction by 35% and 43%, while MOD decreased time to peak contraction 39%, and ~20% difference occurred between HIGH and MOD. According to Wisloff et al. exercise training results in a faster systolic rise and faster diastolic decay of the Ca^{2+} transient, with magnitude of contractility corresponding to the extent of cell shortening and relaxation rates. Furthermore, Wisloff et al. found that exercise training doesn't necessarily seem to increase the Ca^{2+} transient amplitude, but the shorter duration of the Ca^{2+} transient after exercise training implies that more Ca^{2+} is available for activating a synchronous contraction of the whole cell at any given time during the systole, compared with the Ca^{2+} transient in cardiomyocytes from sedentary animals that in comparison is lower and lasts longer. According to several studies, high-intensity exercise training improves cardiomyocyte contraction and Ca^{2+} handling in healthy subjects; it can also improve these variables in subjects who have experienced MI and heart failure.

Although the contractile function of the cardiomyocyte as well as the whole heart mostly depends on excitation, Ca^{2+} induced Ca^{2+} release, and contraction of myofilaments, according to Wisloff et al. (2009) this isn't the only contributing factor. Wisloff et al. believe that a balanced growth of the cardiomyocyte and the whole heart, as well as chamber dilation, also contributes to increase the contractile pump function. In the study by Kemi et al. (2005) exercise induced intensity-dependent cardiomyocyte hypertrophy occurred. The results of Kemi et al.'s study showed that isolated left ventricular cardiomyocytes were 14% longer in HIGH, versus 5% in MOD, and the width and volume increased significantly in HIGH, whereas trends occurred in MOD. Wisloff et al. had similar results from their study in which high-intensity exercise training at 85%-90% of VO_{2max} was found to induce a hypertrophic response in the cardiomyocytes, which was found to be observable already after a few weeks and reach a plateau after approximately 2 months. Wisloff et al. came to the conclusion that the magnitude of cardiomyocyte hypertrophy depends on the intensity of the exercise because high-intensity exercise training induced a substantially larger response than moderate intensity in their study: 14% versus 5% longer cells.

High-intensity interval training has also been found to reverse LV remodeling. In the study by Wisloff et al. (2007) 12 weeks of AIT induced reverse LV remodeling. As a result of the 12 week AIT in this study LV diastolic and systolic diameters decreased by 12% and 15%, estimated LV end-diastolic and end-systolic volumes by 18% and 25%, and pro brain natriuretic peptide (proBNP), a marker of hypertrophy and severity of heart failure, declined by 40%. Wisloff et al. (2009) found similar results in their other clinical human study in which high-intensity interval training was associated with reverse LV remodeling.

LV systolic and diastolic functioning was also improved as a result of high-intensity interval training. Results of the Wisloff et al. (2007) study showed that AIT was highly effective in improving systolic function in which the LV ejection fraction increased by 10 percentage points, which corresponds to 25% in relative terms, the systolic mitral annulus excursion increased by 30%, and stroke volume also increased by 17%. Peak systolic mitral annulus velocity (Ea) increased by 22%, and peak ejection velocity was increased by 19%. In the same study Wisloff et al. found that AIT, but not MCT, improved Ea by 49% and the E/A ratio by 15%. The ratio of transmitral flow velocity (E) versus Ea, according to Wisloff et al., has been proposed as the best indicator to assess LV filling pressure. AIT and MCT in this study also reduced E/Ea by 26% and 15%, and isovolumic relaxation time increased by 22% in AIT.

According to Rakobowchuk et al. (2008) traditional moderate-intensity exercise training has been known to improve central artery distensibility in populations with impaired vasculature, and most training studies showing improvements of artery distensibility have noted changes in the central arterial tree. Also, according to Rakobowchuk et al., similar to artery distensibility, exercise training is an effective stimulus that improves brachial flow-mediated dilation and endothelial function in young healthy and diseased populations. In the study by Rakobowchuk et al. artery distensibility was increased after training in both groups and the change in popliteal cross-sectional area within each heart cycle increased after training both groups. This study also showed that both low-volume SIT and traditional high-volume ET improve absolute popliteal artery flow-mediated dilation (FMD) and endothelial function to the same degree in young, healthy men and women. Peripheral artery distensibility and endothelial function, according to Rakobowchuk et al., are modified effectively with either traditional ET or high-intensity SIT.

