THE EFFECTS OF EXERCISE TRAINING
ABOVE AND BELOW THE VENTILATORY THRESHOLD
IN PATIENTS WITH CORONARY ARTERY DISEASE

by

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A thesis submitted in conformity with the requirements
for the degree of Master of Science
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Abstract

The differential effects of training above and below the ventilatory threshold (VT) were examined in 35 patients with coronary artery disease (CAD). The LO group trained at 91% of the heart rate at the ventilatory threshold (HRvt) while the HI group trained at 107% of the HRvt. Patients exercised between 4 and 5 days per week for 13 weeks, for an average of 35 minutes per session.

Changes in the \( \dot{V}O_2 \) at the VT were not significant in either group. Failure to detect a change in the VT may be due to the low absolute HR at which both groups were training (LO group 87 bpm, HI group 99 bpm). It seems that the absolute training heart rate is more important than the heart rate relative to the VT in providing a stimulus for VT augmentation.

While the \( \dot{V}O_2_{peak} \) increased significantly in both groups, the increases were not significantly different between groups. Thus, training above the ventilatory threshold did not confer a greater augmentation in the \( \dot{V}O_2_{peak} \) than training below the ventilatory threshold in these CAD patients within the intensity ranges experienced in this study.
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Dedication

To my dad Mitchell,
for unwavering support and invaluable advice.
Although unintentionally, you have been my guiding light.
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List of Abbreviations

ACE = angiotensin converting enzyme
ACSM = American College of Sports Medicine
AG II = angiotensin II
AHA = American Heart Association
AT = anaerobic threshold
ATP = adenosine triphosphate
a-vO₂ difference = arterio-venous oxygen difference
BC = Barry Cayen, B.Sc.H.
bpm = beats·min⁻¹
CABGS = coronary artery bypass graft surgery
CAD = coronary artery disease
DM = Donald Mertens, M.D.
ECG = electrocardiogram
EDV = end diastolic volume
EF = ejection fraction
GXT = graded exercise test
HDL = high density lipoprotein
HR = heart rate
HRpeak = peak heart rate
HRR = heart rate reserve
HRvt = heart rate at the ventilatory threshold
LDL = low density lipoprotein
LT = lactate threshold
LVD = left ventricular dysfunction
MET = metabolic equivalent (1 MET = 3.5 ml·kg⁻¹·min⁻¹ VO₂)
MI = myocardial infarction
MVO₂ = myocardial oxygen consumption
OBLA = onset of blood lactate accumulation
RCMA = respiratory compensation for metabolic acidosis
RPE = rating of perceived exertion
PO₂ = partial pressure of oxygen
RER = respiratory exchange ratio
SCD = sudden cardiac death
SEM = standard error of the mean
T₁ = before the exercise program
T₂ = after the exercise program
TLC = Training Level Comparison (a study performed by Jensen et al. 87)
TRI = cardiac program of the Toronto Rehabilitation Institute
VCO₂ = volume of carbon dioxide produced
Vₑ = minute ventilation
VEqCO₂ = ventilatory equivalent for carbon dioxide
VEqO₂ = ventilatory equivalent for oxygen
VO₂ = volume oxygen consumed per minute
VO₂max = physiological maximum rate of oxygen consumption
VO₂peak = peak rate of oxygen consumption
VT = ventilatory threshold
1.1 Purpose

The purpose of this study was to determine the differential effects of prescribing aerobic exercise above or below the ventilatory threshold in patients with coronary artery disease. The effects of the two training programs on aerobic capacity, ventilatory threshold, submaximal exercise responses and body composition were explored.

1.2 Rationale: Ventilatory threshold as a marker for exercise intensity

The ventilatory threshold (VT) can be defined as the rate of oxygen consumption ($\dot{V}O_2$) during incremental exercise when the rate of ventilation ($\dot{V}E$) increases with respect to the $\dot{V}O_2$, but not with respect to the rate of carbon dioxide production ($\dot{V}CO_2$). This "blowing off" of CO$_2$ is a result of the buffering of lactic acid from the processes of anaerobic metabolism$^{173}$. Depending on the location of the VT, patients exercising at the same percent of their peak $\dot{V}O_2$ ($\dot{V}O_{2\text{peak}}$) or heart rate reserve (HRR)$^{91}$, will experience largely varying physiological stress$^{35, 36, 50, 51}$. Those who happen to be training above the VT will habitually expose the cardiac and skeletal muscle to large concentrations of lactic acid. Those patients training below the VT will have negligible lactic acid accumulations. Different adaptations may be elicited in skeletal and cardiac muscle depending on the degree of lactic acid exposure.
Common practice within the cardiac rehabilitation setting is to prescribe exercise at a specific percentage of the patient's VO\textsubscript{2peak}, as predicted or measured on a graded exercise test (GXT). The American Heart Association (AHA) recommends that individuals with cardiac disease exercise at a heart rate (HR) corresponding to 50-80% of the patient's VO\textsubscript{2peak} or 50-75% of their HRR\textsuperscript{57}. The American College of Sports Medicine (ACSM) suggests that cardiac outpatients exercise at an intensity between 60% and 70% of their peak heart rate (HR\textsubscript{peak}). Regardless of whether exercise is prescribed based on the HR\textsubscript{peak}, HRR or VO\textsubscript{2peak}, prescriptions should be at least 10 beats/min below the onset of demonstrated exercise intolerance or myocardial ischemia. During a GXT, exercise intolerance may manifest in light-headedness or abnormal blood pressure responses\textsuperscript{109}. Signs of ischemia include angina, a decrease in systolic blood pressure, greater than 1 mm of ST-segment depression, ventricular arrhythmias or radionuclide evidence of ventricular dysfunction\textsuperscript{109}.

Most cardiac rehabilitation programs tend to prescribe exercise to patients at identical percentages of their VO\textsubscript{2peak} or HRR. This practice may not provide a uniform exercise stimulus between patients. A study of well-trained patients with coronary artery disease (CAD) by Goodman et al.\textsuperscript{63}, demonstrated that the VT within this rather homogeneous cohort can vary between 41 - 73% of the VO\textsubscript{2peak}. The patients in Goodman's study had all been training at the same percentage of their HR\textsubscript{peak}. Seven out of the twenty subjects had been training below their VT and the rest were training above their VT.

A study by McConnell\textsuperscript{115} compared the VO\textsubscript{2} and HR at traditional exercise prescription intensities to the VO\textsubscript{2} and HR at the VT (HR\textsubscript{vt}). Groups of patients with and without beta blocker treatment as well as healthy controls were studied. It was found that
specific training intensities based on either the \( \dot{V}O_{2\text{peak}} \) or HRR could not match the VT in any of the groups. In another study, significant differences existed in \( \dot{V}E, \dot{V}CO_2, \dot{V}O_2 \) and in the extent of blood lactate accumulation between subjects exercising at identical percentages of the \( \dot{V}O_{2\text{peak}} \). It is clear that part of the variation in the metabolic and ventilatory stress at specific percentages of \( \dot{V}O_{2\text{peak}} \) between subjects depends on the location of the VT.

The measurement of a "maximal" \( \dot{V}O_2 \) has many limitations not present in the determination of the VT. The elderly, sedentary or diseased may be unable to reach a true physiological maximum (or "\( \dot{V}O_{2\text{max}} \)" on a GXT. Orthopaedic limitations, a lack of motivation, or being unaccustomed to exercise or the exercise modality may cause a subject to stop the test before a cardiopulmonary limitation is reached. An exercise prescription based on the \( \dot{V}O_{2\text{max}} \) attained during a GXT may be an inadequate training stimulus if a true maximal \( \dot{V}O_2 \) was not reached. Most subjects who do not exercise to their physiological maximum on a GXT, do however exercise beyond their VT. The VT is a physiological point during the exercise test that is independent of patient effort or the motivation given by the technologist. Prescribing exercise intensities with respect to the VT may provide a more uniform physiological stress between patients in a cardiac rehabilitation setting.
1.3 Specific objectives

In order to quantify the differences in the adaptations to training above or below the VT, two exercise groups performed a GXT on a cycle ergometer before and after three months of exercise training. The “HI group” trained at heart rates corresponding to an exercise intensity above their VT while the “LO group” trained below their VT. The following variables were determined before and after training: peak rate of oxygen consumption (\(\dot{V}O_2\)peak), VT, maximum work rate, body fat percentage, double product, and maximum and resting HR. The HR, \(\dot{V}E\), ventilatory equivalent for oxygen (VEqO\(_2\)) and ventilatory equivalent for carbon dioxide (VEqCO\(_2\)), respiratory exchange ratio (RER) and \(\dot{V}O_2\) at submaximal work rates above and below the VT were also examined before and after training.

1.4 Hypotheses

Exercise training above the VT for three months will elicit a greater improvement in:

1) \(\dot{V}O_2\) at the VT and
2) \(\dot{V}O_2\)peak

than training below the VT.
Chapter 2: Related literature

2.1 Introduction to coronary artery disease

2.1.1 Epidemiology and risk factor analysis

The incidence of CAD has been closely correlated with certain physiological and behavioural traits. Obesity, hypertension and high blood cholesterol have all shown to increase the incidence of CAD\textsuperscript{24}. The presence of multiple risk factors in an individual has a synergistic effect on the risk of CAD development. Aerobic exercise training on the other hand, has been shown to attenuate weight gain due to a sedentary lifestyle\textsuperscript{81}, decrease hypertension\textsuperscript{3} and combat hypercholesterolemia\textsuperscript{94, 180}.

Cardiac disease is responsible for forty to sixty percent of deaths in people who develop diabetes after the age of 40\textsuperscript{6}. Diabetes can precipitate from obesity and can result in high blood pressure and hypercholesterolemia. Along with insulin and diet control, exercise is a key way to help prevent the manifestations of diabetes and the impending CAD.

Those who are competitive in nature and feel chronically anxious (Type A behaviour) have a 5 to 10% greater incidence of CAD than those who are more relaxed (Type B behaviour)\textsuperscript{72, 73}. The chronic elevation of serum epinephrine associated with stress seems to be the physiological link between Type A behaviour and CAD\textsuperscript{42}. Habitual exercise has been shown to decrease stress levels as well as decrease basal levels of sympathetic drive.
Smoking as well as a family history of CAD have also shown to be risk factors for CAD.

Physical inactivity

It is now well established that physical activity has a protective effect against CAD. It is interesting to note that physical inactivity alone has been shown to increase the risk of CAD by 10 to 140%. Early epidemiological evidence supporting the role of a sedentary lifestyle as an independent risk for CAD first appeared in the early 1950s when occupational physical exertion and the incidence of CAD was examined in San Francisco longshoremen. The investigators kept accurate and detailed records of job assignments in 6,351 men between the ages of 34 and 74, over a 21-year period. It was found that the relative risk of CAD was 1.8 in those who worked at low intensities (1.5 – 5 kcal/min) versus those worked at high intensities (5.2 – 7.5 kcal/min). The data from Morris et al., although flawed in design, also demonstrated the benefit of relatively active versus inactive occupational activities.

The Framingham Study further demonstrated physical activity to be an independent risk factor for CAD in 1,909 men who were followed for 14 years. Cardiovascular mortality and morbidity rates were 1.1 to 1.3 times higher in those who were “sedentary” versus those who were “active”. The incidence of CAD in the Framingham study was standardized for age, systolic blood pressure, glucose intolerance, cholesterol and electrocardiographic evidence of left-ventricular hypertrophy.

The Harvard Alumni Study was successful in having 16,936 alumni between the ages of 35 and 74 years return a series of questionnaires that determined their total weekly physical activity. It was found that people who expended a total of less than
2000 kilocalories per week (including exercise sessions and other activities of daily living) suffered a 64% greater change of a heart attack than those who exercised more than 2000 kilocalories per week. The benefits of increasing habitual physical activity on cardiac risk showed a distinctive plateau beyond a weekly energy expenditure of approximately 3500 kilocalories.

The benefits of leisure-time physical activity were further studied by Morris et al. between 1968 and 1970. The risk of CAD decreased by 50% among 17,944 male civil servants who habitually expended more than 7.5 kilocalories per minute during leisure-time activities versus those men that did not.

More recently, Blair reported on the effects of changes in physical fitness on mortality in 9777 men. Patients performed two treadmill tests 4.9 ± 4.2 years apart (mean ± SD) and were followed for 5.1 ± 4.2 years after the second test. Patients who achieved an exercise intensity greater that 10 METs on the treadmill test were classified as “fit” and those who achieved less than 10 METs were classified as unfit. Patients who were fit at both examinations showed a 76% decrease in all cause mortality and men who improved from unfit to fit demonstrated a 44% reduction in mortality versus those subjects who were unfit at both examinations.

Regular physical activity increases the likelihood of survival from a myocardial infarction. Endurance training also decreases morbidity and mortality in patients with previously documented CAD. One of the gold standard indications of the development of physical fitness is the lowering of resting heart rate. A positive correlation has been demonstrated between resting heart rate and all-cause death, including death from CAD.
High systolic blood pressure, cigarette smoking and high blood cholesterol levels have similar relative risks as the lack of physical exercise. People with sedentary lifestyles however outnumber those who smoke, have high cholesterol or have high blood pressure. Thus, resolving the lack of physical activity in our population may more strongly effect the incidence of CAD than any other risk factor intervention.

In response to the epidemiological data demonstrating lower mortality rates in those who are more physically active and physically fit, a U.S Surgeon General’s report recently recommended that all people exercise at a “moderate” intensity for a minimum of 30 minutes on most days of the week. There is however, uncertainty as to the most efficacious exercise intensity for improvements in physical fitness.
2.1.2 Pathophysiology

Coronary artery disease is most commonly due to the obstruction of the coronary arteries by atherosclerotic plaques\textsuperscript{113}. The formation of atherosclerotic plaques is thought to be initiated by chronic injury to the intimal surface of the artery\textsuperscript{141}. The failure of a coronary artery to properly dilate may cause turbulent local blood flow and precipitate intimal surface injury. Abnormalities in arterial endothelium-dependent relaxation may be caused by the peroxidation by-products of excess low density lipoprotein (LDL)\textsuperscript{110}. Hypercholesterolemia also stimulates the generation of superoxide radicals which may inactivate endothelium-derived nitric oxide and negatively affect arterial wall dilation\textsuperscript{127}. Chemical irritants in cigarette smoke as well as viral infections also tend to cause intimal injury\textsuperscript{84, 161}.

The formation of lesions in the blood vessels of the heart is a multi-factorial process. Plaques seem to develop mostly near highly convoluted branching points of the coronary vasculature, where turbulent blood flow is likely to exist\textsuperscript{5}. In response to the shear forces caused by turbulent flow, the endothelial cells at these junctures elongate. It is thought that irritation of these elongated endothelial cells increases their permeability to atherogenic lipoprotein particles, mostly derived from LDL. The accumulation of LDL in the endothelial cells has been shown to cause an inflammatory response, attracting macrophages. These scavenger cells engulf the lipoprotein and are thus converted into foam cells. The accumulation of fat and inflammatory cells in the vessel wall decreases the luminal space and causes the vessel to distend in response to the flow of blood with every heart beat. This rhythmic distention seems to cause a migration and
proliferation of smooth muscle cells into the subendothelial space\textsuperscript{141}. The smooth muscle cells also produce collagen, further narrowing the vascular lumen. The cellular debris left from the eventual rupture of the macrophages is manifested as an accumulation of extracellular lipids in the arterial wall. This lipid mass is separated from the lumen by the thin layer of collagen produced by the smooth muscle cells. The pocket of lipids, thinly encased in collagen can rupture from a variety of causes: increased shear stress from blood moving past the plaque, an excessively large accumulation of lipid or the release of free radicals and proteolytic enzymes by the macrophages can degrade the collagen covering and cause the plaque to rupture. The degree of plaque disruption is directly related to the size of the thrombus that forms atop the plaque and therefore the clinical significance of the event. When only the surface of the plaque is disrupted, a small thrombosis forms, causing a clinically silent lesion. When deeper layers of the blood vessel are exposed during plaque disruption, a larger, more dense thrombus is formed. Such thrombi can significantly occlude blood flow through the vessel, invoking symptoms of myocardial ischemia or causing an infarct\textsuperscript{56}. Debris that is released from the plaque (emboli) may travel distally and occlude smaller blood vessels, further increasing the likelihood of a cardiac event.

