ABSTRACT

Cardiovascular disease continues to become increasingly prevalent and despite ongoing development into pharmacological therapy, morbidity and mortality associated with heart disease remains high. The purpose of this review is to revisit current theories regarding the beneficial effects of both aerobic and static exercise training on the cardiovascular system, with a view to optimize individual risk factors thereby improving overall cardiovascular risk. A PubMed literature search was conducted using the key phrases, 'exercise, cardiovascular disease and atherosclerosis.' A total of 3 meta-analyses and a further 11 individual research articles were cited. Data regarding both positive and negative associations with individual cardiovascular risk factors were reviewed and discussed. Conclusion: Data continues to show a positive correlation between at least 30 minutes of both aerobic and static exercise training on cardiovascular outcomes. 30 minutes of aerobic exercise training at more than 50% \( VO_{2\text{max}} \) can improve blood lipoprotein levels, homocysteine levels, blood pressure and vascular inflammation. Static exercise training can also reduce both systolic and diastolic blood pressure in a subset of hypertensive patients.

Key Words: Disease, Heart, Risk factors
INTRODUCTION

The greatest threat to society in both the developing and developed world is cardiovascular disease. It is acknowledged that high cholesterol, high blood pressure, smoking and a sedentary lifestyle can be detrimental to health however these are only three of a far greater number of possible factors associated with cardiovascular risk. Coronary artery disease alone effects approximately 2.6 million people in the UK and is responsible for over 20% of all hospital admissions and 36% of all deaths. (5) In recent decades other cardiovascular risk factors have been identified such as elevated serum homocysteine levels, diabetes mellitus and chronic inflammatory diseases. (2, 3) This, along with the tremendous financial burden involved in the manufacture of medications makes improving modifiable risk factors through non-pharmacological therapy yet more important. Not only is exercise more cost effective than traditional pharmacological treatment, it also has the potential to be of comparable efficacy whilst maintaining a more tolerable side effect profile. The purpose of this article is to revisit the current theories explaining the pathophysiology of atherosclerosis and review both the beneficial and detrimental effects of exercise on the cardiovascular system.

DISCUSSION

Atherosclerosis is the predominant cause of coronary, cerebrovascular and peripheral vascular disease. (26, 19) The process can be seen early in children and adolescents as ‘fatty streaks’, which line the aorta and other blood vessels. (4) Three main steps are involved in the formation of atheromatous plaques; the accumulation of smooth muscle cells (SMC) and migration of inflammatory white blood cells (WBC) into the tunica intima of blood vessel walls, the proliferation of connective tissue from the increased numbers of SMCs and a buildup of lipids, usually in the form of cholesterols, within these cells. (20)

There are several risk factors associated with atherogenesis including lifestyle criteria such as low physical activity, obesity and smoking as well as metabolic diseases such as diabetes mellitus, subclinical insulin resistance and lipid dyscrasias which can be modified with sufficient pharmacological treatment. Unmodifiable risk factors include age, gender, ethnicity and familial hypercholesterolaemia. (22) Lipids play an important role in the development of cardiovascular disease. There is an increased cardiovascular risk associated with high levels of circulating plasma low density lipoproteins (LDL-Cs) and very low density lipoproteins (VLDL-Cs). SMCs take up LDL-C and form plaque associated with atherosclerosis. Triglyceride rich lipoproteins (TRLPs) have also been implicated in atherogenesis and are
involved in the multiplication of SMCs at the site of injury. Activation of peroxisome proliferator activated receptors (PPAR) upregulate the synthesis of apolipoprotein associated high density lipoproteins (HDL-Cs); apolipoprotein A-I (Apo A-I). (20) Apo A-1 protects against the formation of fatty plaque by transporting LDL-C and VLDL-C to the liver. PPAR can also reduce expression of certain genes coding for cellular adhesion, particularly important in the context of macrophages in the endothelial wall. However, once LDL-C is oxidised within a macrophage, upregulation of cellular molecules such as intracellular adhesion molecule-1 (ICAM-1) results in increased endothelial adhesion. (23)