High-intensity aerobic training has also been found to reduce several other CVD risk factors. One of the risk factors it has been found to affect is cholesterol and lipoprotein levels. In the study by O'Donovan et al. (2005), after 24 weeks of training, changes in total cholesterol (TC), LDL-C, and non-HDL were significantly different or lower in the high-intensity group compared with the control and moderate-intensity groups. The reduction in TC enjoyed by the high-intensity group in this study, according to O'Donovan et al., is sufficient to decrease CHD incidence by 54%. High-intensity exercise has also been associated with improved weight, BMI, fat mass, fat-free mass, and waist girth. O'Donovan et al. also found in their study that waist girth and percent body fat significantly decreased after 24 weeks in the high-intensity group. Duscha et al. (2005) found similar results in their study in which body mass was reduced in the LAHI and HAHI groups but remained unchanged in the LAMI group, and although all exercise groups lost an average of 1.3 kg following exercise, this body mass loss was not different between the three exercise groups. Heart rate (HR) recovery has also been shown to be improved. Duscha et al. report that HR recovery at one minute was > 13 beats/min vs. peak HR in all groups, which indicates a low risk for a sudden cardiac event in this population. HR recovery at one minute in this study improved in all groups but only reached significance in the LAMI and HAHI groups.

Finally, improved endothelial function was also observed as a result of high-intensity interval training. In Wisloff et al.'s (2007) study a close relationship between improved aerobic capacity and improved FMD and a greater improvement in FMD by AIT than by MCT was observed. Wisloff et al. also observed that AIT patients increased their antioxidative status by 15%, which indicates a lower level of reactive oxygen species and higher NO production. Also, enhanced FMD as a result of AIT in this study was found to be correlated with increased total

antioxidant status in blood plasma, and AIT also reduced plasma levels of oxidized low-density lipoprotein cholesterol (LDL) by 9%.

Similar CV effects of high-intensity exercise have also been found in trials done on rats. For example, Wisloff et al. (2009) found similar results in rats, compared to human subjects, in which the effect of regular high-intensity interval training at 85%-90% of Vo_2max amounted to about twice that of moderate exercise intensity at 65%-70% of Vo_2max. Wisloff et al. also did a separate portion of their study on rats with heart failure after MI, and they found that treadmill running induced substantial beneficial adaptations in their Vo_2max and work economy, in which Vo_2max increased on average 10% per week until it plateaued at weeks five through six, and total improvement in work economy was 16% in trained animals. High-intensity training was also found to improve cardiomyocyte shortening and rate of relaxation in rats. In their study performed on post-MI heart failure rats, Wisloff et al. found that 2 months of high-intensity exercise training at 85%-90% of Vo_2max restored fractional shortening and the rate of relaxation in cardiomyocytes to levels comparable to sedentary health controls. The restoration of the rate of relaxation with the exercise training in this study was closely associated with improved rates of Ca^{2+} handling, which regressed toward healthy levels. In the same study by Wisloff et al., exercise training reduced the levels of resting diastolic Ca^{2+}, and restored the Ca^{2+} transient amplitude. Studies on rats have also shown that exercise in general can improve survival rates of heart failure mortality and all-cause mortality. In a study done on hypertensive heart failure rats for example, chronic low-intensity exercise training (LIET) was found to significantly improve survival compared with sedentary animals when analyses were restricted to heart failure mortality and all-cause mortality (Chicco, McCune, Emter, Sparagna, Rees, Bolden et al., 2008). In the same study by Chicco et al., LIET induced mild transient effects on blood pressure and

echocardiographic parameters compared with sedentary animals, and LIET significantly attenuated the increase in systolic blood pressure observed in sedentary animals between 16 and 20 months of age, indicating that training elicited slight antihypertensive effects not observed previously in this model. Training in this study also prevented the decline in blood pressure associated with end-stage heart failure between 20 and 25 months, and led to a slight attenuation of systolic dysfunction between 23 and 25 months of age in these animals.