The potential for thrombosis formation is affected by various factors. Chronically high levels of systemic epinephrine as caused by smoking or mental stress can increase platelet aggregation and thrombus formation. High levels of norepinephrine as caused by exercise however, seems to have an opposing effect, inhibiting coronary thrombosis\textsuperscript{106}. People with hypercholesterolemia, diabetes mellitus, or even a strong family history of coronary artery disease have demonstrated a higher than average platelet reactivity and coagulability. Chronic exercise can increase levels of high density lipoprotein (HDL)
which can directly prevent thrombus formation (in addition to its effect of mobilizing systemic cholesterol to the liver for oxidation)\textsuperscript{56}.

Alternatively, plaque composition may be predominantly collagenous and therefore sclerotic in nature. These “hard” plaques can also decrease luminal size but have little lipid composition and are less apt to lysis. Such plaques are frequently the cause of more stable coronary syndromes.

2.1.3 Symptoms

\textit{Silent ischemia}

When myocardial ischemia occurs without associated pain, it is referred to as silent myocardial ischemia. Most patients do however experience some sort of referred chest pain due to myocardial ischemia, as described in the next section. Painless ischemia may be due to autonomic neuropathy as experienced by some diabetics, a generally high pain threshold from excessive endorphin release or a less severe ischemic episode \textsuperscript{61}.

Myocardial ischemia occurs when oxygen delivery is below the level needed by the myocardium for adequate ATP synthesis. This is usually due to restricted blood flow through the coronary vessels. Ischemia results in a series of cardiac abnormalities known as the ischemic cascade \textsuperscript{83}. The relaxation of the myocardium is affected initially, causing diastolic dysfunction. Secondly, systolic function is impaired, as demonstrated by decreased ejection fraction and/or wall motion abnormalities. Repolarization deficiencies as demonstrated by electrocardiographic abnormalities such as T-wave
inversion or ST-segment depression or elevation are secondary to myocardial ischemia, as are life-threatening cardiac arrhythmias if the ischemic episode is severe \(^{156}\).

Decreased left ventricular function caused by CAD is strongly associated with low exercise tolerance. The impaired cardiac output results in an insufficient transport of oxygenated blood to the working muscles for aerobic ATP synthesis. Anaerobic ATP production uses glycogen stores inefficiently and causes an accumulation of lactic acid. Such metabolic activity leads to lower muscular endurance and power output.

**Angina**

Angina pectoris is referred pain from an area of ischemic myocardium. The pain can be referred to the arms, jaw, neck, substernal region, epigastrum and interscapular areas. The feeling is usually described as tightness, pressure, heaviness, fullness, squeezing, burning, aching or boring \(^{156}\).

Stable angina is brought on by exertion, stress, heat, cold or meals and is typically relieved by rest or nitroglycerin administration. Overt symptoms typically occur when luminal obstruction exceeds 70% \(^{18}\). Stable angina is defined as heart pain that occurs at a specific myocardial oxygen requirement (M\(\dot{V}\)O\(_2\)) that can not be met by myocardial oxygen supply \(^{61}\). Frequently, this specific M\(\dot{V}\)O\(_2\) can be predicted by the patient as a specific level of physical activity. In addition, ventricular wall tension is a direct determinant of the M\(\dot{V}\)O\(_2\). According to the Law of Laplace, the factors that contribute to wall tension include systolic blood pressure, ventricular volume and wall thickness. Other factors that increase M\(\dot{V}\)O\(_2\) are an increased heart rate and contractility. Oxygen supply is further mediated by the degree of vasospasm, collateral circulation and local vascular regulation.
Angina that occurs at rest, during sleep or without a predictable stimulus is known as unstable angina. Most patients who suffer from unstable angina have severe obstructive CAD and episodes of stable angina. The unpredictable onset of angina can be due to platelet aggregation from a hypercoagulable state, as caused by an increased serum concentration of tissue plasminogen activator, for example. Platelet aggregation may also be secondary to plaque rupture. The thrombosis that forms may exist for 10 to 20 minutes, significantly impeding coronary blood flow, causing the angina before it dissolves and the pain dissipates. In addition, vasomotor hyperreactivity may lead to coronary spasm, causing the narrowing of the vascular lumen. Endothelial dysfunction can promote the release of vasoconstrictive substances such as endothelin-1 or inhibit the release of vasodilators such as prostacyclin. This can also decrease coronary blood flow and precipitate myocardial ischemia.

**Myocardial infarction**

With severe rupture of a coronary plaque, thrombotic occlusion can persist for an hour or longer. Long-lasting coronary occlusion can cause various degrees of myocardial cell death, or myocardial infarction (MI). Left ventricular systolic and diastolic abnormalities are common following an MI. If the MI involves a large enough myocardial area, ventricular remodelling, resulting in dilation of the ventricle can decrease ejection fraction. This series of events can culminate in congestive heart failure. An MI can also stimulate deadly ventricular arrhythmias, and weaken ventricular or septal walls to the point of rupture.
**Sudden death**

Acute ischemia produces electrical, mechanical and biochemical dysfunction which can lead to irreversible cardiac arrhythmias, inadequate cardiac output and death\textsuperscript{61}. In 20 to 25 percent of all patients with CAD, death occurs within 2 hours of the first manifestations of the disease\textsuperscript{61}. Autopsy studies have demonstrated that the incidence of such sudden cardiac death (SCD) is directly proportional to the severity of the coronary stenosis. Some causes of SCD are coronary spasm, thrombosis or plaque fissure and exercise-induced ischemia.

**2.1.4 Pharmacological Treatment of CAD**

**Nitrates**

Nitroglycerin preparations are used to alleviate or prevent angina pectoris. This class of drug is a vascular smooth muscle relaxant, acting as a nitric oxide donor. Nitrates decrease venous tone allowing blood to pool in the veins. The redistribution of blood decreases the end diastolic volume and pressure in the heart. The lower preload on the heart decreases myocardial oxygen demand and helps to prevent angina.

Nitroglycerin increases exercise tolerance in patients with effort-induced angina by decreasing the \( \text{MV}_\text{O}_2 \) at a given work load. Administration of a long acting nitrate has been shown to delay the symptoms and electrocardiographic abnormalities of myocardial ischemia during exercise stress testing. It has been demonstrated that one sublingual nitroglycerin tablet may improve a patient’s functional capacity by about 1 MET on a treadmill test\textsuperscript{112}. 
**Beta blockers**

Patients with CAD have experienced less angina and fewer incidences of ST-segment depression as well as an increase in aerobic exercise capacity when prescribed beta blockers. When titrated properly, non-selective beta blockers, β₁-selective blockers, and those beta blockers with intrinsic sympathomimetic activity fare equally well in increasing exercise capacity in patients with exercise-induced myocardial ischemia.

Cardioactive beta blockers inhibit the inotropic and chronotropic effects of endogenous catecholamines by binding to beta adrenergic receptors on the myocardium. The suppression of heart rate and contractility lowers MVO₂. Beta blockers also lengthen the diastolic period which allows a longer time for coronary perfusion. These drugs effectively lower O₂ demand and increase O₂ supply, helping to prevent myocardial ischemia.

Most studies suggest that improvements in VO₂peak with exercise training is not attenuated with beta blockade. However, one study suggests that exercise-induced improvements in the VO₂ at the anaerobic threshold (AT) can be hampered in those receiving beta blockade. The results of this study may be questioned since large increments in work rate during the GXT may have prevented the detection of small changes in the AT.

The chronotropic effects of beta blockade can decrease a patient’s resting heart rate from 10 to more than 20 beats per minute at rest. At a given heart rate, a patient may be exercising well above or well below their ventilatory threshold depending on the plasma concentration of a beta blocker. It is important to prescribe training heart
rates based on exercise tests performed near the time of day that the exercise training sessions are to occur. This can better control for the effects of diurnal variations in beta-blocker concentration\textsuperscript{136}.

\textit{Calcium channel blockers}

Calcium channel blockers are used primarily as antihypertensive agents. These drugs act to decrease calcium influx into the vascular smooth muscle. The reduction of intra-muscular calcium concentration decreases the constriction potential of the vasculature thereby decreasing blood pressure. Cardiac afterload is therefore reduced, lowering the $\text{MV}_2\text{O}_2$ at a given cardiac output. Hypertensive patients with CAD exhibit less exercise-induced angina and ST-segment depression and an increase in exercise capacity under calcium channel blockade\textsuperscript{93}.

In addition to effects on the vasculature, calcium channel blockers such as diltiazem and verapamil act on the myocardium, having additional negative chronotropic and inotropic effects\textsuperscript{148,149}. Nicardipine and nifedipine are selective for the vascular smooth muscle, decreasing coronary and peripheral vascular resistance without a large effect on heart rate or myocardial contractility. No study, to our knowledge has demonstrated these drugs to cause an attenuation in the training effects of habitual aerobic exercise.
**Angiotensin-converting enzyme inhibitors**

Angiotensin-converting enzyme (ACE) inhibitors have proven to be effective drugs in combating hypertension by means of blocking the production of angiotensin II (AG II). AG II is a powerful vasoconstrictor and indirectly increases water retention. It is interesting to note that AG II also stimulates vascular smooth muscle growth and proliferation\(^2^8\), which is one of the pathphysiological mechanisms of coronary stenosis. ACE inhibitors therefore decrease blood pressure by direct action on the blood vessels, by decreasing blood volume and may help to decrease plaque formation and vascular remodelling.

ACE inhibitors such as captopril and enalapril have been shown to cause a decrease in blood pressure during acute bicycle exercise in hypertensive patients\(^9^3, ^{1^1}\). There is no documented evidence suggesting that ACE inhibitors attenuate the conditioning response to habitual aerobic exercise.

**Diuretics**

Used in the treatment of hypertension, diuretics increase renal sodium and water excretion. This action causes a general decrease in blood volume and therefore blood pressure \(^9^3\). In patients with ischemic heart disease, thiazide diuretics can cause some ST-segment depression due to hypokalemia. This effect can easily be confused with ST-segment depression induced by myocardial ischemia. The possibility of hypokalemia can be averted by using potassium-sparing diuretics.
The low blood volume caused by diuretics can augment exercise induced
tachycardia and post-exercise hypotension. The initiation of diuretic therapy may also
cause a slight attenuation of the blood pressure response to exercise.

2.2 Exercise training and rehabilitation in patients with coronary artery disease

2.2.1 Historical perspectives

The rehabilitation of patients with coronary artery disease has made a complete
reversal in approach since the first clinical description of myocardial infarction (MI) in
the early 1900's. Patients were originally confined to strict bed rest for 6 to 8 weeks after
their infarction. The rationale for bed rest was that the injured myocardium required
approximately 6 weeks to form a stable scar from the initial ischemic necrosis. Bed
rest has since been shown to cause pulmonary embolism, skeletal muscle deconditioning
and fails to improve cardiac function. The largest contributor to the deleterious effects
of bed rest is the lack of gravity-induced orthostatic challenge.

In the 1940s, the practice of strict bed rest was first questioned by Levine (1944)
and Taylor (1949). In an attempt to decrease venous return, stroke volume and
M\textsuperscript{VO}2, Levine (1952) proposed bouts of sitting in a chair in addition to bed rest. It is
interesting to note that sitting requires a larger M\textsuperscript{VO}2 than lying in bed.

Ambulation of the cardiac patient earlier in the rehabilitation process became
more common in the 1950's. A key study by Cain in 1961 reported on the safety
and efficacy of an early, in-hospital ambulatory program (currently known as a Phase I
cardiac rehabilitation program) for post-MI patients. A graded activity program from
basic personal grooming to stair-climbing was carried out on 335 patients. 81% of the patients entered the program within 15 to 35 days after their MI. Only patients 12 died from cardiac causes and none of these deaths were reported to be exercise-induced. 72% of patients were successful in climbing stairs at the end of the program.

Further evidence for the benefits of physical activity in the rehabilitation of cardiac patients was provided by a controlled study conducted in 1974 by Bloch et al.\textsuperscript{11}. They found that patients who had undergone mobilization beginning 2 to 3 days after their infarction showed less disability one year after the cardiac event than those who did not undergo physical therapy.

Two key meta-studies by O‘Connor and Oldridge conducted in the late 1980s demonstrated that patients who underwent a cardiac rehabilitation program had a 20 to 37% lower mortality rate one year after an acute cardiac event than patients who did not participate in a rehabilitation program\textsuperscript{126,128}. Mortality rates were lowered further by the continuation of the rehabilitation program beyond 8 to 12 weeks\textsuperscript{128}. After an initial cardiac event, the incidences of non-fatal re-infarction, total cardiac events and disease-related unemployment are lowered in those who exercise and receive risk factor education\textsuperscript{75}.

\subsection*{2.2.2 Effective exercise training for cardiac rehabilitation}

The critical components of an exercise training program are the \textit{intensity} of effort, the \textit{duration} of the exercise sessions, the \textit{frequency} of the exercise sessions and the type, or \textit{modality} of exercise. Epidemiological evidence has demonstrated that the incidence of death from heart disease is inversely proportional to the total energy expenditure of the
average exercise session. Total energy expenditure can be considered as the "volume" of the exercise stimulus. If this "volume" can be imagined as a cube, frequency, intensity and duration would define the three dimensions of this object and, for a given volume, be inversely related to each other. Large deformations of this cube have delivered effective exercise training stimuli.

**Frequency of exercise training**

The AHA suggests that patients recovering from a MI, coronary artery bypass graft surgery (CABGS), or angioplasty exercise at least three times per week. A group of post-MI patients who trained either two or three times per week showed no differences in the improvements of treadmill duration, VO2peak, or in training-induced bradycardia. Although the statistical power and the training stimulus in this study were weak, others report that diminishing advantages are gained by exercising more frequently than three times per week in recent post-MI patients.

**Duration of exercise training**

It has been demonstrated that exercise sessions lasting 10 to 15 minutes yield significantly smaller benefits than do sessions of 30 to 60 minutes. The accumulation of 30-45 minutes of aerobic exercise, excluding warm-up and cool-down is recommended by the AHA, ACSM, American Association for Cardiovascular and Pulmonary Rehabilitation and the Center for Disease Control.

Similar aerobic improvement is seen if the exercise prescription is completed in either a single bout or multiple bouts, as long as the total volume of exercise (measured in calories) is comparable. One must realize that a warm-up and cool-down period
exists for each bout of exercise. Multiple bouts of exercise therefore require a longer total time commitment when taking into account each warm-up and cool-down period. The short duration / high frequency approach is most suited for more physically deconditioned cardiac patients who may not be able to exercise for a long periods of time. It is recommended that the duration of exercise increase by approximately 5 minutes per week until a total of 45 minutes of exercise per day is achieved\textsuperscript{136}.