Serum levels of LDL-C and HDL-C are considered to be one of the most important risk factors when assessing cardiovascular risk. An extensive meta-analysis conducted by Leon et al. explored whether dose dependant variabilities in aerobic exercise training (AET) could influence serum LDL-C levels. Despite including 28 randomised control trials, 52 exercise routines and a 4700 sample size, no statistically significant association could be drawn between intensity of exercise and resultant LDL-C. However, it was observed that over a 12 week period of high intensity AET HDL-C increased by 4.6% with a reduction in LDL-C by 5% and total triglyceride levels dropped by approximately 3.7%. (18) Furthermore, Halverstadt et al. enrolled 100 sedentary 50 to 75 year olds (mean age 58) and measured both serum LDL-C and VLDL-C following graded AET. Each participant trained in a variety of aerobic exercises using treadmills, bikes and ellipticals. Subjects trained for 3 sessions per week over a 24 week period. Both length and intensity varied from 20 minutes at 50% VO2max to 40 minutes at 70% VO2max. It was found that at 24 weeks the average LDL-C level had fallen significantly by 0.7mg/dL (±1.7mg/dL, P<0.001). Results were also favourable in terms of large and small VLDL-C particle concentration with both falling by 0.7nmol/L (±0.4nmol/L, P<0.001) and 1.1nmol/L (±1.7nmol/L, P<0.001) respectively. (12)

It should be noted however that changes in lipoprotein levels were only statistically significant after the addition of a body fat variable which indicates that exercise must act independent from body fat loss in this context. The findings here merely strengthen the results found by Kraus et al. who established that endurance training equivalent to a 12-20 mile jog per week (at an intensity of 65%-80% VO2max) can improve lipid profiles and cardiovascular risk with even minimal weight loss. This emphasises that reductions in plasma lipoprotein levels can occur with prolonged exercise despite low variability in baseline body fat percentage. (13)

Kodama et al. investigated the role of exercise in relation to cardioprotective HDL-C molecules. Their meta-analysis included 35 trials with a total of 1404 subjects. The age range varied between 23 and 75 years and the mean length of intervention was approximately 27 weeks. On average 3.7 sessions of aerobic exercise were carried out each week lasting approximately 40.5 minutes with an intensity of 64.8% VO2max. This resulted in a mean weekly energy expenditure of 1019kcal per
week. It was found that the mean difference in HDL-C when comparing those who exercised with those who did not was approximately 2.53mg/dL (95% CI; 1.36-3.30mg/dL) after training. It was concluded that exercise duration had the most significant role in dictating how greatly one could increase their HDL-C. For every 10 minute increase in aerobic exercise HDL-C was found to increase by 1.4mg/dL provided the total length of exercise was between 23 and 74 minutes. There was no statistically significant gain in HDL-C if the length of exercise fell below 30 minutes. Exercise intensity, age and gender were not found to be related to statistically significant rises in HDL-C following exercise. It was also noted that subjects with high total cholesterol and smaller body habitus experienced an exaggerated response. Those with total cholesterol levels greater than 220mg/dL or with a BMI of less than 28kg/m² experienced a rise in plasma HDL-C of approximately 2.1mg/dL. The data suggests that exercise sessions of greater length are more effective at increasing plasma HDL-C levels than those of higher intensity and shorter duration.(14) This data is supported by the findings in the HERATIGE trial which used a population of 675 subjects all of whom undertook a 5 month graduated training programme initially ranging from 30 minutes to 50 minutes. It was found that both males and females experienced modest increases in HDL-C (3.4% and 3.9% respectively, P<0.07) with again no statistically significant association between HDL-C and intensity (measured in VO₂max).(17)

Wilcken and Wilcken first associated homocysteine (Hcy) with atherogenesis in 1976. Not only does it place the host in a hypercoagulable state by increasing platelet production and altering serum clotting factors, but it also reduces mitosis in endothelial cells, upregulates SMC mitosis and increases free radical production, all of which accelerate atherosclerosis.(30) Hcy has also been implicated in arterioconstriction at vascular injury sites through stimulation of thromboxane A₂. An increase in WBC endothelial adhesion results in a higher uptake of inflammatory cells into the tunica intima and reduces the generation of the vasodilator nitric oxide (NO) which reduces the flow mediated vasodilatation of blood vessels and SMC hyperplasia subsequently decreases blood vessel diameter.(11) From a clinical perspective high levels of circulating Hcy is most commonly associated with deficiencies in B vitamins, genetic diseases, drugs and renal failure.(16)