The results of the studies mentioned above demonstrate that high-intensity exercise training can be critical for improving cardiac function and that it can produce larger beneficial adaptations in the CV system than moderate-intensity continuous exercise or endurance training. Vo_2max can be improved in both healthy individuals and those who may suffer from chronic heart failure or impaired CV function using high-intensity exercise. According to the results of the previously mentioned studies, high-intensity training may also play a significant role in reversing LV remodeling, especially in post-MI patients, improving aerobic capacity, and even improving overall quality of life in healthy individuals and patients with postinfarction heart failure or even cancer patients undergoing chemotherapy treatment. These findings, according to Wisloff et al. (2007) may be important implications for exercise training programs for individuals who may be undergoing cardiac rehabilitation because of the added CV benefits of programs that include high-intensity exercise compared to programs that incorporate low to moderate exercise intensities. The rationale for high-intensity interval training, according to Wisloff et al., is that it allows for rest periods that make it possible for patients with HF to complete short work periods at a higher intensity (which challenges the heart's pumping ability) than would be possible during continuous exercise.

Long-Duration, Endurance Training

Regular physical activity is considered to play a significant role in the prevention and management of hypertension by lowering blood pressure (BP) and reducing mortality from CVD. Regular physical activity has also been shown to reduce the risk of CAD, as well as reduce the risk of cardiac death in individuals who have not yet shown manifestations of CAD (Windecker, Allemann, Billinger, Pohl, Hutter, Orsucci, Blaga, Meier, & Seiler, 2002). Endurance training, as mentioned previously, according to Ventura-Clapier et al. (2006) has been found to improve endothelial function and coronary perfusion, decrease peripheral resistance, induce cardiac and skeletal muscle cell remodeling, leading to increased oxygen uptake, substrate oxidation, and resistance to fatigue in patients with CHF. Baggish et al. (2008) have also found that there is a LV structural adaptation in response to aerobic EET characterized by increased LV chamber dimensions, wall thickness, and mass. It has also been found that relatively short-term moderate- to high-intensity endurance exercise training in older sedentary men can induce cardiac adaptations characterized by a modest volume-overload LV hypertrophy and improvement in LV systolic function at peak exercise (Seals, Hagberg, Spina, Rogers, Schechtman, & Ehsani, 1994). However, despite these findings, according to Iwasaki et al. (2003) the "dose" of exercise required to achieve and optimize these responses remains uncertain. Therefore, in this section, we will be looking at the effects of endurance training on different CV adaptations and CVD risk factors.

It is well known that regular exercise can significantly improve the hemodynamics of the heart, one of these factors being reduced BP. In one study, the average net changes in resting blood pressure ranged from -20.0 to +9.0 mmHg for systolic BP (SBP) and from -11.0 to + 11.3 mmHg for diastolic BP (DBP), and the overall weighted net effect on BP was -3.0 mmHg

(Cornelissen & Fagard, 2005). In other studies reviewed by Cornelissen & Fagard that reported on blood lipids, the net training-induced changes in BP as a result of endurance training were -1.4 mmHg for SBP and -1.5 mmHg for DBP. They also found in 18 other study groups in this study that training reduced mean BP by 4.3% or 4.7 mmHg, systemic vascular resistance (SVR) decreased significantly by 7.1%, HR decreased by 9.3% or 6.8 bpm, and SV increased by 15.5%. In the long-term longitudinal study of progressive endurance training on the dose-response relationship between intensity and amount of exercise training and regulation of HR and BP done by Iwasaki et al. (2003) it was found that SBP and DBP decreased after 3 months of training, and remained unchanged up to 9 mo. Endurance training in the Iwasaki et al. study was also found to significantly reduce HR, and increase stroke volume at 3, 6, 9, and 12 months of training. Cornelissen & Fagard found in their study that resting HR decreased by 4.8 bpm. In the study by Baggish et al. (2008), resting HR (60 $\pm$ 8 vs. 49 $\pm$ 7 beats/min) and diastolic BP (58 $\pm$ 6 vs. 49 $\pm$ 6 mmHg) were reduced after 90 days of EET. In another study performed on subjects who ran in a 46 kilometer race at altitude, the time course of the changes in autonomic control of the heart and arterial vessels in response to this prolonged exercise at altitude was studied and it was found that thirty minutes after the race the BP was lower than at baseline (a.k.a. before the race), and no significant changes in autonomic modulation were observed in the supine position and after sympathetic activity by orthostasis or slow neck suction stimulation, indicating that the effect of sympathetic modulation of vessels was, at least partially preserved after the race (Bernardi, Passino, Robergs, & Appenzeller, 1997).