\textit{Modality of exercise training}

In order to increase aerobic fitness, cardiac patients should participate in exercise that involves large muscle groups, recruited in a rhythmic nature, for a prolonged period of time\textsuperscript{109}. Effective types of exercise include walking, jogging, cycling, rowing, cross country skiing or other highly aerobic activities. The use of the leg muscles during training is more effective than use of the arms only in acutely increasing heart rate and \(\dot{V}O_2\) and thus aerobic capacity. The type of exercise chosen should maximize compliance and minimize the possibility for injury. Stationary cycling for instance may be more appropriate than walking or jogging for people with orthopaedic limitations. Similar improvements in \(\dot{V}O_2\)\textsubscript{peak}, and body composition are found with walking, running and stationary cycling when frequency, intensity and duration are controlled\textsuperscript{17}. Considering the efficacy of intermittent exercise and of various modalities of exercise in increasing aerobic functioning, a circuit training approach involving a variety of modalities during an exercise session is also an appropriate training stimulus.
**Intensity of exercise training**

A large range of exercise intensities has yielded improvements in aerobic capacity. These exercise intensities have been expressed in an equally large variety of ways. Ratings of perceived exertion (RPE), percent of heart rate reserve (HRR), percent of HR_{peak} and percent of \( \dot{VO}_{2peak} \) are just some of the expressions used to describe exercise intensity. The AHA suggests that cardiac patients initially train at an intensity equal to 50 to 60% of the \( \dot{VO}_{2peak} \) as determined by a GXT. Alternatively, a rating of perceived exertion of 12 to 13 ("somewhat hard") on the 15-point (6-20) Borg scale has been recommended as an appropriate training intensity\(^{15, 57}\). The ACSM however, suggests an even larger range of effective training intensities, corresponding to 40-85% of the patient’s \( \dot{VO}_{2peak} \)\(^{168}\). Others have suggested training intensities corresponding to an RPE of 12 to 16 ("somewhat hard" to "hard") or 60-90% of HR_{peak} or 50-85% of the patient’s HRR\(^{70, 109, 136}\).

\[
50 \text{ to } 85\% \text{ of HRR} = [(\text{maximal heart rate} - \text{resting heart rate}) \times 50 \text{ to } 85\%] + \text{resting heart rate.}
\]

Training in the upper part of the recommended training intensity range may not confer significantly greater increases in aerobic fitness than training at more modest levels. Boone et al. performed a study in which patients who trained at 57% of the \( \dot{VO}_{2peak} \) developed a 13% increase in \( \dot{VO}_{2peak} \) while those who trained at 78% of \( \dot{VO}_{2peak} \) showed a 16% gain\(^{14}\). It was suggested that the extra cardiovascular and orthopaedic risk of training at high intensities might not be worth the extra 3% increase in aerobic capacity.
The ACSM recently indicated that unfit individuals can show an improvement in the $\text{VO}_{2\text{peak}}$ and in the anaerobic threshold from training intensities as low as 40-50% of the HRR\textsuperscript{135}. Higher intensity exercise is required for aerobic improvement in people who are more fit.

Training intensities can also be prescribed based on the anaerobic threshold (AT). The anaerobic threshold is the intensity of exercise during which anaerobic metabolism begins to significantly supplement aerobic metabolism\textsuperscript{162}. It has been suggested that training intensities should be prescribed slightly below the AT in order to ensure that the patient is performing aerobic work\textsuperscript{69}.

2.2.3 Physiological and clinical adaptations to exercise training

Patients with CAD have shown improvements in aerobic exercise capacity of 10 to more than 30% due to endurance training. The rate of improvement is greatest during the first 3 months of training and in the most unfit individuals. In patients with previous MI and CABGS, exercise training augments $\text{VO}_{2\text{peak}}$ to the same degree as those with documented angiographic CAD without MI or revascularization\textsuperscript{155}.

Central adaptations

The effect of training on cardiac output in CAD patients has been equivocal. It seems that in post-MI patients and those who experience exercise-induced ischemia, or have cardiomyopathy, the ability of the heart to increase stroke volume in response to aerobic training is impaired. Cobb found no changes in ejection fraction (EF) or end diastolic volume (EDV) after training in post-MI patients\textsuperscript{30}. The observed decrease in
HR at submaximal exercise levels in this study therefore points to augmented peripheral oxygen extraction. After endurance training, Froelicher found a trend towards increased SV and cardiac output in only those patients who did not suffer angina\textsuperscript{59}. Williams however did demonstrate an increased EF during submaximal workloads due to a lower end systolic volume after exercise training\textsuperscript{181}. An augmented EF at submaximal exercise levels theoretically leads to the observed decrease in heart rate and M\textsubscript{VO\textsubscript{2}}.

An increase in the rate-pressure product at the anginal threshold and less ST-segment depression at a given M\textsubscript{VO\textsubscript{2}} has been demonstrated after exercise training\textsuperscript{116,182}. With the aid of thallium perfusion scanning, myocardial blood flow has been shown to increase in some CAD patients after aerobic training\textsuperscript{58,59}. This offers some explanation for the decrease in ischemia at a given M\textsubscript{VO\textsubscript{2}} after endurance training. The improved myocardial blood flow may be secondary to an augmented coronary collateral circulation and coronary artery diameter as demonstrated in animal studies\textsuperscript{116,165}. However, angiographic evidence of changes in the appearance of coronary vessels, atherosclerotic lesions or in the extent of collateral circulation as a result of exercise training is sparse in CAD patients\textsuperscript{30}.

In a year-long study, by Hambrecht et al.\textsuperscript{68}, coronary angiography revealed the progression of CAD in 45% of control patients who did not exercise and in only 10% of those who underwent exercise training. Lesions seemed unchanged in 62% of those who exercised and in 49% of those who did not exercise. Regression of the atherosclerotic plaques occurred in 28% of exercisers and in 6% of controls. The low sensitivity of angiographic techniques to detect changes in the coronary vasculature may contribute to the lack of evidence linking coronary collateral circulation to exercise training.
Angiography can only detect vessels larger than 100μm and coronary collaterals range in size from 20-200μm\textsuperscript{116}.

Exercise training may prevent the progression of CAD by reducing other known cardiac risk factors such as lowering LDL and increasing HDL levels, lowering blood pressure, decreasing glucose intolerance, reducing platelet aggregation and blood viscosity and decreasing sympathetic activity.

**Peripheral adaptations**

Although there appears to be only limited support for "central" adaptations following training in cardiac patients, peripherally located oxygen delivery, extraction and consumption mechanisms are known to improve with exercise training. Exercise training increases muscle capillary density, thus augmenting the perfusion of blood through a given area of muscle. This increase in capillary to muscle fibre ratio improves the diffusion of oxygen into the musculature. Increases in capillary density lengthen the mean transit time of red blood cells through the capillaries, augmenting oxygen extraction at a given arteriolar blood flow.\textsuperscript{143} The size and density of the mitochondria as well as the concentration and activity of aerobic enzymes inside these organelles increase with aerobic training \textsuperscript{67,96}. Myoglobin concentration in the muscle cells increase with training, augmenting the transport of oxygen from the blood to the site of aerobic metabolism\textsuperscript{23}. These changes allow for more effective diffusion of oxygen from the blood to the electron transport chain. Improvements in the skeletal muscle’s ability for aerobic respiration can delay the accumulation of lactic acid.

The peripheral adaptations mentioned above increase oxygen extraction at the level of the skeletal muscle, thus augmenting the arterio-venous oxygen difference (a-vO\textsubscript{2}...
difference). The widening of the a-vO₂ difference increases the \( \dot{V}_{O_2} \) at a given cardiac output. Thus, for a given \( \dot{V}_{O_2} \), HR is attenuated, thus decreasing the M\( \dot{V}_{O_2} \) at a given work load and delaying the onset of myocardial ischemia.

2.3 Clinical role of cardiopulmonary exercise testing in patients with coronary artery disease

Standard practice in exercise rehabilitation is to prescribe exercise at an intensity based on HRR, a percentage of maximal HR or \( \dot{V}_{O_2\text{peak}} \). Such "maximal" values are best obtained from a clinically supervised graded exercise test (GXT). Such GXTs are important in determining the level of supervision required during an exercise training regimen. Serious cardiac abnormalities may only be evident during a GXT and can also determine the level of aerobic improvement gained by a patient in a rehabilitation program. Exercise prescriptions can then be modified according to the results of such tests. GXTs are performed mostly on cycle ergometers or treadmills. Some of the cardiopulmonary parameters that are assessed during a GXT include oxygen consumption, heart rate, oxygen pulse, minute ventilation, respiratory exchange ratio and the ventilatory threshold.
2.3.1 Modality

Graded exercise tests are normally conducted on a treadmill or on a cycle ergometer. Cycle ergometers usually yield a 10-15% lower \( \dot{V}O_2 \text{peak} \) than the treadmill but provide a smoother increase in \( VO_2 \) with incremental work rates, less motion artefact for most physiological measures and has a lower risk of injury from falling\(^{65} \).

Some physiological variables are altered by the modality of exercise. At a given heart rate for instance, treadmill exercise elicits a higher \( VO_2 \) than cycle ergometry\(^{8} \). At a given lactate concentration however, no statistical differences in heart rate have been observed between cycle and treadmill exercise\(^{159} \), nor is the heart rate at the ventilatory threshold different between modalities\(^{153} \).

2.3.2 Selected cardiopulmonary variables

\[ \dot{V}O_2 \text{peak} \]

The gold standard measure of aerobic capacity is the maximal volume of oxygen consumed per minute (\( \dot{V}O_2 \text{max} \))\(^{178} \). High levels of physical fitness as measured by a GXT are associated with reduced mortality\(^{62} \). The \( \dot{V}O_2 \text{max} \) is dependent mainly on heart rate, stroke volume and oxygen extraction at the periphery. The \( \dot{V}O_2 \text{max} \) has been defined as a plateau in \( \dot{V}O_2 \) despite increments in power output. Due to a multitude of causes such as orthopaedic limitations, a lack of patient motivation or a reluctance of the patient to continue such strenuous activity, it has been suggested that approximately 25% of people do not achieve a plateau in \( \dot{V}O_2 \)\(^{145} \). The maximal \( \dot{V}O_2 \) reached in such cases is called the
Because the VO₂max is affected by many non-physiological factors other measures of aerobic fitness, such as the ventilatory threshold (discussed in section 2.4) have attracted much attention.

**Oxygen pulse**

The oxygen pulse (calculated as VO₂/HR) according to the Fick equation is equal to the product of stroke volume times the a-vO₂ difference. The oxygen pulse (O₂ pulse) more closely correlates to stroke volume than to the a-vO₂ difference in people without pulmonary dysfunction or anemia at maximal¹¹⁴,¹⁷⁹ and submaximal⁸⁰ exercise levels. On the other hand, increases in VO₂peak in the elderly have been associated with an augmented a-vO₂ difference and not an increase in stroke volume¹⁴⁴. Regardless of the mechanism responsible for a training-induced increase in the O₂ pulse, such an adaptation suggests a lower MVO₂ at a given work rate and therefore delayed cardiac ischemia.

**Minute ventilation**

Minute ventilation (VE) is the volume of air expired per minute during exercise and is measured in litres·minute⁻¹. The VE in elderly cardiac patients is lowered in response to submaximal exercise after endurance training¹¹⁴. It is possible that lower breathing rates at submaximal exercise levels may decrease exertional dyspnea and improve tolerance for activities of daily living.
Respiratory exchange ratio

Defined as the ŔCO₂ divided by the ŔO₂, the respiratory exchange ratio (RER) is a good indication of substrate utilization. At low exercise intensities, fat is the major fuel metabolised yielding an RER close to 0.7. As exercise intensity increases, glucose becomes the major fuel source yielding an RER close to 1.0. At maximal exercise intensities, the RER approaches 1.1 to 1.2 as “non-metabolic” CO₂ from the buffering of lactic acid supplements the CO₂ expired from glucose metabolism. Training tends to decrease the RER at a given exercise intensity as glycogen sparing is augmented and lactate accumulation is attenuated.
2.4 “Anaerobic threshold”

2.4.1 Introduction

It has been documented as early as 1909 that high intensity exercise causes the production of lactate which in turn stimulates increased respiration\(^{47}\). In 1964, Wasserman first reported that a specific exercise threshold existed for each person during which the oxygen requirements of working muscle exceeded the capacity for the cardiopulmonary system to deliver that oxygen. In response to an inadequate oxygen supply, muscle metabolism was then hypothesized to proceed anaerobically, producing lactic acid. This increased anaerobic metabolism could be detected by analyzing expired air for large increases in the respiratory exchange ratio (RER = $\dot{V}_{CO_2}/\dot{V}_{O_2}$)\(^{174}\). The term “anaerobic threshold” (AT) was coined at that time and has since undergone considerable scrutiny as to its validity. Lactate production has since been shown to occur during non-anaerobic states. In addition, the associated increase in ventilation has been shown to occur without the production of lactate \(^{169}\). Nevertheless, the concept remains a generally accepted response to acute exercise.

The classical rationale behind the AT is that a specific $\dot{V}_{O_2}$ exists for each person beyond which anaerobic metabolism significantly contributes to energy production. The $\dot{V}_{O_2}$ at which this occurs is dependent on the efficacy of the oxygen delivery and extraction mechanisms. When the oxygen supply is inadequate to fully oxidize the pyruvate produced from glycolysis, pyruvate is converted to lactate during the oxidation
of cytosolic NADH. The hydrogen ions produced from the accumulation of lactate is buffered by bicarbonate in the muscles and in the blood:

\[ \text{H}^+ \text{La}^- + \text{Na}^+ \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 + \text{Na}^+ \text{La}^- \rightarrow \text{H}_2\text{O} + \text{CO}_2 + \text{Na}^+ \text{La}^- \]

The carbon dioxide produced from the buffering of lactic acid is a stimulus for increased ventilation. The AT is referred to as the “lactate threshold” (LT) when it is detected by a non-linear increase in blood lactic acid concentration in response to a linear increase in work rate. When the AT is detected by measuring large increases in \( V_E \) or \( V\text{CO}_2 \), the AT is referred to as the “ventilatory threshold” (VT). The reader is directed to comprehensive reviews on the anaerobic threshold and its associated lactate and ventilatory responses. The lactate and ventilatory thresholds are explained in more depth below.

### 2.4.2 Lactate threshold

For most individuals, a reproducible \( \dot{V}\text{O}_2 \) exists during a graded exercise test, at which point there is an upwards deflection in the slope of the blood lactate versus \( \dot{V}\text{O}_2 \) plot. This inflection point is called the lactate threshold (LT). The LT is lower in heart failure patients than in normal subjects. Similarly, endurance trained athletes have an LT that occurs at a higher \( \dot{V}\text{O}_2 \) than untrained subjects. Figure 2.1 demonstrates the lactate thresholds from samples of various populations.

The \( \dot{V}\text{O}_2 \) at the LT has been correlated to endurance performance. It has also been demonstrated that the achieved running speed at the LT has a closer correlation with
overall marathon performance than either running economy, relative body fat, \( \text{VO}_{2\text{peak}} \), or percentage of slow-twitch muscle fibres\(^{36}\). In addition, the degree of blood lactate accumulation has profound effects on endurance time. Wasserman found that all of the 10 healthy subjects in one of his studies\(^{171}\) could cycle for a target duration of 50 minutes with blood lactate concentrations of less than 1.0 mM/L. No subject could sustain 50 minutes of exercise with blood lactate levels above 2.5 mM/L. Other investigators have found it useful to relate endurance performance to a blood lactate concentration of 4 mM/L\(^{90,152}\). This specific blood lactate concentration was coined the “onset of blood lactate accumulation” or OBLA. Although endurance performance and the \( \text{VO}_2 \) at OBLA do show correlations, the ventilatory threshold (described later), more closely corresponds to the LT than it does to the OBLA\(^{37}\). Although the LT is a good indicator of endurance performance, the exact mechanism responsible for it has been highly debated.

Wasserman originally found an increase in the lactate/pyruvate ratio in contracting muscle cells at the LT\(^{173}\). It was postulated that sufficient \( O_2 \) supply to the mitochondrion is necessary in order for NADH to be reoxidized by the “proton shuttle” of the mitochondrial membrane. However when \( O_2 \) supply is inadequate, some NADH is reoxidized by the catabolism of pyruvate to lactate. The conversion of pyruvate to lactate by lactate dehydrogenase is further potentiated by the \( H^+ \) produced from anaerobic glycolysis\(^{169,173}\). Oxygen supply is mediated by adequate cardiac function as well as peripherally located factors. Mitochondrial density, aerobic enzyme activity, capillary density and fibre type composition are some of the major peripheral mediators of oxygen utilization and thus affect the LT\(^{169}\).
Figure 2.1: Lactate thresholds from various populations

Figure 2.1: Display of lactate concentration versus VO2 for individual subjects of various populations. The sudden increase in lactate concentration with increasing VO2 is known as the lactate threshold (LT). Trained subjects experience the LT at a higher VO2 than normal or heart diseased subjects.