Unt et al. investigated whether plasma Hcy levels could be influenced by AET. The study included 77 former athletes who were subclassified into those still actively exercising and those who were not, and 33 non-athlete controls. The sedentary controls had a total Hcy level of 10.55µmol/L (±2.5µmol/L, P<0.001), the sedentary ex-athletes had the highest Hcy level of 12.32µmol/L (±4.49µmol/L, P<0.001) and the still active ex-athletes had the lowest Hcy level of 9.43µmol/L (±2.12µmol/L, P<0.001). This indicates that Hcy is influenced by current exercise practices and not related to past history of exercise even at a professional level. Lower Hcy in the active athletes could have been attributable to a higher consum-
tion of B vitamins, as there is a greater possibility that those who peruse an active lifestyle will also eat what are perceived to be a healthier diet such as fruits, vegetables and lean meats.(27) These findings are contrary to those of Rinder et al. who observed an increase of Hcy in 10 athletes compared to 10 controls, but careful analysis of the research showed that the athletes had higher total cholesterol levels and mean diastolic blood pressures, which are also independent markers of CVD, resulting in significant confounding of data within the small sample size.(24)

To measure the effect of endurance training on blood pressure a large scale meta-analysis was carried out by Fagard et al. involving 72 different trials spanning 105 study groups and a total of 3936 subjects. The test group was standardised adequately with 57% being male and ages ranged from 21 years to 83 years (median 47 years). The studies varied in length from 4 to 52 weeks (median 16 weeks) and the frequency of exercise ranged from 1 to 7 days per week (median 3). Exercise intensity was between 30% VO$_{\text{2max}}$ and 87.5% VO$_{\text{2max}}$ (median 65% VO$_{\text{2max}}$) and training sessions lasted between 15 and 63 minutes (median 40 minutes). It was found that resting heart rate fell on average by 4.8 beats per minute and peak oxygen uptake had increased by 4.0ml/min/kg over and above the baseline figure of 31.1ml/min/kg. Mean blood pressure levels fell significantly by 3.0/2.4mmHg (P<0.001) and daytime ambulatory blood pressure by 3.3/3.5mmHg (P<0.01). In a hypertensive sub-group pressures fell by 6.9/4.9mmHg (P<0.001) and in normotensives by 1.9/1.6mmHg (P<0.001). Mean peripheral vascular resistance was reduced by 7.1% (P<0.05) and plasma renin activity fell by 20% (P<0.05).(10) Within 17 study groups a 7.1% drop in systemic vascular resistance was reported with no significant change in cardiac output. It was found that a 9.3% drop in heart rate was buffered by a 15.4% increase in stroke volume. In the ‘fitter’ state lower levels of circulating noradrenaline (-29%) and renin (-20%) provided evidence to suggest that decreased autonomic nervous system activity could be responsible for a fall in peripheral vascular resistance through cardiac remodeling and ultimately a lower blood pressure.(7)