EET has also been found to improve other hemodynamic factors such CO and TPR. According to Iwasaki et al. cardiac output (CO) increased, and total peripheral resistance (TPR) decreased significantly at 3, 6, and 9 months of training.

In the study by Seals et al. (1994), peak exercise CO was 16 percent higher in the endurance athletes than in the sedentary older men in the study, and this difference became more striking when CO was normalized for body surface area, in which a 31 percent difference was found, or fat free mass, which caused a 35 percent difference. TPR in the study by Seals et al. also declined a greater extent in the older endurance athletes than in the sedentary controls, and vasodilatory reserve was significantly greater in the EET group than in the sedentary older men.

Just as in high-intensity exercise, endurance training was also shown to improve Vo_2max and peak Vo_2, as well as counteract the age-related decrease in Vo_2max and thus partially prevent the progressive decline in Vo_2max in older subjects. All subjects in the Iwasaki et al. (2003) study completed a marathon, triathlon, or 100-mile endurance cycling race as the ultimate performance goal of the training program, and as a result, Vo_2max increased at 3, 6, 9, and 12 months compared with baseline data. In the Cornelissen & Fagard (2005) study Vo_2max increased by four $mL/min^{-1} \cdot kg^{-1}$. The results of the bicycle spiroergometry tests in the Windecker et al. (2002) showed that Vo_2max normalized for body weight, maximum ergometric workload, and maximum workload per body weight increased significantly during the exercise period. In their study on older EET adult males, Seals et al. (1994) found that Vo_2max was considerably higher in the master athletes than in the older sedentary men, and peak Vo_2 during supine cycle ergometer exercise was 2.36 ± 0.14 L/min and 2.03 ± 0.06 L/min in the master athletes and sedentary men. Finally, in a clinical study done on older coronary patients, results of this study revealed that 3 months of endurance aerobic conditioning increased peak Vo_2 by 16 percent, and at 12 months peak Vo_2 increased by 20 percent (Ades, Waldmann, Meyer, Brown, Poehlman, Pendlebury et al., 1996). Men and women in the study by Ades et al. were also found

to similarly improve their peak Vo_2 with conditioning at 3 months, and an increase of 17 percent in men and 16 percent in women.

EET has also been found to improve LV structural measurements and LV systolic function. In the study by Baggish et al. (2008), LV end-diastolic major dimension ($\Delta = 2.8 \pm 1.2$ mm) and end-systolic major dimension ($\Delta = 2.2 \pm 1.6$ mm) were increased significantly after EET. In a similar fashion in this study by Baggish et al., LV end-diastolic volume (EDV) ($\Delta = 15.6 \pm 8.6$ ml), end-systolic volume (ESV) ($\Delta = 10.2 \pm 6.0$ ml), stroke volume (SV) ($\Delta = 6.5 \pm 4.9$ ml), and mass ($\Delta = 29 \pm 7$ g) were larger at the conclusion of the study period. Similarly, in the study by Seals et al. (1994), a 90-day period of training led to LV hypertrophy and dilation with a significant enhancement of systolic function. In the study on the effects of bed rest on cardiac atrophy in women by Dorfman et al. (2007), when endurance-type exercise was performed while the subjects in this study were confined to bed rest, there was not a significant reduction in LV volume, and there was a significant increase in LV mass and adjusted LV mass. To go along with this, Dorfman et al. found that when exercise was performed when subjects were confined to bed rest, there was not a significant reduction in RV mass as well as adjusted RV mass. LV systolic function was also found to be enhanced by EET. In the study by Seals et al., several improvements in LV systolic function were found. First, when normalized for body surface area, resting SV was significantly higher in the master athletes (55 ± 1.0 ml/min/m^2 vs. 45 ± 1.5 ml/min/$m^{2)}$ than in the older sedentary men, and peak exercise SV was also considerably larger in the master athletes than the sedentary men. It was also found that LV exercise reserve, from rest to exercise, was higher in the master athletes compared to the sedentary subjects, and at comparable increments of EDV during submaximal exercise, the increases in ejection fraction (EF) were larger in the master athletes. LVEDV at rest was also