Lactate begins to accumulate in the blood when production exceeds its catabolism. The H⁺ that dissociates from lactic acid decreases blood pH, inhibits muscle function, causes the sensation of pain and can limit endurance performance. For a given ATP yield, muscle glycogen use is 18-19 times faster during exercise above the LT than during exercise below the LT. Only 3 ATP are yielded from one molecule of glycogen during anaerobic glycolysis while upwards of 36 ATP are yielded from one molecule of glycogen during oxidative phosphorylation. Elevated blood lactate also inhibits lipolysis and forces obligatory carbohydrate utilization. Thus, prolonged exercise above the LT can lead to a much higher rate of glycogen depletion (per ATP produced) and fatigue than exercise below the LT. The \( \dot{V}O_2 \) at constant workloads above the LT increases continuously towards the \( \dot{V}O_2 \text{peak} \) due to high blood lactate and catecholamine levels, further precipitating fatigue.

A hypoxic muscular environment may not be the only stimulus for lactate accumulation. There is a high correlation between lactate levels and plasma catecholamine concentration. The inflection point for plasma norepinephrine has shown to mirror the lactate threshold. It has also been demonstrated that beta-blockade attenuates the increases in blood lactate concentration with incremental exercise. The sympathetic activity demonstrated at the LT may be stimulated by increased potassium efflux from working muscles, decreased blood glucose levels, or hypoxic pulmonary arterial blood.

The increased recruitment of anaerobic muscle fibre types during a graded exercise test can also contribute to lactate accumulation. Type IIb muscle fibres, for instance have limited aerobic enzyme activity and can produce lactate despite adequate
local PO$_2$. The shift in fibre type recruitment however may either contribute to the cause, or be a result of the LT. The decreased pH and consequently lower contraction potential of aerobic muscles associated with lactate accumulation may be a stimulus for the recruitment of anaerobic muscle fibres$^{121}$.

It is important to realize that the accumulation of lactate in the blood depends on both its rate of production and removal. The point at which blood lactate begins to accumulate does not correspond to the onset of muscle lactate production. Increases in blood lactate concentration only demonstrate that lactate production has exceeded its catabolism. It is recognized that during exercise, lactate is a fuel for the heart and for slow-twitch skeletal muscle fibres. Lactate is also an important precursor for liver gluconeogenesis$^{121}$. Decreases in plasma pH also augment lactate removal by the kidneys$^{169}$.

The differences in metabolic stress above and below the AT underscore the importance of determining the AT for prescribing exercise and identifying aerobic fitness levels in CAD patients. The ability to deliver and utilize the oxygen required for the "aerobic" reoxidation of NADH is negatively affected by poor cardiac function and peripheral detraining characteristics demonstrated by many patients with CAD. The VO$_2$ at the AT represents the intensity of activity that can be theoretically tolerated for an extended period of time.
2.4.3 Methods of determining the ventilatory threshold using respiratory data

Overview

As the exercise intensity increases linearly during a graded exercise test, $\dot{V}_E$, $\dot{V}O_2$ and $\dot{V}CO_2$ increase linearly as well. At a point corresponding to the AT, an upwards, non-linear increase in the slopes of both $\dot{V}_E$ and $\dot{V}CO_2$ occurs during incremental exercise, as the slope of $\dot{V}O_2$ against work rate remains relatively linear \(^{150}\). The anaerobic threshold is more specifically called the "ventilatory threshold" (VT) when it is elucidated by analyzing expired gases. A variety of methods have been used in order to determine the VT using gas exchange data (shown in figure 2.2). This section compares the three most widely used procedures. The V-Slope method labels the VT as an upward deflection in the slope of the $\dot{V}CO_2/\dot{V}O_2$ graph. The ventilatory equivalent method describes the VT as an increase in the ventilatory equivalent for $O_2$ without a concomitant increase in the ventilatory equivalent for $CO_2$. Finally, the VT using the minute ventilation method relates to the first upward deflection in the $\dot{V}_E$ versus $\dot{V}O_2$ graph.
**Figure 2.2: Various methods of determining the ventilatory threshold**

**Figure 2.2a: V-slope method**
\( \dot{V}CO_2 \) plotted against \( \dot{V}O_2 \) exhibits an increase in slope at the VT. Although reliable, this method is difficult to perform without computer algorithms.
From Wasserman, K. Determinants and detection of anaerobic threshold and consequences of exercise above it. Circulation: 76(suppl VI), VI36, 1987

**Figure 2.2b: Ventilatory equivalent method**
At the VT, an increase in the ventilatory equivalent for \( O_2 \) (o) occurs without a concomitant increase in the ventilatory equivalent for \( CO_2 \) (+). From Wasserman, K. Determinants and detection of anaerobic threshold and consequences of exercise above it. Circulation: 76(suppl VI), VI37, 1987

**Figure 2.2c: Minute ventilation method**
The first breakpoint in the VE versus work rate graph occurs close to the VT (dashed line marked "A"). The second breakpoint in the VE versus work rate graph is the RCMA. (dashed line marked "B"). From Wasserman K, Hansen JE, Sue Dy, Whipp BJ: Principles of exercise testing and Interpretation. Philadelphia: Lea & Febiger, 1987.
**V-slope method**

During an incremental exercise test, the RER ranges between 0.85 and below 1.0 when carbohydrates are the predominant fuel and anaerobic metabolism is negligible. The slope of the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot from GXT data is equal to the RER. At a reproducible exercise intensity, CO$_2$ is released into the blood from the buffering of lactate by bicarbonate. This supplements the CO$_2$ produced from cellular respiration and causes an increase in the $\dot{V}CO_2$. The "break point" at which the slope of the $\dot{V}CO_2$ /$\dot{V}O_2$ plot changes from less than 1.0 to much greater than 1.0 is identified as the ventilatory threshold (VT) (see Figure 2.2a) $^{170}$. At exercise above the VT, it is not uncommon for the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot to have a slope greater than 1.15. The VT using the V-slope method correlates well with the LT in cardiac patients$^{54}$.

It is argued that the VT using the V-slope method is slightly higher than the LT. It is postulated that some cellular proteins in addition to phosphate may buffer some of the lactate produced before it is buffered by bicarbonate $^{173}$. Because the amount of extra CO$_2$ from the bicarbonate buffering system is so large, determination of the VT using the V-slope method is not likely to be affected by irregular breathing patterns or slight hyperventilation.

**Ventilatory equivalent method**

Ventilatory drive is significantly augmented when CO$_2$ produced from the buffering of lactate by bicarbonate supplements the CO$_2$ produced from cellular respiration. The increase in $V_E$ is not accompanied by a large increase in $\dot{V}O_2$ but $\dot{V}CO_2$ increases accordingly. Thus, the VT according to the ventilatory equivalent method
occurs when the ventilatory equivalent for oxygen ($\text{VEqO}_2 = \frac{\dot{V}_E}{\dot{V}O_2}$) increases without a concomitant increase in the ventilatory equivalent for carbon dioxide ($\text{VEqCO}_2 = \frac{\dot{V}_E}{\dot{V}CO_2}$) (see Figure 2.2b). At the VT there is hyperventilation with respect to $O_2$ but not to $CO_2^{172,173}$. Thus, during an incremental exercise test, the $\text{VEqO}_2$ curve falls initially, then flattens out and then proceeds to rise again. This triphasic pattern makes the VT more easily discernible than the $\dot{V}_E$ or $\dot{V}CO_2$ curves which rise continually throughout an exercise test.

The $\text{VEqO}_2$-$\text{VEqCO}_2$ relationship is useful in subjects with normally sensitive chemoreceptors and in those who have a normal ventilatory response to increases in $CO_2$ production. A correlation of 0.80 ($p < 0.001$) has been reported between this method of determining the VT and the LT in post-MI patients$^{129}$, however irregular breathing patterns may hamper a clear discerning of the VT using this method.

**Minute ventilation method**

At low exercise intensities, $\dot{V}_E$ increases linearly with $\dot{V}O_2$. At the ventilatory threshold, an upwards deflection in the $\dot{V}_E$ occurs in response to the release of $CO_2$ by the bicarbonate buffering system. This initial deflection in the $\dot{V}_E$ can be regarded as the VT (see Figure 2.2c).

At exercise levels above the AT, metabolic acidosis occurs when the bicarbonate buffering system reaches its capacity and lactic acid concentration increases in the blood. The metabolic acidosis that ensues provides an even stronger ventilatory stimulus than the $CO_2$ produced from the buffering of lactic acid. This causes a second upward deflection of the $\dot{V}_E$ versus $\dot{V}O_2$ slope. This occurs without a concomitant increase in the slope of either the $\dot{V}CO_2$ or $\dot{V}O_2$. This is the point of "respiratory compensation for
metabolic acidosis” (RCMA). During RCMA, VEqCO₂ as well as VEqO₂ increase against work rate⁷⁹. The RCMA has previously been mistaken as the VT, but in fact occurs significantly after the start of anaerobic metabolism⁶⁶, ¹⁷².

During graded exercise there are therefore two “breakpoints” on the Vₚ versus work rate graph. The first breakpoint is close to the VT and the second breakpoint is the RCMA. It is important to realize that the LT corresponds more closely to the VT than to the RCMA.

Comparison of methods

The V-slope method relies solely on the buffering of lactic acid since it takes into account the VO₂ and VC₀₂ and is not strongly affected by irregularities in the Vₚ. The minute ventilation and ventilatory equivalent methods however are dependent on respiratory chemoreceptor sensitivity since the Vₚ measurement affects the slopes of these plots. Irregular breathing patterns (a common problem in the sedentary and those unaccustomed to breathing through a mouthpiece) can weaken the latter two methods of determining the VT.

The reliability and repeatability of determining the VT using the three methods mentioned above were compared against the LT by Caiozzo et al. in 1982 ²². In analyzing the gas exchange variables, VC₀₂, VEqO₂-VEqCO₂ and Vₚ were plotted against time. (Although these parameters are normally plotted against VO₂, such a discrepancy is minor since in healthy subjects such as those in Caiozzo’s study, VO₂ and time are linearly related at submaximal work rates.) It was found that the ventilatory equivalent method had the highest correlation to the LT (r = 0.93, p <0.001) and on
average, came closest to the LT, underestimating the LT by only 0.01 L·min⁻¹. The ventilatory equivalent method also showed the highest test-retest correlation 

\( r = 0.93, p < 0.001 \). The V-slope method correlated less well with the LT 

\( r = 0.83, p < 0.001 \). Gas exchange and lactate data were only collected once every 30

seconds. This infrequent collection frequency may have made the more subtle break-

points in the \( \dot{V}E \) and \( \dot{V}CO_2 \) graphs less easy to discern.

The V-slope and the ventilatory equivalent methods of determining the VT were compared by Shimizu using breath-by breath gas exchange data \(^{146}\). A greater number of
tests were uninterpretable using the V-slope method as compared to the ventilatory

equivalent method. The VT using the ventilatory equivalent method was not different

than using the V-slope method when \( \dot{V}O_2 \) was expressed in absolute terms. The

ventilatory equivalent method however yielded a 2 percent higher VT than the V-slope

method when expressed as a percentage of each patient's \( \dot{V}O_{2peak} \).

2.4.4 Other possible mechanisms of the ventilatory threshold

The CO₂ produced from the buffering of lactic acid and from oxidative

phosphorylation as well as the \( H^+ \) released from the dissociation of lactic acid and from
glycolysis, both act on the carotid bodies to stimulate an increase in ventilation.

However, central regulators of ventilation have also been identified which increase \( \dot{V}E \) in
response to acid infusion. Such findings have been shown in animals after carotid body
denervation \(^{169}\). Patients with McArdle’s syndrome exhibit a VT even though they lack
lactate dehydrogenase and can not produce lactic acid. This demonstrates that CO₂ and
\( H^+ \) may not be the only stimulators of the VT. Plasma catecholamines as well as
increased potassium concentrations in the blood also stimulate carotid body discharge and subsequent $V_E$ augmentation. There also exists a point during a GXT that EMG signals within the skeletal muscle abruptly change their pattern. It has been found that this "EMG threshold" coincides with the VT even when peripheral chemoreceptor activity has been experimentally attenuated. Thus, neuronal activity originating from the exercising muscle and higher motor centers also contribute to the VT. The isolated stimulation of group III and IV skeletal muscle afferent nerves has been shown to change breathing patterns in a similar fashion to the changes that occur at the VT. These group III and IV neurons are sensitive to increases in $K^+$, $H^+$, catecholamines and decreases in $PO_2$.

2.4.5 Relationship between the lactate and ventilatory thresholds

The changes in blood lactate concentration and ventilation were observed to occur in concert with each other as early as 1927. Both the V-Slope and ventilatory equivalent methods of determining the VT rely on the release of excess $CO_2$, without a concomitant excess in $O_2$ consumption. Wasserman reasoned that the excess $CO_2$ release was the product of bicarbonate buffering lactic acid as reliance on anaerobic glycolysis increased during exercise above the "anaerobic threshold". However, the existence of a causal relationship between an increased reliance on anaerobic metabolism and excess $CO_2$ release has been hotly debated.

A good correlation exists between the VT and the LT in post-MI patients as revealed in a study by Dickstein. Breath-by-breath data were obtained using a metabolic cart and smoothed with an eight breath rolling average. A single VT was
determined using the average from all three methods mentioned above in 30 patients.
The LT was determined as the point where lactate concentration (collected every 20
seconds) increased systematically above baseline levels. The correlation coefficient
between the LT and the VT was 0.77 (p < 0.01). There was no significant difference in
the absolute $\dot{V}O_2$ between the LT and VT.

A significant departure of the LT from the VT (using the ventilatory equivalent
method) was demonstrated using a ramp protocol on a cycle ergometer in 39 male
athletes (aged 20 ± 2 years, $\dot{V}O_{2\text{max}} = 63 \pm 8 \text{ ml-kg}^{-1}\cdot\text{min}^{-1}$) \textsuperscript{27}. The VT was found to be
significantly lower than the LT (41 versus 44 ml-kg\textsuperscript{-1}\cdotmin\textsuperscript{-1}). These results demonstrate a
possible uncoupling of the VT and LT during a ramp protocol in young athletes.

A review by Loat\textsuperscript{102} on the other hand suggests that most of the published
evidence points to a high correlation between the VT and the LT ($r = 0.95$ by Davis in
1976, $r = 0.94$ by Reinhard in 1979, $r = 0.80$ by Bouhuys in 1966, and $r = 0.92$ by
Anderson & Rhodes in 1991) \textsuperscript{2, 16, 39, 140}. Some of these studies are reviewed below.

Reinhard et al. found a high correlation ($r = 0.94$) between the VT (using the
ventilatory equivalent method) and the LT (from capillary blood analysis) during cycle
ergometry in 15 volunteers\textsuperscript{140}. Reinhard mentioned that there is no necessity for invasive
measurements in order to determine the anaerobic threshold. In a similar study by Davis
et al., the minute ventilation method of determining the VT was compared to the LT \textsuperscript{39}.
In 9 subjects the mean values for VT and LT were 59.8 ± 7.4 and 59.7 ± 7.1 % of
$\dot{V}O_{2\text{peak}}$, respectively ($r = 0.95$).

Improvements in the VT and LT were shown to occur in concert when Denis et al.
trained 5 cyclists for 40 weeks \textsuperscript{41}. The VT determined from exercise tests at weeks 0, 10,
20, 30 and 40 were 74, 75, 83, 81 and 81% of $\dot{V}O_{2\text{peak}}$, respectively, while LT values
were 72, 74, 80, 82 and 79% of VO\textsubscript{2peak}. Correlations between the VT and LT were significant (r= 0.79, p < 0.001). The minute ventilation method, which has been shown to overestimate the LT, was used by Denis et al.\textsuperscript{40} to determine the VT. Correlations between the VT and LT may have been even stronger had he used either the V-slope or ventilatory equivalent method of determining the VT.