Evidence also suggests that static resistance training can improve resting blood pressure in hypertensives as identified by Cornelissen et al. A meta-analysis of 9 randomized controlled trials involving 341 subjects found that resting blood pressure fell by 3.2/3.5mmHg (95%CI; -7.1 to -0.7/6.1 to -0.9 mmHg). Training sessions were between 2 and 3 days per week and intensity ranged from 30% to 90% of their one repetition maximum. No statistically significant change in basal heart rate was observed which indicates no measureable change in sympathetic tone.(8) Data which supports this, by Vanhoof et al. and Coconie et al., could also not elicit any change in basal heart rate following resistance training or circulating noradrenaline levels respectively. No evidence was found to suggest that static exercises for strength gaining resulted in an increased resting systolic or diastolic blood pressure.(28, 6)
Vascular endothelial tone and homeostasis is controlled by antithrombic, vasodilator and vasoconstrictor substances. NO and prostacyclin act as potent vasodilators and inhibit platelet activation but if damaged the normal action of these vasodilators can be impaired. Alterations could result in the production of vasoconstrictors such as prostaglandins and thromboxane $A_2$. Platelet aggregation also occurs at the site of injury and causes migration of WBCs, specifically monocytes, to the tunica intima which can cause herniation of the wall and subsequent obstruction of the lumen. Further mediators facilitate the phagocytosis of lipid molecules into the WBCs and may be implicated in the rupture of fibrous atherosclerotic plaque and subsequent platelet aggregation. Proliferation of tumour necrosis factor alpha, interleukins, interferons and growth factors are also associated with local activation of inflammatory cells following uptake of oxidised LDL-C. Endothelial leukointegrins bind inflammatory cells to the endothelium at bifurcations where turbulence is most prominent. Acute plaque rupture usually occurs at the site where WBCs enter the lesion and could be the result of gene expression coding for proteolytic enzymes and collagenases by T-lymphocyte activation.

Kojda et al. observed the effects of exercise on vascular wall homeostasis in a study which involved patients awaiting coronary artery bypass surgery. Following 4 weeks of AET part of their internal mammary arteries were harvested during surgery to assess the effects of exercise on endothelial structure and function. Analysis of the specimens showed that AET increased endothelial dilatation most likely due to exaggeration of NO-synthase expression and phosphorylation. Exercise may also influence endothelial oxidative stress. Increased NO production through regular exercise may decrease metabolism by free radical species with antioxidant formation and direct reduction in free radical production.

Walther et al. also investigated the role of local vascular inflammation in cardiovascular disease and followed 101 males with coronary artery disease to observe the effects of exercise ($n=51$) versus percutaneous vascular intervention ($n=50$). Baseline high sensitivity C-reactive protein (HsCRP) and interleukin-6 (both markers of inflammation) were taken before intervention and then repeated after 2 years. It was observed that HsCRP and interleukin-6 had decreased in the exercise group by approximately 41% and 18% respectively with no change in the group who underwent percutaneous intervention only. It was also found that at 2 years 78% of the exercise group had survived without any further cardiac events as opposed to 62% of the percutaneous intervention group ($P=0.039$) which supports the hypothesis that inflammation could be involved in the proliferation and maintenance of the atherosclerotic plaque in cardiovascular disease and modification can modulate vascular inflammation and subsequent cardiovascular risk.

Limited evidence exists suggesting whether exercise can be associated with acute myocardial infarcts and sudden cardiac death. It is almost exclusively observed in sedentary adults with previously unknown extensive coronary artery
disease who perform high intensity exercise and young children and adolescents with structural heart disease and electrophysiological abnormalities. (21)

CONCLUSION

The data cited in this article confirms that both aerobic exercise training and static resistance training can positively modify factors associated with raised cardiovascular risk. Although there is currently insufficient non-inferiority data comparing exercise with pharmacological treatment in both short and long term cardiovascular outcomes, exercise can significantly reduce blood levels of LDL-C, VLDL-C, homocysteine, blood pressure and vascular inflammation. Serum LDL-C, VLDL-C, HDL-C and triglyceride levels seem most effectively influenced by total length of exercise training session as opposed to intensity of exercise, with little variability between 50% and 70% \( \text{VO}_{2\text{max}} \). Optimal exercise sessions should be at least 30 minutes with no significant benefit observed beyond 73 minutes and further research is required to assess the impact of serum cholesterol levels in very long AET. Both aerobic and static exercise training is also noted to improve resting blood pressure with an exaggerated response seen in hypertensives with simultaneous optimisation of endothelial wall homeostasis through down-regulation of locally acting inflammatory cytokines. It should also be noted that cardiovascular risk appears to increase in the absence of AET which indicates that cardioprotection declines despite previous fitness and long term outcomes can be compromised if exercise regimens are stopped with morbidity comparable to sedentary individuals.

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Nil.

REFERENCES


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