found to be 15 percent larger in the master athletes of the Seals et al. study, which this finding is consistent with volume-overload hypertrophy. ESV at rest was also larger in the EET subjects vs. the sedentary subjects. The final significant improvement in LV systolic function found in the Seals et al. study was that the older EET athletes had a higher fractional shortening (FS) at peak exercise and also exhibited a larger increase in FS from rest to exercise than did controls (ΔFS: 18.4 $\pm$ 2% vs. 6.7 $\pm$ 2%), and end-systolic diameter decreased to a greater extent in the EET subjects versus older sedentary subjects. Similar results were found in the study by Baggish et al. in which significant increases in LVEDV following EET were observed, which according to the authors is most likely due to the eccentric LV hypertrophy with an enhancement of diastolic function, which tends to accompany EET. Also, systolic strain, which according to Baggish et al. reflects myocardial contractility, and tissue velocity data from this study show that a significant increase in systolic function does occur despite a static LV ejection fraction among individuals engaging in EET. Furthermore, LV radial strain, longitudinal strain, and peak systolic velocity were found to have increased in all myocardial measurements in this study as a result of EET, which in turn improved LV systolic function. Finally, in the study by Ades et al. (1996), although there were no measurable increased in peak exercise CO after endurance conditioning, there was a tendency to a higher peak exercise ejection fraction, and peak exercise ejection fraction divided by peak EDV was increased after three months of conditioning, which suggests an improvement in peak LV performance.

As previously mentioned above, regular exercise can help reduce the risk of CAD and CAD mortality. Haskell et al. (1993) explain that one way habitual activity might reduce the clinical manifestations of CAD is to increase coronary blood flow by increasing the diameter of the coronary arteries. In the Windecker et al. (2002) study coronary artery cross-sectional areas

at all except two measurement sites increased significantly in response to the endurance training exercise program. In the same study Windecker et al. found that in response to intracoronary adenosine, the proximal left coronary artery calibers increased significantly after the exercise program, and endothelium-independent vasodilation using nitroglycerin showed significantly larger coronary artery calibers after compared with before exercise at the site of the left main coronary artery. In fact, the endurance program in this study was associated with bigger coronary arteries at 28 of a total 32 proximal coronary angiographic measurement sites. However, in the study Haskell et al. there were no systemic differences in the cross-sectional area of coronary arteries between the endurance runners and inactive male subjects. However, LV mass index was larger for the runners than for inactive men, and total LV (g) was slightly but not significantly larger for the runners in the study by Haskell et al. Haskell et al., however, had similar results as that of Windecker et al. once nitroglycerin was administered to the test subjects. The cross-sectional area of all artery segments in both groups of this study increased, with the average magnitude of increase being 2.2 fold greater for the runners than for the inactive men. Windecker et al. also found similar results in left ventricular mass in their study in which end-diastolic ventricular septal and posterior wall thickness of the left ventricle and left ventricular mass as well as mass index increased significantly during the endurance exercise training program.

Exercise training prior to myocardial infarction can have protective effects in which it can reduce infarct size, ventricular enlargement, improve remodeling, increase systolic function, and improve expression of cytochrome oxidase subunits, ventricular atrial natruiretic peptide, sarcoplasmic reticulum calcium ATPase and fatty-acid binding protein according to Ventura-Clapier et al. (2007). Endurance training, according to Ventura-Clapier et al. can positively affect

cardiac metabolism in heart failure, skeletal muscle metabolism in heart failure, and skeletal muscle oxidative capacity and energy transfer. Ventura-Clapier et al. found in their review that endurance training has been found to improve cardiac energy metabolism in patients with chronic heart failure. According to this review exercise improves coronary blood flow and endothelium-dependent vasodilatation, and increases resistance vessel sensitivity to the metabolic mediator adenosine, which improves oxygen and substrate supply to the failing heart in individuals with CAD and pacing induced heart failure. Ventura-Clapier et al. go on to point out that VO_{2peak} has been consistently found to increase as a result of endurance exercise training, along with improvements in global indices of muscle metabolism like lesser phosphocreatine (PCr) decrease, lower Pi/PCr ratio and higher PCr resynthesis rates for a given workload after training. Finally, in their review Ventura-Clapier et al. found that endurance training in chronic heart failure patients can reduce PCr depletion and adenosine diphosphate (ADP) increase during exercise, enhance the rate of PCr resynthesis after exercise indicating a substantial improvement of skeletal muscle oxidative capacity, and increase mitochondrial size, which causes an increased muscle oxidative capacity in skeletal muscles, resulting in increased exercise tolerance.