Given the evidence found in the literature, it is likely that exercise above the ventilatory threshold does indeed correspond to higher blood lactate concentrations than exercise below the VT. Thus, during exercise above the VT, a distinct metabolic stress, different than exercise below the VT is experienced.

2.4.6 Increases in the \(\text{\textit{\textsc{V}}}\text{O}_2\) at the ventilatory threshold with exercise training

The direct correlation between the \(\text{\textit{\textsc{V}}}\text{O}_2\) at the LT and endurance performance\textsuperscript{4,133} suggests that improvements in the VT can increase the intensity with which activities of daily living can be performed in elderly patients with CAD. The location of the VT may serve as a useful gauge for the quality of life\textsuperscript{114}.

Improvements of 44% in the VT were documented by Davis et al.\textsuperscript{38} in previously sedentary middle-aged males after 9 weeks of training 4 days per week, for 45 minutes per session. Exercise intensities were prescribed at a heart rate that was half-way between the VT and VO\textsubscript{2peak} for the first 4 weeks. Training intensities were then increased for the last 5 weeks to 70% of the difference between the HR at the VT (HR\textsubscript{vt}) and the VO\textsubscript{2peak}.

A short study by Doi et al.\textsuperscript{44} began training post-MI patients free of beta-blocker therapy, two weeks after their infarction. The VT was measured prior to training in order
to set the exercise intensity at 90% of the HRvt. One group of patients entered a two-week exercise training program, walking 20 minutes daily (n = 21), while others acted as controls and were not prescribed exercise (n = 12). In only two weeks, the exercise group experienced a significantly greater increase in the VT (2.3 ml·kg⁻¹·min⁻¹) than the control group (0.2 ml·kg⁻¹·min⁻¹). Correlations between VT improvement and patient age or the size of the infarction were poor. Interestingly, a strong correlation between the time to the AT and the time to the turning point of EF (the point when EF no longer increases, but decreases during an incremental exercise test) were confirmed in Doi's study (r = 0.80). This helps demonstrate that improved cardiac function can contribute to an increase in the VO₂ at the AT in response to exercise training. Although peripheral adaptations are said to be the main contributor to VT improvement with training, this is not the first report of a connection between cardiac function and the VT. It has been reported in another study that post-MI patients with a low VT have more severe exercise-induced ventricular dysfunction compared to those with a higher VT.

In response to exercise training, Koyal et al. reported an increase in VT, both in absolute terms (from 1.43 to 1.86 L·min⁻¹) and as a percentage of VO₂peak (from 68.2% to 73.6%) in CAD patients receiving beta-blockade. Patients in the Koyal study exercised at 75-85% of their HRpeak for 12-16 weeks, 3 times per week for 30-40 minutes.

Another study designed to examine changes in the VT in response to exercise training involved 41 patients with documented CAD. One group of patients (n = 19) underwent supervised exercise training for 30 to 45 minutes per session, on average 2.2 days per week, for one year. Training intensities were aimed at 60% to 85% of VO₂peak using the HRR method. The average initial VT of the subjects in this study was measured at 62% of VO₂peak. Control subjects (n = 22) were given home-based exercise
programs with exercise intensities of less than 50% $\dot{V}O_2$peak. Although the exercise group demonstrated a significant increase in absolute $\dot{V}O_2$peak and in treadmill time, improvements in the VT did not occur. Sensitivity to changes in the VT was not optimal given that gas exchange samples were taken once per minute. Compliance in this study was quite poor, ranging from 25% to 97% of a three-day per week exercise prescription. Out of the 19 patients in the exercise group, 7 participated less than twice per week.

Thomas et al.\textsuperscript{163} presented further evidence of the equivocal nature of the VT in response to training. Previously inactive elderly males (mean age = 62 ± 5 years) were randomized into a control group that performed no exercise (n = 44) or an experimental group that trained for 30 minutes per day, on average 2.9 times per week at 73% of HRR (n = 45). After one year of training, the exercise group exhibited a statistically significant increase in the $\dot{V}O_2$peak (from 2.28 to 2.70 L·min\(^{-1}\)) but increases in the VT (from 1.31 to 1.39 L·min\(^{-1}\)) were not significant. The intensity with which the exercise group trained was equated to 65 to 80% of $\dot{V}O_2$peak while the VT was initially measured at a mean of 58% of $\dot{V}O_2$peak. No changes in either the $\dot{V}O_2$peak or the VT were measured in the control group after one year.

Gaesser and Poole analyzed the changes in the VT versus changes in the LT after 3 weeks of training \textsuperscript{60}. Six subjects trained 6 days per week at 70-80% of $\dot{V}O_2$peak for 30 minutes per session. The $\dot{V}O_2$ at the LT and the VT (using the ventilatory equivalent method) were not significantly different before training. The 30% increase in the LT was significant after training however the 7% increase in the VT was not significant. The LT was significantly higher than the VT after training despite a high correlation between the two parameters ($r = 0.86, p < 0.05$). There exists the possibility that the mechanisms responsible for the improvements in the LT and the VT are different.
Further evidence is needed in order to more clearly elucidate the effects of exercise training on the VT, since the data available in the literature are inconclusive. Certain subpopulations may be more prone than others to increases in the VT with exercise training. It is the purpose of this study to determine the VT response to training in an elderly cohort with CAD. The intensity threshold for improvements in the VT has been difficult to pinpoint. While such high intensity exercise has failed to increase the VT, patients training below the VT have enjoyed VT improvements.

2.4.7 Training above or below the ventilatory threshold

It has been established that the metabolic stresses experienced above and below the VT are distinct. Exercise above the VT is associated with metabolic acidosis, decreased exercise endurance, increased ventilatory drive, altered VO₂ and VCO₂ kinetics and altered substrate utilization when compared to exercise below the VT\textsuperscript{170}. It is reasonable then to hypothesise a differential effect between training above the VT and training below it. Some investigation on this topic has already been carried out.

Casaburi examined differential training intensities by dividing 27 healthy people into three training groups\textsuperscript{23}. One group trained at a work rate below the LT, a second group trained slightly above the LT and a third well above the LT. All subjects performed the same amount of work per session, five times per week for five weeks. Even though the lowest intensity training group worked at an average of 43\% of their VO₂peak (below the ACSM's recommended training intensity), training-induced reductions in \(\dot{V}_E\), \(\dot{V}CO_2\), \(\dot{V}O_2\), HR, lactate concentration and catecholamine levels at submaximal exercise intensities were not significantly different between groups.
Significant differences between groups in blood lactate concentration during the training sessions did not confer any advantage in training adaptations. Changes in the $\dot{V}O_2\text{peak}$ or the $\dot{V}O_2$ at the LT were not reported for any patients. Although the exercise stimulus for this study was well controlled, there was a small number of subjects per group and the duration of the study was quite short.

The Training Level Comparison (TLC) study by Jensen et al.$^8$ analyzed the differential training effects of exercise at 50% of the $\dot{V}O_2\text{peak}$ (low group) and 85% of the $\dot{V}O_2\text{peak}$ (high group). 186 men with CAD trained three times per week for 45 minutes per session. The VT increased significantly ($p < 0.003$) for both groups (from 15.7 to $16.2 \text{ml\cdotkg}^{-1}\cdot\text{min}^{-1}$ in the low group and from 15.9 to $17.5 \text{ml\cdotkg}^{-1}\cdot\text{min}^{-1}$ in the high group) after 6 months of training. The VT was significantly higher in the high group after training ($p < 0.003$). Six months of training significantly increased the $\dot{V}O_2\text{peak}$ in both groups, with the high group exhibiting a significantly higher $\dot{V}O_2\text{peak}$ after training (from $24.3 \text{to} 26.1 \text{ml\cdotkg}^{-1}\cdot\text{min}^{-1}$ (+ $7.4\%$) in the low group versus $25.3 \text{to} 27.2 \text{ml\cdotkg}^{-1}\cdot\text{min}^{-1}$ (+ $7.5\%$) in the high group, $p < 0.001$ for both time and treatment effects).

The purpose of the TLC study was to determine if differential benefits occurred between those patients who exercised at either extreme of the ACSM's recommended exercise prescription intensity of 50 - 85% of the $\dot{V}O_2\text{peak}$. Although it was not the intention of the TLC study to compare the effects of training above and below the ventilatory threshold, Jensen points out that the low group exercised, on average below the VT (mean VT = 65% of the $\dot{V}O_2\text{peak}$, training range = 40-90% of the $\dot{V}O_2\text{peak}$ at baseline) and the high group exercised, on average above their VT (mean VT = 63% of the $\dot{V}O_2\text{peak}$, training range = 43-88% of the $\dot{V}O_2\text{peak}$). The patients within each group however trained at various degrees of anaerobic metabolism. Those patients in the low
group with a VT close to 50% of the $\dot{V}O_{2\text{peak}}$ would have had significantly higher blood lactate concentrations than those patients in the low group a VT closer to 80% of the $\dot{V}O_{2\text{peak}}$. Conversely, those patients in the high group, exercising above their VT may have had similar blood lactate levels as those patients in the low group exercising above their VT. Thus, the metabolic stress between groups in the TLC study may not have been significantly different.

In a study by Henritze\textsuperscript{77}, 11 college-aged women trained at work rates corresponding to 69 Watts (W) above their LT (LT group) and 12 women trained at their LTs (=LT group) for 12 weeks, 5 times per week, while 12 women acted as controls. The total work performed per session was controlled between exercise groups. No differences in the $\dot{V}O_{2\text{peak}}$, $\dot{V}O_{2}$ at the LT or LT/$\dot{V}O_{2\text{peak}}$ were observed between the exercise groups before or after training. The >LT group showed a significant increase in the $\dot{V}O_{2}$ at the LT after training while both the >LT and the =LT groups increased their LT/$\dot{V}O_{2\text{peak}}$ as a result of training.

The sensitivity of the LT determination in Henritze’s study was quite low. Blood lactate was drawn during each stage of a discontinuous incremental exercise test. Each increment in exercise intensity however corresponded to increases in $\dot{V}O_{2}$ that were 10-15\% of the $\dot{V}O_{2\text{peak}}$. As a result, increases in the LT were more likely to be detected in the >LT group than in the =LT group since such changes were likely to be smaller in the latter group. While the LT increased in the >LT group by 48\% ($p < 0.05$) and only 18\% in the =LT group ($p > 0.05$) this disparity can not be carried over to the population that is to be examined in the current study. The initial fitness of the women in Henritze’s study was very high (mean = 41 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}) whereas the subjects in the current study have
not been exercising. It is likely that low intensity training has a more profound effect on the previously sedentary than on those who have good initial aerobic fitness.

The effects of high versus low intensity training were examined in a previously sedentary, elderly cohort (aged 65-75 years) in a study by Belman7. A low intensity group (LI) trained at 35% of the HRR (n = 9) while a high intensity (HI) group trained at 75% of the HRR (n = 8). The subjects trained for 8 weeks, 4 days per week, for 30 minutes per session. All subjects in the LI happened to be training below their LTs (mean training intensity = 72% of LT) while those in the HI group all trained above their LTs (mean training intensity = 121% of LT). The VO2peak and LT increased equally in both groups. Since the exercise prescriptions were based on the HRR and not the LT, some patients in opposite groups were likely to have had similar blood lactate concentrations during their training sessions.

In a study by Sady, overweight females in their early twenties trained 4 times per week for 8 weeks at either 80% of the VO2peak (HI group, n = 7) or at 40% of the VO2peak (LO group, n = 7). All subjects in the LO group trained below the VT while all subjects in the HI group trained above the VT. Total VO2 per session was controlled between groups. Improvements in the VO2peak were not significantly different between groups. The high intensity group showed a statistically significant increase in the VT (59%, p < 0.05) whereas the low intensity group only showed trends towards such improvements (27%, p > 0.05)142. The small number of subjects in this study may have decreased the power to identify some between-group differences.

A summary of the studies comparing high and low exercise training regimens is given in table 2.4.3.
To our knowledge, an effective separation in the anaerobic stress experienced between two exercise groups has not been reported to date in an elderly cohort with CAD. This distinction in anaerobic stress can be accomplished by prescribing exercise training intensities either above or below the VT. When prescribed exercise based on the VT, the differences in training intensities when expressed as a percentage of the $\dot{V}O_{2peak}$ may not necessarily be large between groups. This may succeed however, in providing a differential training stimulus. Significantly different responses to training above or below the VT should be elucidated, if they exist, in order to further clarify the most efficacious training stimulus for an elderly cohort with CAD. It is the purpose of the present study to examine the effects of training prescriptions based on exercise intensities above and below the VT.
<table>
<thead>
<tr>
<th>Investigator, Year</th>
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<tr>
<td>Behan, 1991.</td>
<td>17 sedentary elderly</td>
<td>LI group: 35% HRR HI group: 75% HRR</td>
<td>VO_{2peak} and VO_2 at LT increased equally in both groups</td>
</tr>
<tr>
<td>Casaburi, 1994.</td>
<td>27 healthy individuals</td>
<td>Group 1: below LT Group 2: slightly above LT Group 3: well above LT</td>
<td>Decreases in V_E, VCO_2, VO_2, HR, lactate concentration and catecholamine levels at submaximal exercise not different between groups</td>
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<td>Hentritze, 1985.</td>
<td>35 healthy women</td>
<td>&gt;LT group: 69 W above LT =LT group: at LT Control group: no exercise</td>
<td>VO_{2peak} unchanged after training in all groups VO_2_{peak} increased significantly in both groups post-training VO_{2peak}, VT higher in HI group than in LO group</td>
</tr>
<tr>
<td>Jensen, 1996.</td>
<td>186 men with CAD</td>
<td>LO group: 50% VO_{2peak} HI group: 85% VO_{2peak}</td>
<td>VO_{2peak} increased in both HI and LO groups VT increased significantly in HI group</td>
</tr>
<tr>
<td>Sady, 1980.</td>
<td>18 overweight females</td>
<td>LO group: 80% VO_{2peak} HI group: 40% VO_{2peak} Control group: no exercise</td>
<td>VO_{2peak} increased in both HI and LO groups VT increased significantly in HI group</td>
</tr>
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Chapter 3: Methods

3.1 Design

Subjects were randomly assigned to aerobically train either above (HI group) or below (LO group) their ventilatory threshold for 13 weeks. The patient care was provided by the Cardiac Program of the Toronto Rehabilitation Institute (TRI)\textsuperscript{92}. Cardiopulmonary variables assessing cardiovascular fitness were measured before (T1) and after (T2) the training period. Anthropometric data were also collected before and after training. All data collection was performed at the TRI.

3.2 Subject selection

All patients in the TRI are referred to the program by their family physician or cardiologist. In order to qualify for participation into the study, subjects were required to have a documented CAD event within the previous 24 months. Acceptable CAD events included myocardial infarction, greater than 70% occlusion in a major coronary artery, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty or stenting. Patients were required to have a detectable ventilatory threshold and achieve a minimum of 3 METS on a graded cycle ergometer exercise test for inclusion into the study. Subjects were excluded from the study if their VT exceeded 80% of their VO\textsubscript{2peak}. Patients with orthopaedic ailments, intermittent claudication or other non-cardiac related illnesses that prohibited walking or stationary cycling were excluded from the study. Individuals with heart failure, high-grade arrhythmias, unstable angina, uncontrolled type
I or type II diabetes or hypertension were excluded. Patients who were involved in an exercise program within a 12-month period prior to the start of this study were also excluded from participation. Patients who had altered their dose or type of medication less than one month prior to, or during the study were excluded. Informed consent (Appendix 1) was obtained from the patients and any questions they had were answered. The Ethics Committee of the TRI approved the protocol.