The final significant effect of endurance training found in the literature was that it also has a significant effect on weight loss, percent body fat and abdominal adiposity, as well as cholesterol levels. Windecker et al. (2002) found that body weight and surface area decreased significantly during the endurance exercise period in their study. Endurance training decreased weight by 1.2 kg, percent body fat by 1.4%, an average decreased waist circumference of 2.8 cm, and reduced the waist-to-hip ratio by 0.0092 in the Cornelissen & Fagard (2005) study. In this same study HDL cholesterol showed a significant increase, whereas glucose, insulin, and the

HOMA index decreased. Similarly, Ades et al. (1996) found in their study of older coronary patients that although body weight was unaltered, estimated fat-free mass increased from 52.4 ± 8 to 53.6 ± 8 kg, and fat mass decreased from 24.5 ± 7 to 22.5 ± 9 kg in a subset of 10 intervention patients over three months.

Endurance training is able to produce several CV benefits and adaptations such as improved Vo_2max and Vo_{2peak}, reduced BP, increased SV, increased diameter of coronary arteries, and improved cardiac skeletal muscle metabolism and oxidative capacity and energy transfer in patients with CHF. In order to produce these effects, however, the results of the Iwasaki et al. (2003) study suggest that moderate amounts of exercise training (from 80-100 kcal/10min for 180-200 min/wk) are sufficient enough to achieve substantial changes in BP and dynamic regulation of HR. The results of this study go on to point out that more prolonged and possibly intense training does not necessarily lead to greater enhancement of the CV adaptations due to exercise, and therefore, it may not provide an added protective benefit against CV mortality. Overall, moderate or high-intensity exercise should be recommended for both healthy individuals and patients undergoing cardiac rehabilitation. Although endurance training has several CV benefits, it may not ideal for those suffering from CAD, CVD, or any other CV related illness to undergo prolonged bouts of exercise due to added stress on cardiac muscles from the prolonged activity, as well as decreased compliance by patients with CVD.

Chapter III

SUMMARY

Exercise and physical activity help prevent or reduce all-cause mortality rates in older and younger men and women, and lowers the risk of CHD, hypertension, cancer, obesity, and type II diabetes as well as reduce the severity of existing heart disease, according to Haennel & Lemire (2002). Although physical activity is recommended as an important component of a healthy lifestyle, the effects of intensity, duration, and frequency of physical activity required to produce healthy changes in the CV system, reduce CVD risk factors, and protect against CHD and stroke is unclear, and according to Wisloff et al. (2009) mode, frequency, duration, and intensity are essential factors to know the extent of the effects of exercise training.

High-intensity exercise has been found to be effective in producing beneficial adaptations in the CV system. The results of several studies have demonstrated that high-intensity training can be critical for improving cardiac function and that it can even produce larger beneficial adaptations in the CV system than that of endurance training or moderate-intensity exercise. In fact, in several studies the results of high-intensity training produced nearly twice the amount of CV benefits than that of endurance and moderate-intensity training. O'Donovan et al. (2005) state that low cardiorespiratory fitness is a powerful predictor of CHD mortality, and concluded from the results of their study that a high-intensity exercise intervention is more effective in improving cardiorespiratory fitness than a moderate-intensity intervention of equal energy cost. Wisloff et al. (2009) found in their clinical human study that Vo_{2peak} increased more with high-intensity interval training than moderate-continuous training at 70% of peak heart rate (46% vs. 14%). High-intensity exercise, according to Wisloff et al. has also been found to improve cardiomyocyte contractile functioning, Ca^{2+} handling, and produces growth of the cardiomyocyte

and the whole heart, as well as chamber dilation, which contributes to increasing the contractile pump function. High-intensity training may also play a significant role in reversing LV remodeling, especially in post-MI patients, and improving aerobic capacity.

Endurance training has also been shown to produce several well-established CV benefits. Endurance training, according to Ventura-Clapier et al. (2007), can improve endothelial function and coronary perfusion, decrease peripheral resistance, induce cardiac and skeletal muscle cell remodeling, and can also reduce the risk of CAD. After reviewing several studies on the effects of endurance training on CV adaptations I found that it can improve Vo_2max and Vo_{2peak}, reduce BP, increase SV, increase diameter of coronary arteries, and improve cardiac skeletal muscle metabolism and oxidative capacity and energy transfer in patients with chronic heart failure. Baggish et al. (2008) concluded from the results of their study, that 90 days of EET led to concomitant LV dilation and hypertrophy with the enhancement in LV systolic function, as reflected by increased strain and tissue velocities. Seals et al. (1994) found similar results in their study on older endurance trained men, in which their findings suggest that volume-overload LV hypertrophy with moderate cardiac enlargement in older endurance trained athletes is a benign and physiological phenomenon because it is associated with enhanced LV function during exercise and excellent prognosis. The results of the study by Seals et al. also indicate that larger SV and CO play a significant role in maintaining a higher peak Vo_2 and Vo_2max in older endurance athletes. The levels of improvement, however, were found to have the same or less of an impact than that produced by high-intensity training. As previously stated above, Iwasaki et al. (2003) suggest that moderate amounts of exercise training (from 80-100 kcal/10min for 180-200 min/wk) are sufficient enough to achieve substantial changes in BP and dynamic regulation of HR, and they go on to point out that more prolonged training does not necessarily lead to

greater enhancement of the CV adaptations due to exercise, and therefore, it may not provide an added protective benefit against CV mortality. Overall, moderate or high-intensity exercise, instead of endurance-type exercise, should be recommended for both healthy individuals and patients undergoing cardiac rehabilitation. Although endurance training has several CV benefits, it may not be ideal for those suffering from CAD, CVD, or any other CV related illness to undergo prolonged bouts of exercise due to possible added stress on cardiac muscle, as well as decreased adherence to these types of programs by patients with these conditions.

Although high-intensity interval training and endurance training have been shown to produce well-established CV benefits, it appears from the reviewed literature that higher intensity exercise produces the same, if not greater CV adaptations. In fact, several of the reviewed studies showed that high-intensity training produced twice the effect as that of endurance training. Therefore, it is important to consider incorporating high-intensity interval exercise into any training program because of the added CV benefits it produces.

Chapter IV

IMPLICATIONS AND RECOMMENDATIONS

Many studies have proven that exercise and physical activity help prevent or reduce all-cause mortality rates, lower the risk of hypertension, CAD, CHD, stroke, and risk of recurrent CV events. These well-established benefits emphasize the importance of incorporating exercise into our daily lives. According to Wisloff et al. (2009) sport science has established that mode, frequency, duration, and intensity are essential for the extent of the effects of exercise training, and therefore it is important to establish which of these factors most prominently produces CV benefits. Despite all the research that exists on exercise and its benefits, it remains a bit unclear as to whether high-intensity or long-duration, endurance-type exercise produces greater CV benefits. A majority of the research comparing different types of exercise in producing CV benefits has compared moderate-intensity vs. high-intensity or moderate-continuous vs. endurance training, while little research comparing high-intensity vs. long-duration exercise exists. Because of this fact, additional research comparing the effects of intensity vs. duration of exercise must be conducted to determine exactly which produces greater CV adaptations and the magnitude of these adaptations.

The research on high-intensity exercise that does exist has shown that high-intensity exercise is extremely effective in producing CV adaptations. Many studies, like that of Iwasaki et al. (2003), suggest that moderate-intensity exercise is sufficient to reduce the risk of CVD; however, according to Wisloff et al. (2007) there are some indications that middle-aged men need vigorous exercise to achieve protection. Other clinical studies have also suggested that high-intensity exercise induces greater aerobic and CV adaptations in comparison to low-to-moderate intensity exercise. High-intensity exercise has been shown to improve Vo_2max and

Vo_{2peak} in both healthy individuals and those who may suffer from CHF or impaired CV function. According to O'Donovan et al. (2005), low cardiorespiratory fitness is a powerful predictor of CHD mortality, and concluded from the results of their study that a high-intensity exercise intervention is more effective in improving cardiorespiratory fitness than a moderate-intensity intervention of equal energy cost. In their clinical human study Wisloff et al. (2009) found that Vo_{2peak} increased more with high-intensity interval training than moderate-continuous training at 70% of peak heart rate (46% vs. 14%). High-intensity exercise, according to Wisloff et al. has also been found to improve cardiomyocyte contractile functioning, Ca^{2+} handling, and produces growth of the cardiomyocyte and the whole heart, as well as chamber dilation, and may also play a significant role in reversing LV remodeling, especially in post-MI patients, and improving aerobic capacity.