3.3 General health assessment

After subjects were screened and had consented to the study, a general health assessment was performed immediately before the GXT at T1 and at T2. Patients were asked about current smoking habits, medication changes, recent hospital visits, orthopaedic problems, and the amount of exercise currently performed. Patients were also asked how much time had passed since they last took their medication or ingested caffeine.
3.3.1 Anthropometry

In order to predict body fat percentage, three skinfold measurements were taken from the right side of the patients using skin callipers (John Bull, British Indicators Ltd, London). The triceps fold was taken as a vertical line midway between the acromion process and the ulna. The supra-iliac fold was taken as the diagonal line two inches above the iliac crest. A subscapular fold was taken as the diagonal fold one inch below the subscapular process. The percentage body fat was calculated (from Durnin and Rahaman, 1967) as follows:

i) sum of skinfolds (SOS)
   \[= 2 \cdot \text{triceps mm} + 2 \cdot \text{subscap mm} + 3 \cdot \text{suprailiac mm}\]

ii) body fat % for men
    \[= -0.0011 \cdot (\text{SOS})^2 + 0.3659 \cdot \text{SOS} + 3.1925\]

iii) body fat % for women
     \[= -0.0011 \cdot (\text{SOS})^2 + 0.3796 \cdot \text{SOS} + 10.531\]

Body weight, subject height as well as abdomen and hip girths were also measured.

3.3.2 Graded exercise test

Prior to the exercise test, a twelve-lead ECG tracing was acquired from the patients after 3-4 minutes of quiet supine rest. Patients then cycled in an upright position on an electronically-braked cycle ergometer (Sensormedics Ergo-metrics 800S, Yorba Linda) while a seven-lead ECG recording was constantly monitored using a multi-channel stress testing system (Marquette Electronics Incorporated, Milwaukee).
ST-segment depression, ST-segment slope, ectopic beats and a 25-beat average tracing were calculated automatically.

Patients performed a warm-up by pedalling at 60 revolutions per minute with no resistance on the cycle for 2 minutes. After the warm up, the resistance on the cycle was increased by 17.6 W every minute in a step-wise fashion until the patient reached exhaustion or until the supervising physician stopped the test. Reasons for stopping the test before the patient wilfully did so included i) greater than 4mm of ST-segment depression, ii) complex cardiac arrhythmias, iii) other electrocardiographic signs of significant cardiac ischemia, or iv) a plateau in \( \dot{V}_{O_2} \) despite an increasing work rate.

During exercise, arterial blood pressure was measured every minute from the right arm using an automated sphygmomanometer (Quinton Model 412, Japan). The automated blood pressure readings were verified manually by the attending physician at rest and at maximal exercise using a manual blood pressure cuff on the left arm (W.A. Baum Co. Inc. "Baumanometer", Copiague). A rating of perceived exertion based on the 14-point (6-20) Borg scale\(^{15} \) was also determined every minute.

Throughout the exercise test, the subjects breathed through a three-way valve (Hans Rudolph Inc., Kansas City) connected to a metabolic cart (Sensormedics 2900, Yorba Linda). Expired gases were collected breath by breath into a mixing chamber, sampled continuously and 20-second averages were reported using on-board software (Sensormedics 2900 Elite 2, Yorba Linda). The volume of expired gas (\( \dot{V}_{E} \)) was analyzed by a mass flow sensor (Sensormedics, Yorba Linda). Air was dried using a Perma-Pure line and analyzed by an infrared CO\(_2\) analyzer (Andros 412A, Berkeley). The air then travelled through a soda lime chamber to remove the CO\(_2\) and was subsequently analyzed by a zirconium O\(_2\) analyzer (Sensormedics, Yorba Linda).
The metabolic cart was turned on at least 30 minutes prior to the GXT to allow for adequate warm up and equilibration of the gas analyzers. The O₂ and CO₂ analyzers were calibrated using known concentrations of gases (mixture 1: O₂ 16%, CO₂ 4%, balance N₂; mixture 2: O₂ 26%, CO₂ 0%, balance N₂). Volume calibration was accomplished using a three-liter syringe.

### 3.3.3 Gas exchange analysis

In order to compare the \( \dot{V}O_{2\text{peak}} \) data before and after training, the fraction of patients achieving a “true” maximal \( \dot{V}O_{2} \), or “\( \dot{V}O_{2\max} \)”, was determined at T1 and T2. Three criteria were used in order to determine if a \( \dot{V}O_{2\max} \) had been attained: 1) an increase in the \( \dot{V}O_{2} \) of less than 140 ml·min\(^{-1}\) during the last minute of incremental work; 2) a peak RER greater than 1.15; 3) demonstrated respiratory compensation for metabolic acidosis. If two of the three criteria mentioned above were met, the maximal \( \dot{V}O_{2} \) attained during the GXT was considered to be a “\( \dot{V}O_{2\max} \)”. However, the “maximal” rate of oxygen consumed by the subjects during the GXTs in this study will be referred to as the \( \dot{V}O_{2\text{peak}} \). The \( \dot{V}O_{2\text{peak}} \) implies that the patient may not have necessarily reached a cardiovascular limitation during the GXT. The \( \dot{V}O_{2\text{peak}} \) (measured in L·min\(^{-1}\) and in ml·kg\(^{-1}\)·min\(^{-1}\), STPD) was calculated as the maximum volume of oxygen consumed during any 20-second average.

The \( \dot{V}O_{2} \) at the ventilatory threshold (measured in L·min\(^{-1}\) and in ml·kg\(^{-1}\)·min\(^{-1}\), STPD) was determined independently by two observers using the three methods outlined in section 2.4.3. Samples of the V-slope, ventilatory equivalent and minute ventilation graphs are displayed in Figures 3.1, 3.2 and 3.3. The VT gathered by
BC from the ventilatory equivalent graph was used for the final analysis in this study. The thresholds from the other graphs and those from DM were used as confirmation. Discrepancies between the graphs and between observers were discussed between DM and BC on an individual basis.

Discrete 20-second averages of $\dot{V}_E$ (L·min$^{-1}$, BTPS), $\dot{V}O_2$, and the RER were smoothed by a 3-point rolling average for data analysis. RPE (6-20 point Borg Scale$^{15}$), heart rate (beats·min$^{-1}$ = bpm) and blood pressure data (mmHg) recorded every minute were not smoothed. The elapsed time (seconds) from the start of exercise to the VT was interpolated using the smoothed $\dot{V}O_2$ data. $\dot{V}_E$ at the VT was also interpolated using the smoothed $\dot{V}_E$ data. RPE and heart rate at the VT were interpolated using the discrete RPE and heart rate data.

The $O_2$ pulse (ml·beat$^{-1}$) was calculated as the $\dot{V}O_2$ divided by heart rate and the double product (mmHg·beat·min$^{-1}$) was calculated as the systolic blood pressure times heart rate.

Cardiopulmonary data were also collected at two submaximal work rates. The first submaximal work rate was chosen to be between 16.7 and 33.4 W above VT at both T1 and T2 for each patient. The second work rate was chosen to be between 16.7 W and 33.4 W below the VT at T1 and T2.
Figure 3.1: Sample of Output used to determine VT with V-slope Method

Figure 3.1 The arrow indicates the VT = 1.317 L·min$^{-1}$. 
Figure 3.2: Sample of Output used to determine VT with Ventilatory Equivalent Method

Figure 3.2 The arrow indicates the $VT = 1.318 \text{ L} \cdot \text{min}^{-1}$. 
Figure 3.3: Sample of Output used to determine VT with Minute Ventilation Method

The arrow indicates the \( VT = 1.524 \text{ L} \cdot \text{min}^{-1} \).
3.4 Exercise prescription

The intensity of exercise prescribed to each subject was calculated based on the VT. Those randomised to exercise above the VT trained at a heart rate corresponding to a \( \bar{VO}_2 \) that was 10% above the VT/\( \bar{VO}_2 \)peak as interpolated from the GXT data. Those randomized to exercise below the VT were prescribed a heart rate corresponding to a \( \bar{VO}_2 \) that was 10% below the VT/\( \bar{VO}_2 \)peak. (This method of prescribing exercise intensity was not the standard practice at the TRI.) GXT data from T1 were used to determine target heart rates. An example is presented below:

**Patient randomized to exercise above the VT:**

**Measured Parameters:**

\[
\begin{align*}
\bar{VO}_{2\text{peak}} & = 2.0 \text{ L} \cdot \text{min}^{-1} \\
\text{VT} & = 1.2 \text{ L} \cdot \text{min}^{-1}
\end{align*}
\]

**Training Intensity Calculations:**

\[
\begin{align*}
\text{VT/}\bar{VO}_{2\text{peak}} & = 1.2/2.0 \\
& = 60\%
\end{align*}
\]

Training intensity = VT/\( \bar{VO}_2 \)peak + 10%

= 60% + 10%

= 70% of \( \bar{VO}_2 \)peak

70% \( \bar{VO}_{2\text{peak}} \) = .70 \times 2.0 \text{ L}

= 1.4 \text{ L} \cdot \text{min}^{-1}

*The training intensity for this subject would therefore be at a heart rate corresponding to a \( \bar{VO}_2 \) of 1.4 L·min⁻¹.*

All patients were instructed to walk five times per week. Each workout was preceded by a 10-minute warm-up of light stretching and slow walking. The duration of exercise was set at 1.6 km for the first two weeks of the training regimen. The walking distance was then increased by 1.6 km every 2 weeks, depending on the level of tolerance.
displayed by the patient, until a maximum of 4.8 km was accomplished. At the end of each exercise session, patients were instructed to cool-down by walking slowly for 5 minutes.

Patients in this investigation were instructed to exercise at a specific target heart rate. Patients were trained to determine their heart rates by radial artery palpation. Those patients who were not able to reliably determine their heart rates were given a walking speed (in minutes per mile) by the exercise leaders, determined on an individual basis to elicit the appropriate training heart rate. Patients exercised under physician supervision once per week on the indoor track at the TRI during which time exercise leaders checked palpation skills and the appropriateness of the training prescription. For the remaining 4 weekly exercise sessions, patients were instructed to determine a route of suitable distance outdoors, close to their homes. Patients were instructed to walk outside if the sidewalks were not iced-over or if the wind-chill factor was above -10 °C. During inclement weather, patients were instructed to walk inside shopping malls and were given appropriate maps outlining the distances that could be covered at various locations.

Each week before the exercise session at the TRI, the patients received counselling on cardiac risk factor reduction and education on a range of topics relating to their rehabilitation.
3.5 Compliance

Patients were instructed to complete an exercise training log (example shown in Appendix 2) and return it to the TRI on their weekly visits to the centre. The exercise prescription, the total distance (miles) and time (min) of each workout as well as the pre- and post-exercise 10-second pulse were documented in the log. Patients were instructed to document symptoms as well as reasons for not completing the exercise prescription.

3.6 Statistical analysis

A two-way analysis of variance was performed in order to examine between group differences. However, within-subject changes examined using the two-way ANOVA can not detect the efficacy of training above the ventilatory threshold and below the ventilatory threshold separately. In order to examine the efficacy of each training stimulus, within group differences were examined using paired, two-tailed Student's t-tests. Compliance and exercise stimulus data were compared using unpaired two-tailed Student's t-tests. In order to examine between group differences in meeting the VO$_{2\text{max}}$ criteria, a Wilcoxon t-test for dependent samples was used as the non-parametric statistical tool.
Chapter 4: Results

4.1 Subject characteristics

In the final analysis, the LO group consisted of 20 males and 3 females. The HI group consisted of 12 males. There were no significant differences in age between the groups. The mean age of the HI group was 61.6 ± 3.5 years at T1 while the mean age of the LO group was 62.4 ± 2.1 years (all values are means ± standard error).

All patients in the study had documented coronary artery disease and had suffered at least one cardiac event prior to commencement of the study. Table 4.1 shows the frequency of cardiac events in the LO and HI groups. One patient may have contributed to more than one category if numerous events were suffered.

Table 4.1: Distribution of cardiac events

<table>
<thead>
<tr>
<th>Event</th>
<th>LO Group (n = 23)</th>
<th>HI Group (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Coronary Bypass</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
4.2 Exercise compliance

4.2.1 Attrition

At T1, 27 people were randomized into the LO group and 30 were to participate in the HI group. During the training period, 11 patients in each group were excluded from the study for a variety of reasons outlined in Table 4.2. Cardiac events included angioplasty (2), MI (1), onset of exercise-induced angina (2), and emergency bypass surgery (1). Other illnesses included pneumonia (1), influenza (1) and cancer (1). Three people in the LO group were dissatisfied with their low intensity exercise prescription and requested to be excluded from the study.

| Table 4.2: Subject dropout |
|-----------------------------|-----------------|-----------------|
|                             | LO Group | HI Group |
| Patients Tested at T1       | 27       | 30       |
| Reasons for Dropout         |          |          |
| Change in Beta-Blocker Medication | 2   | 0       |
| Cardiac Event               | 2        | 4       |
| Other Illness               | 2        | 1       |
| Did not Comply to Exercise Intensity | 3   | 0       |
| Did not Exercise            | 2        | 6       |
| Total Dropouts              | 11       | 11      |
| Patients Tested at T2       | 16       | 19      |

4.2.2 Group assignment

At T2, the exercise diaries of the remaining 16 patients in the LO group and 19 patients in the HI group were examined in order to determine adherence to the exercise
prescription. The heart rates during the training sessions as well as the duration of each training session were analyzed. It was found that 3 people in the LO group were actually training at heart rates corresponding to exercise intensities above the VT. Conversely, 10 people in the HI group were found to be training below their VTs. The data in this study were analyzed such that the patients who “crossed over” from the LO group were included for analysis in the HI group and vice-versa. The reassignment of patients from one group to the other is shown in Table 4.3.

### Table 4.3: Subject reassignment

<table>
<thead>
<tr>
<th></th>
<th>LO Group</th>
<th>HI Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random Assignment</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Crossed Over</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Post-Training Reassign</td>
<td>23</td>
<td>12</td>
</tr>
</tbody>
</table>

#### 4.2.3 Training intensity

The average training heart rates of the patients were calculated from the exercise diaries that were submitted. The training heart rates were subtracted from the HRvt (T1) for each patient. The average differences between the training heart rates and the HRvt for the LO and HI groups are compared in Figure 4.1. On average, the LO group exercised 8 ± 1 bpm below their HRvt while the HI group exercised 6 ± 2 bpm above their HRvt (p < 0.001 between groups).
4.2.4 Training frequency

Although the training regimen spanned 13 weeks, all patients did not submit a complete set of weekly exercise logs. It was considered that no exercise was completed in weeks for which no logs were submitted. According to the exercise logs, the LO group trained on average 4.4 times per week for 11.1 weeks while the HI group exercised 4.5 times per week for 11.3 weeks. There was no statistical difference in training frequency between groups.

4.2.5 Training duration

The patients recorded the duration of each exercise session in their diaries. The LO group trained for 37 ± 2 minutes per session while the HI group averaged 33 ± 3 minutes per session (p = 0.288). The cumulative duration of training over the 13-week program was averaged for each group and compared in Figure 4.2. On average the LO group exercised for 1903 ± 210 total minutes while the HI group averaged 1785 ± 280 minutes. There was no significant difference in total time exercised between groups.

4.2.6 Total training volume

Total training “volume” for each week was calculated by multiplying the weekly duration of exercise (measured in min) by the average heart rate achieved during exercise in that week (beats·min⁻¹). The units of this training volume measurement are therefore in “heart beats” (beats). The weekly training volumes for the entire program were
totalled for both groups. Figure 4.3 shows that the two groups did not differ significantly in total training volume. The LO group averaged 166,695 ± 19,857 total heart beats and the HI group averaged 178,873 ± 33,514 total beats.
Figure 4.1: Training heart rate minus heart rate at the VT

Training intensities expressed as heart rates above the VT (> 0) or below the VT (< 0), averaged from all exercise sessions. Error bars denote the mean ± SEM.

a: p < 0.001
Figure 4.2: Total training duration

Training duration expressed as the accumulated time exercised during the 13-week training period. Error bars denote means ± SEM.
Figure 4.3: Total training "volume"

Training "volume" calculated as the accumulation of training heart rate-duration of exercise for all sessions of the 13-week training program. Error bars denote means ± SEM.
4.3 Cardiopulmonary exercise tests

4.3.1 Peak oxygen uptake

At T1, 77% of all patients satisfied the $\dot{V}O_{2\text{max}}$ criteria while at T2, 69% satisfied the criteria. There were no significant differences between T1 and T2 ($p = 0.405$).

The peak oxygen consumption or $\dot{V}O_{2\text{peak}}$ (ml·kg$^{-1}$·min$^{-1}$) improved significantly in both the HI and LO groups after training (see Figure 4.4). The $\dot{V}O_{2\text{peak}}$ of the LO group increased from $17.8 \pm 0.8$ to $19.3 \pm 0.8$ ml·kg$^{-1}$·min$^{-1}$ with training ($p = 0.015$) while the HI group improved from $18.5 \pm 1.1$ to $21.2 \pm 1.3$ ml·kg$^{-1}$·min$^{-1}$ ($p = 0.002$). There were no significant differences between groups at either T1 ($p = 0.614$) or T2 ($p = 0.207$), nor was there any significant difference in the degree of improvement between groups ($p = 0.814$). Analysis of the absolute $\dot{V}O_{2\text{peak}}$ (L·min$^{-1}$) yielded the same statistical relationships.

The training heart rate, when expressed in terms of the HRvt or the HRR, did not correlate with changes in the $\dot{V}O_{2\text{peak}}$, as indicated in Table 4.4 below. The correlation between the percent change in $\dot{V}O_{2\text{peak}}$ and the training heart rate minus the HRvt is shown in Figure 4.5.

The change in $\dot{V}O_{2\text{peak}}$ with training did not correlate well with the $\dot{V}O_{2\text{peak}}$ before training in absolute ($r = 0.11$, $p = 0.54$) or relative terms ($r = -0.15$, $p = 0.40$). However, the change in $\dot{V}O_{2\text{peak}}$ (L·min$^{-1}$) was negatively correlated with the age of the patients ($r = -0.47$, $p = 0.005$), as shown in Figure 4.6.
4.3.2 Ventilatory threshold

There was a slight increase in the VT in both groups after training (see Figure 4.7), however the changes were not significant for either the LO group ($11.0 \pm 0.4$ versus $11.2 \pm 0.3$ ml·kg$^{-1}$·min$^{-1}$, $p = 0.656$) or the HI group ($11.2 \pm 0.5$ versus $11.9 \pm 0.6$ ml·kg$^{-1}$·min$^{-1}$, $p = 0.211$) between T1 and T2, respectively. There was no significant difference between the groups at either T1 ($p = 0.765$) or T2 ($p = 0.221$) nor was the change in VT different between the groups ($p = 0.403$). Similar statistical relationships were demonstrated when the VT was expressed in absolute terms (L·min$^{-1}$). The changes in the VT are shown for each subject in Figure 4.8. Training heart rate did not correlate with changes in the VT as shown in Figure 4.9. There was a negative correlation between the initial VT and the change in the VT with training as shown in Figure 4.10. Inter- and intra-observer agreement for the determination of the VT is shown in Appendix 3 and 4, respectively. Agreements between the ventilatory equivalent method and the minute ventilation and V-slope methods are shown in Appendix 5.
Table 4.4: Selected correlations between training heart rate and changes in fitness

<table>
<thead>
<tr>
<th></th>
<th>Training Heart Rate minus VT Heart Rate</th>
<th>Training HR as %HRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in relative $\dot{V}O_2_{peak}$</td>
<td>Pearson Correlation: 0.225</td>
<td>0.193</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed): 0.195</td>
<td>0.267</td>
</tr>
<tr>
<td></td>
<td>n: 35</td>
<td>35</td>
</tr>
<tr>
<td>Percent change in relative $\dot{V}O_2_{peak}$</td>
<td>Pearson Correlation: 0.183&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.203</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed): 0.294</td>
<td>0.241</td>
</tr>
<tr>
<td></td>
<td>n: 35</td>
<td>35</td>
</tr>
<tr>
<td>Change in relative $\dot{V}O_2$ at the VT</td>
<td>Pearson Correlation: 0.282</td>
<td>0.152</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed): 0.101</td>
<td>0.384</td>
</tr>
<tr>
<td></td>
<td>n: 35</td>
<td>35</td>
</tr>
<tr>
<td>Percent change in relative $\dot{V}O_2$ at the VT</td>
<td>Pearson Correlation: 0.207&lt;sup&gt;β&lt;/sup&gt;</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed): 0.232</td>
<td>0.497</td>
</tr>
<tr>
<td></td>
<td>n: 35</td>
<td>35</td>
</tr>
</tbody>
</table>

<sup>a</sup> represented in Figure 4.5
<sup>β</sup> represented in Figure 4.9

4.3.3 Cardiopulmonary parameters above and below the ventilatory threshold

Cardiopulmonary parameters in the LO group were obtained from average work rates of $34.1 \pm 3.6$ and $83.1 \pm 4.1$ W during both T1 and T2. These work rates corresponded to exercise intensities that were below and above the VT, respectively, at both T1 and T2. Data from the HI group was reported the same way, with data obtained from work rates of $36.9 \pm 5.4$ W (below the VT for all patients in the HI group) and at $87.7 \pm 7.2$ W (above the VT for all patients in the HI group) at both T1 and T2. There was no statistical difference in the work rates below, or above the VT between groups.

The percent change $(100 \cdot (T2-T1)/T1)$ in the means of various cardiopulmonary variables
are shown in Table 4.5 below. Corresponding pairwise levels of significance are also given.

The \( \dot{V}O_2 \) at the work rates above and below the VT did not change with training. Differences between the \( \dot{V}O_2 \) measured at T1 and T2 for both submaximal work rates are displayed for the individual subjects in Figure 4.11. Figure 4.12 displays the RER at the work rates below and above the VT for both groups at T1 and T2. The HI group demonstrated a statistically significant decrease in the RER above the VT after training \((p = 0.006)\). Changes in RER with training were not statistically different between the groups at either work rate. The power to detect such differences however was 0.305 at the work rate above the VT and 0.158 at the work rate below the VT.

The heart rates above and below the VT are shown in Figure 4.13. The LO group demonstrated significant decreases in HR above \((p = 0.045)\) and below \((p = 0.028)\) the VT. No such changes were demonstrated in the HI group. Changes in HR at either work rate were not significantly different between the groups. The power to detect a difference between the groups below the VT was 0.058 and the power to detect such changes above the VT was 0.094.

The oxygen pulse in the HI group was significantly higher than the low group at T1 and T2 at the work rate above the VT as displayed in Figure 4.14. The oxygen pulse increased significantly with training within the LO group at the work rates above and below the VT. An improvement of 5.8\% was demonstrated below the VT \((p = 0.017)\), while a 6.0\% improvement was seen above the VT \((p = 0.007)\) within the LO group. Changes within the HI group did not reach statistical significance. Changes due to training were not significantly different between groups.
Table 4.5: Cardiopulmonary changes at work rates above and below the ventilatory threshold

<table>
<thead>
<tr>
<th></th>
<th>Work rate Below VT</th>
<th>Work rate Above VT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LO Group</td>
<td>HI Group</td>
</tr>
<tr>
<td></td>
<td>(34.1 ± 3.6 W)</td>
<td>(83.1 ± 4.1 W)</td>
</tr>
<tr>
<td>VE</td>
<td>-1.3% p = 0.413</td>
<td>+2.8% p = 0.568</td>
</tr>
<tr>
<td>VEqO₂</td>
<td>-2.4% p = 0.175</td>
<td>+1.5% p = 0.851</td>
</tr>
<tr>
<td>VEqCO₂</td>
<td>-1.0% p = 0.391</td>
<td>+1.7% p = 0.504</td>
</tr>
<tr>
<td>VO₂</td>
<td>+1.1% p = 0.871</td>
<td>+1.8% p = 0.837</td>
</tr>
<tr>
<td>RER</td>
<td>-1.5% p = 0.224</td>
<td>-0.2% p = 0.876</td>
</tr>
<tr>
<td>RPE</td>
<td>+1.3% p = 0.733</td>
<td>-3.1% p = 0.378</td>
</tr>
<tr>
<td>HR</td>
<td>-5.1% p = 0.028</td>
<td>-0.3% p = 0.838</td>
</tr>
<tr>
<td>O₂ Pulse</td>
<td>+5.8% p = 0.017</td>
<td>+0.1% p = 0.985</td>
</tr>
</tbody>
</table>

[□]: statistically significant change after training
[□]: non-significant change after training
4.3.4 Resting and peak heart rate

The resting heart rate decreased from 62 ± 2 bpm to 60 ± 2 bpm (p = 0.099) in the LO group and from 66 ± 4 to 65 ± 3 bpm (p = 0.754) in the HI group. There were no significant differences between groups at either T1 or T2, nor were the changes over time significantly different between groups (p = 0.207).

Although the heart rate at maximal exercise increased from 125 ± 5 to 130 ± 6 and from 122 ± 7 to 127 ± 9 bpm in the LO and HI group, respectively, these changes with training were not significant (p = 0.143 and p = 0.127). Changes between groups were not significantly different (p = 0.744).

4.3.5 Peak oxygen pulse

The peak oxygen pulse of the HI group was significantly higher than that of the LO group at T1 (12.8 ± 0.9 versus 10.7 ± 0.5 ml·beat⁻¹, p = 0.032) and at T2 (13.9 ± 0.9 versus 11.5 ± 0.5 ml·beat⁻¹, p = 0.017). Pairwise comparisons revealed that the LO group improved significantly with training (p = 0.004) while the improvement in the HI group was not statistically significant (p = 0.127). These relationships are shown in Figure 4.15. The changes in the peak oxygen pulse between groups were significantly different (p = 0.017).
4.4 Anthropometry

No significant changes in measures of waist or hip girth, body mass, body mass index, body fat percentage or lean mass were detected between T1 and T2 in any of the groups.
Figure 4.4: Peak oxygen consumption

The effects of training on VO₂ (ml·kg⁻¹·min⁻¹) between groups. Error bars denote means ± SEM.

a: significant difference between Time 1 and Time 2 within LO group (p = 0.015)
b: significant difference between Time 1 and Time 2 within HI group (p = 0.002)
Figure 4.5: Percent change in $\dot{V}O_{2\text{peak}}$ versus training intensity

Relationship between the changes in $\dot{V}O_{2\text{peak}}$ and training intensity.

$r = 0.183, p = 0.294$
Figure 4.6: Change in $\dot{V}O_{2\text{peak}}$ versus patient age

Figure 4.6 Relationship between patient age and $\dot{V}O_{2\text{peak}}$ response to training.

$r = -0.467$, $p = 0.005$
**Figure 4.7**  
\( \dot{\text{VO}}_2 \) **at the ventilatory threshold**

The effect of training on the \( \dot{\text{VO}}_2 \) at the ventilatory threshold (ml·kg\(^{-1}\)·min\(^{-1}\)). Error bars denote means ± SEM.
Figure 4.8: Individual changes in the ventilatory threshold

The effect of training on individual changes in the VO2 at the VT. Bars extending above the zero line denote an increase in the VT after training while those below the zero line demonstrate a decrease in the VT.
Figure 4.9: Percent change in $\dot{V}O_2$ at the ventilatory threshold versus training intensity

Relationship between training heart rate (as it relates to the HRvt) and the change in $\dot{V}O_2$ (ml·kg$^{-1}$·min$^{-1}$) at the ventilatory threshold. $r = 0.207$, $p = 0.232$

Note: When the two outliers at 50% and 57% are removed from the analysis, $r = 0.300$, $p = 0.090$. 
Figure 4.10: Initial ventilatory threshold versus the change in ventilatory threshold with training.

Figure 4.10  Relationship between initial fitness (VO$_2$ at the ventilatory threshold) and the response to training (change in VO$_2$ at the ventilatory threshold).

$r = -0.574$, $p < 0.001$
Figure 4.11: Changes in $\dot{V}O_2$ at a workload above and below the ventilatory threshold

![Graph showing changes in $\dot{V}O_2$](image)

Figure 4.11: Each black and white pair of bars denotes the effect of training (T2 minus T1) on the $\dot{V}O_2$ at the two submaximal work rates in a single patient. The white bars represent the changes in $\dot{V}O_2$ below the VT and the black bars represent changes above the VT. No significant changes in $\dot{V}O_2$ due to training were found at these work rates. The dashed bars represent a change of less than 10 ml·min$^{-1}$. 
Figure 4.12: RER at a submaximal work rates above and below the VT

RER at two submaximal work rates before and after training. Error bars denote means ± SEM.

*L: mean work load below VT for LO group = 34.1 ± 3.6 W
^L: mean work load above VT for LO group = 83.1 ± 4.1 W
*H: mean work load below VT for HI group = 36.9 ± 5.4 W
^H: mean work load above VT for HI group = 87.7 ± 7.2 W

b: significant difference between Time 1 and Time 2 within HI group, above the VT (p = 0.006)
Figure 4.13: Heart rates at work rates above and below the ventilatory threshold

Heart rates at two submaximal work rates before and after training. Error bars denote means ± SEM.

*L*: mean work load below VT for LO group = 34.1 ± 3.6 W
*L*: mean work load above VT for LO group = 83.1 ± 4.1 W
*H*: mean work load below VT for HI group = 36.9 ± 5.4 W
*H*: mean work load above VT for HI group = 87.7 ± 7.2 W

*a*: significant difference between Time 1 and Time 2 within LO group, below the VT (p = 0.028)
*aa*: significant difference between Time 1 and Time 2 within LO group, above the VT (p = 0.045)
Figure 4.14: Oxygen pulse at work rates above and below the ventilatory threshold

Figure 4.14: Oxygen pulse at two submaximal work rates before and after training. Error bars denote means ± SEM.

*L: mean work load below VT for LO group = 34.1 ± 3.6 W  
^L: mean work load above VT for LO group = 83.1 ± 4.1 W  
*H: mean work load below VT for HI group = 36.9 ± 5.4 W  
^H: mean work load above VT for HI group = 87.7 ± 7.2 W

a: significant difference between Time 1 and Time 2 within the LO group, below the VT (p = 0.017)  
aa: significant difference between Time 1 and Time 2 within the LO group, above the VT (p = 0.007)  
c: significant difference between the HI and LO groups above the VT:  
  Time 1 (p = 0.021)  
d: significant difference between the HI and LO groups above the VT:  
  Time 2 (p = 0.023)
Figure 4.15: Maximum oxygen pulse

Figure 4.15 The effect of training on the maximum oxygen pulse. Error bars denote means ± SEM.

a: significant difference between Time 1 and Time 2 within the LO group (p = 0.004)
b: significant difference between the HI and LO groups at Time 1 (p = 0.032)

d: significant difference between the HI and LO groups at Time 2 (p = 0.017)
e: changes with training significantly different between groups (p = 0.007)
Chapter 5: Discussion

5.1 Introduction

The main finding of this study was that exercise training performed either above or below the ventilatory threshold (VT) elicited similar effects in improving exercise tolerance in patients with coronary artery disease. This was demonstrated by statistically similar increases in VO2peak between groups. Both groups demonstrated a reduction in submaximal heart rates, however these changes reached statistical significance only in the LO group, likely due to its larger sample size. Finally, the ventilatory threshold was not affected by exercise training in either group, contrary to the hypothesis stated in Chapter 1.

5.2 Ventilatory threshold

The increases in the VO2 at the ventilatory threshold in response to training were not statistically significant in either group. These results are in contrast to the Jensen’s Training Level Comparison Study (TLC) 87. To date, the TLC study is the most comprehensive look at the effects of training intensity in the CAD population, with enrollment into the study spanning three years, examining 186 men 102,103. All the patients in the TLC study exercised under supervision at a cardiac rehabilitation centre three times per week. The “low group” trained at 50% of the VO2peak while the “high group” trained at 85% of the VO2peak. Six months of training in the TLC study produced an increase in the VO2 at the VT of 0.5 ml·kg⁻¹·min⁻¹ in the low group and
1.6 ml·kg⁻¹·min⁻¹ in the high group. Significant differences in the VT between groups occurred only after the differential training stimulus.