Given the pronounced cardiac benefits found in these studies, according to Wisloff et al. (2007) high-intensity exercise may be an important success factor when designing effective exercise programs for those who may be undergoing cardiac rehabilitation programs because high-intensity exercise may produce more significant CV benefits and improve cardiac function more than that of low-to-moderate exercise. Wisloff et al. also rationalize that high-intensity interval training is ideal for patients who are post-MI, have CVD, CAD, or CHF because this type of exercise training allows for rest periods that make it possible for patients with heart failure to complete short work periods at a higher intensity (which challenges the heart's pumping ability) than would be possible during continuous, prolonged exercise. In concordance with this, results from the study by Kemi et al. (2005) indicate that the beneficial effects of regular exercise result from several mechanisms that may depend differentially on intensity; those associated with myocardial function seem to require high-intensity training over several

weeks to be fully active, whereas endothelium-dependent effects may plateau at lower intensity, depending on gender, age, function at baseline and other background variables. On the other hand, according to Wisloff et al. (2009), despite the fact that exercise at high relative intensity seems to induce larger beneficial adaptation in the CV system, we do not know whether this type of training is a safe method to use in patient cohorts and whether it affects complication rates in patients more favorably than exercise at low-to-moderate. Chicco et al. (2008), go on to support the recommendations by Wisloff et al. by pointing out that despite the evidence that high-intensity exercise generally elicits greater cellular adaptations to the myocardium and may provide superior short-term benefits to HF patients than low- or moderate-intensity training, care should be taken before assuming that these effects will result in, or are obligatory for, the favorable effects of exercise on the long-term prognosis in hypertensive heart disease. In conclusion, further research must be done to determine the magnitude of the CV benefits produced by high-intensity vs. low-to-moderate or endurance-type exercise, and the effects it might have on a larger cohort of patients with CVD, CAD, and other chronic CV diseases. However, it is my belief that high-intensity interval training should still be used in rehabilitation programs for patients who are post-MI, or suffer from CVD, CAD, or CHF because of the established benefits of this type of training.

Endurance exercise training has also been shown to produce several prominent cardiac adaptations. As previously mentioned, according to Ventura-Clapier et al. (2006) endurance exercise has been found to improve endothelial function and coronary perfusion, decrease peripheral resistance, induce cardiac and skeletal muscle cell remodeling, which leads to increased oxygen uptake, substrate oxidation, and resistance to fatigue in patients with CHF. Endurance training, according to Ventura-Clapier et al., induces an improvement of muscle

resistance to fatigue and justifies that endurance training programs could be considered as countermeasures of muscle weakness in HF patients because of its ability to reverse the deleterious effects of HF on skeletal muscle energy metabolism, even though this is less clear for cardiac muscle. However, although studies have shown that endurance exercise is an effective means of producing beneficial CV adaptations in patients with CVD, CAD, and CHF, several of these studies state that endurance training may not be an ideal exercise regimen for these patient cohorts. The results of the Iwasaki et al. (2003) study suggest that moderate exercise training for three months is sufficient to achieve a clinically meaningful reduction in BP and in mortality from CVD, and substantial changes in dynamic regulation of HR. Endurance training programs are more difficult for patients to comply with because of the prolonged duration of the exercise sessions, and the results of these programs were not as pronounced as those found in high-intensity exercise regimens.

Given the CV adaptations produced from high-intensity and endurance training it is important to emphasize the importance of exercise to patients with CVD, hypertension, high cholesterol, type II diabetes, and other chronic diseases. Given the results found in multiple studies, high-intensity interval exercise should be emphasized more prominently in exercise programs for patients suffering from CVD, CHD, stroke, and other CV diseases because of the more prominent adaptations that occur, and the patients' ability to withstand high-intensity interval training.

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