In the present study, the LO group demonstrated increases in the VT of $0.2 \pm 0.4$ ml·kg⁻¹·min⁻¹ while the HI group showed an increase of $0.7 \pm 0.5$ ml·kg⁻¹·min⁻¹. The changes in the VT were not statistically significant in either group. Similar VT changes between groups in the current study may be due to the small differences in exercise intensities between the two groups when ignoring the location of the VT. When expressed as a percentage of the $\dot{V}O_2_{\text{peak}}$, the difference in training intensities between the two groups in the present study was much less pronounced than in the TLC study. The LO group in the current study exercised slightly below their VTs, which averaged 63% of their $\dot{V}O_2_{\text{peak}}$. The HI group exercised above their VTs, which averaged 61% of their $\dot{V}O_2_{\text{peak}}$. The TLC study was designed to separate the training intensities of its two groups by 35% of the $\dot{V}O_2_{\text{peak}}$.

The low group in the TLC study exercised at a lower percent of their $\dot{V}O_2_{\text{peak}}$ than the LO group in the current study (50% versus 63% of $\dot{V}O_2_{\text{peak}}$, respectively) but exhibited a larger increase in the VT. Upon closer review, a disparity in the absolute training heart rates between the TLC and the current study was found as displayed in Table 5.1 below. The low group of the TLC study trained at a higher mean heart rate than either the HI or LO groups in the current study ($99.9 \pm 1.8$ vs. $87.0 \pm 2.7$ and $98.6 \pm 5.5$ beats per minute, respectively). Thus the low group of the TLC study trained at a lower percent of $\dot{V}O_2_{\text{peak}}$ however, at a higher heart rate than either group in the current study and demonstrated a larger increase in the VT.

The contrasting training effects between the TLC study and the current study also occur in the face of similar metabolic stresses with respect to the VT. The low group in
the TLC study exercised on average below the VT, while all the subjects in the LO group in the current study exercised below the VT. The high intensity group in the TLC study and the HI group in the current study both trained above the VT. These comparisons suggest that the threshold for improving the \( \dot{V}O_2 \) at VT may occur in response to an absolute training heart rate and not to a specific percentage of the \( \dot{V}O_2^{\text{peak}} \), or a specific percentage of the VT. In fact, Klainman and Koyal also reported improvements in the VT in their CAD patients who trained at heart rates greater than 100 bpm \(^{97,99}\). This is not the first implication of an absolute training heart rate threshold for aerobic improvement. De Vries suggested that an exercise heart rate in the range of 95-100 bpm was sufficient to improve aerobic capacity in the elderly \(^{40}\).

A possible mechanism for the importance of heart rate for improvements in the VT is that a minimum training blood flow requirement may exist at the periphery in order to stimulate some of the peripheral adaptations to training \(^{82}\). Although peripheral blood flow during training was not analyzed in the studies mentioned above, assuming that stroke volume and peripheral vasodilation were similar, it is reasonable to assume that blood flow at the periphery is proportional to heart rate. Since it is likely that the peripheral adaptations in response to training are responsible increases in the VT\(^{33}\), the hypothesis that a peripheral blood flow threshold exists for improvements in the VT seems reasonable.
Table 5.1: Comparison of training stimuli between the TLC and the current study

<table>
<thead>
<tr>
<th>STUDY:</th>
<th>TLC (Jensen, 1996)</th>
<th>CURRENT (Cayen, 1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Achieved training HR (bpm)</td>
<td>99.9 ± 1.8</td>
<td>122.3 ± 2.0</td>
</tr>
<tr>
<td>Achieved training %(\bar{V}O_2\text{peak})</td>
<td>&gt; 50</td>
<td>&lt; 85</td>
</tr>
<tr>
<td>Pretraining VT/(\bar{V}O_2\text{peak}) (%)</td>
<td>65</td>
<td>63</td>
</tr>
</tbody>
</table>

There are a variety of peripheral adaptations that can increase the \(\bar{V}O_2\) at the VT. Older coronary patients have exhibited increases in peripheral muscle capillary density and augmented oxidative enzyme activity after only 3 months of endurance training. Such augmented oxygen delivery, diffusion and reduction mechanisms may delay the reliance on anaerobic metabolism. In addition to these changes, older individuals have demonstrated increases in Krebs cycle, electron transport chain and \(\beta\)-oxidation enzymes in response to endurance training. A morphology shift towards more aerobic type II muscle fibres has also been reported. The improvement in central nervous system recruitment of skeletal muscle fibres seen after resistance training is likely also a mechanism of augmented peripheral oxygen utilization after endurance training. All these physiological changes can delay the reliance of the skeletal muscle on anaerobic metabolism during a graded exercise test. Such changes would therefore increase the \(\bar{V}O_2\) at the VT.

When contrasted with the TLC study, the blunted increases in the VT in the current study may also be due to the small sample size and the shorter time frame of the present study. In the current study, 18 out of 23 patients in the LO group submitted
exercise diaries that indicated training more than 3 times per week for 10 weeks and 9 out of 12 subjects in the HI group submitted diaries to that effect. In the TLC study however, approximately 70% attendance was achieved in six months of a three-day per week prescription, involving 186 patients. Although the frequency of exercise may have been lower for the TLC study, the exercise stimulus was experienced for more weeks and by many more people.

The effect that the training heart rate has on the VT is further demonstrated in a study by Klainman97. This long-term investigation involved training 3 groups of patients with various degrees of CAD and 1 group of patients with left ventricular dysfunction (LVD) at an exercise intensity equal to the VT, for 6 to 9 months, 2 to 3 times per week. Ranking the groups according to the degree of improvement in the VT/VO2peak directly follows the intensity of training when expressed as an absolute heart rate: The single-vessel disease group showed the greatest increase in the VT/VO2peak, followed by the LVD group and the 2-vessel disease group, while the 3-vessel disease group showed the lowest percentage improvement in the VT/VO2peak. Values for percentage improvement in the VT/VO2peak were +9%, +8%, +5% and -4%, respectively, while training intensities were 104, 102, 101 and 92 beats per minute, respectively. This was despite a similar metabolic stress with respect to the VT, since training heart rates corresponded to the HRvt for all groups (see Table 5.2, page 102). These results seem to support the notion that improvements in the VT occur in response to the absolute training heart rate despite similar stress relative to the VT.

It is important to note that the single vessel disease group in Klainmans’ study were younger (age mean ± SD = 53 ± 10 years) than those in the current study and none of the patients in the present study had LVD. The age and etiology of disease of the two-
vessel and three-vessel disease groups in Klainman's study however were more related to the patients in this investigation and experienced more similar changes in the VT/VO2peak.

In further examining the effects of training heart rate and metabolic stress with respect to the VT, it is useful to outline some training studies conducted on healthy elderly subjects. Training intensity was explored by Belman who trained two groups of elderly subjects (age = 69 ± 1 years), four days per week, for eight weeks. The high intensity (HI) group exercised at 75% of their HRR (mean training HR = 127 bpm) and the low intensity (LI) group exercised at 35% of their HRR (mean training HR = 100 bpm). The anaerobic threshold in this study was not based on the ventilatory threshold but was based on the lactate threshold (LT). It was calculated that the HI group trained at an average of 121% of their LT and the LI group trained at approximately 72% of their LT. Significant improvements in the VO2 at the LT occurred in both the LI group (Δ = + 2.3 ml·kg⁻¹·min⁻¹) and in the HI group (Δ = + 1.8 ml·kg⁻¹·min⁻¹). Both the current study and Belman's study involved high intensity and low intensity groups that trained above and below the anaerobic threshold, respectively. However, the training heart rates of the subjects in the current study were lower, and the subjects exhibited less improvement in the anaerobic threshold than those in the Belman's study. Again it seems that the adaptation in anaerobic threshold is more responsive to absolute heart rate than it is to the "anaerobic stress" during training.

It is important to note however that blood lactate measurements were not performed in the current study. It is possible that in the present study, age-related decreases in H+ diffusion or respiratory insensitivity to H+ could have blunted changes in the VT in the face of an improved LT. This could explain the observations that the LI group in Belman's study, training at 100 bpm showed an increase in the
lactate threshold while the HI group in the present study, training at 99 bpm did not show an increase in the ventilatory threshold.

The responsiveness of the VT to the absolute training heart rate and not the training intensity relative to the VT is further exhibited when comparing the present study to a study on healthy elderly subjects conducted by Fabre et al. In Fabre's study, one group trained at an exercise intensity equal to 50% of the heart rate reserve ("Standard Group") while a second group trained at the VT ("Individual Group")\(^5\). Training heart rates in the Standard Group averaged 115 bpm while the Individual Group trained at 129 bpm. Since the HR\(_{vt}\) in the Standard Group averaged 127 bpm, this group trained 12 bpm below their VT, similar to the LO group in the current study which trained 8 bpm below their VT. Using the V-slope method, Fabre found an increase in the VT of 2.0 ml·kg\(^{-1}\)·min\(^{-1}\) in the Standard Group versus a 4.1 ml·kg\(^{-1}\)·min\(^{-1}\) increase in the Individual Group. While both of these changes were statistically significant, the changes in the VT were not statistically different between the groups. The Standard Group in Fabre's study trained at 92% of the HR\(_{vt}\) and similarly, the LO group in the present investigation trained at 91% of the HR\(_{vt}\). The only difference in the training intensity between these two groups was the absolute training heart rate (115 bpm in the Standard Group versus 87 bpm in the LO group). This provides even further evidence that increases in the VT are more responsive to absolute training heart rate than to the heart rate relative to the VT.

The training heart rates in the current study (34% of HRR in the LO group and 58% of HRR in the HI group) can also be compared to the training heart rate of 70% of HRR in 33 healthy elderly studied by Blumenthal et al.\(^1\). Sixteen weeks of training 3 days per week elicited changes in the VT from approximately 750 ml·min\(^{-1}\) to approximately 850 ml·min\(^{-1}\) in these patients who averaged 67 years of age. Blumenthal
does not compare the training intensities of his subjects to their initial VT. Although the subjects in Blumenthal's study were healthy, the disparity in training heart rate between his study and this investigation, coupled with the concomitant increase in the VT can not be ignored.

Although training intensity is important in increasing the VT, the frequency and duration of exercise are also an integral part of the training "volume". At a training intensity of 129 bpm, 19 CAD patients in a study conducted by Sullivan demonstrated no change in the VT after exercising for approximately one hour per week (30-40 min·d\(^{-1}\) X 2 d·wk\(^{-1}\))\(^{158}\). It is likely that training one hour per week was too small a training stimulus to elicit changes in the VT.

High training heart rates also elicited improvements in the VT in a study by Koyal et al.\(^{99}\). Nine young patients with CAD, demonstrated increases of 30% in the VT after four months of training 30-40 minutes per day, 3 times per week at heart rates ranging from 98 to 128 beats per minute. Since the initial VT/\(\dot{V}O_2\)peak was 0.68 (range 0.57 to 0.78), all patients were likely to be exercising farther above their VT than the HI group did in the present study. Patients in the Koyal study averaged 52 ± 7 years of age, or 10 years younger than patients in the current study. Again it was demonstrated that high training heart rates elicited increases in the VT.

Table 5.2 summarizes the findings of the studies reviewed in this section in addition to the current study. It is demonstrated that despite the method by which exercise prescriptions were administered (%HRR method, %\(\dot{V}O_2\)peak method, % HR\(_\text{peak}\) or HR\(\text{vt}\)), the VT responded significantly to training heart rates above approximately 100 bpm. One must realize that 100 bpm is not a strict threshold and that small improvements in the VT have been shown to occur below this intensity (such as in the
subjects of the present study). However, only 5 out of the 12 elderly CAD patients in the HI group of the current study showed an increase in their VT. It is therefore recommended that in order to increase the VT in elderly patients with CAD, exercise prescriptions should be at heart rates higher than 100 bpm.

Finally, in agreement with the current study, a meta-analysis conducted by Londere in 1997 found that exercise intensity, when expressed in terms of metabolic stress, had no statistical effect on the degree of improvement in the VT. Thirty-four studies on the effects of exercise training on the anaerobic threshold (AT) were examined. Londere’s meta-study did not include those by Fabre, Jensen, Klainman, Koyal or Sullivan. Training intensities in the meta-analysis were categorized as -1) “detraining” (subjects became less active), 0) “control” (no exercise), 1) “trained below the lactate or ventilatory threshold”, 2) “trained at the lactate or ventilatory threshold”, 3) “trained at the OBLA or RCMA” and 4)“trained above the OBLA or RCMA”. Metabolic stress from level 1 to 4 did not have significantly different effects on the ventilatory threshold ($p > 0.22$) or the lactate threshold ($p > 0.13$). There was however a general increase in the AT with training. These results further diminish the importance of metabolic stress on changing the AT and leave room for other explanations such as the absolute training heart rate hypothesis proposed here. Twenty-two out of the thirty-five studies analyzed by Londere however were performed on subjects under the age of 32. This of course differs significantly from the subjects in the current study who averaged 62 years of age.
In addition to the proposed greater importance of absolute heart rate rather than metabolic stress in improving the VT, other explanations may exist that explain the findings in the current study and those found in the literature. Considering Belman's study, it is possible that the lactate threshold (LT) and the ventilatory threshold (VT) are affected differently by exercise training as outlined in detail in section 2.4.

Exercise training may preclude an effective determination of the VT using the ventilatory equivalent method. Gaesser points out that exercise training may cause a decrease in the $\dot{V}_E$, thus flattening the slope of the VEqO₂. Possible mechanisms for a decreased $\dot{V}_E$ in response to training include a training-induced decrease in functional residual volume. Such higher tidal volumes would allow a lower breathing frequency for a given $\dot{V}_E$. Lower breathing frequencies are associated with a lower dead space to tidal volume ratio. Thus, higher lung volumes at a given work load could decrease the $\dot{V}_E$ due to the decreased fraction of air that is not in contact with gas exchange membranes. In the present study, no statistically significant change in the $\dot{V}_E$ was noted when the HI and LO groups were considered separately. Indeed upon further examination, when the $\dot{V}_E$ data of the two exercise groups were pooled, it was found that the $\dot{V}_E$ did decrease at the work rate above the VT after training from 37.0 ± 1.1 L·min⁻¹ to 35.8 ± 1.1 L·min⁻¹ ($p = 0.022$; Figure 5.1)

The results of this study compared to those studies involving younger subjects suggest that the elderly may demonstrate a blunted increase in the VT in response to training. Aging decreases the ratio of fast-twitch to slow-twitch muscle fibres. Since it has been postulated that the VT reflects a shift in use from the oxidative to glycolytic muscle fibres, it is possible that the attrition of glycolytic muscle fibres
generally experienced by the elderly can blunt changes in the VT with training. A decreased rate of lactate diffusion\textsuperscript{166} and decreased respiratory sensitivity to CO\textsubscript{2}\textsuperscript{100} has also been attributed to aging. Given the classic explanation that the VT is the result of increased CO\textsubscript{2} production as bicarbonate buffers lactic acid\textsuperscript{170}, decreased lactate diffusion and respiratory insensitivity to CO\textsubscript{2} may attenuate a change in the VT with aging. It is also possible that the loss of muscle mass associated with aging may decrease the number or activation of the peripheral nerves\textsuperscript{145}. It is the peripheral neural afferents that have been demonstrated to cause an increase in $\dot{V}_E$ associated with the VT.

The results of the current study also demonstrated a negative correlation between the initial VT and the change in the VT with training ($r = -0.574$, $p < 0.001$, see Figure 4.10). This suggests that those who are less fit respond more positively to light intensity exercise training than those who are more fit. These results are supported by epidemiological data demonstrating that the greatest benefit is achieved when the least fit take up exercise\textsuperscript{71}.

In summary, the data from the present study compared to that in the literature indicate that the VT is more responsive to absolute training heart rate than it is to the heart rate relative to the VT. It is also possible that the failure to detect a change in the VT may be partially due to the old age of the subjects in the current study. A low statistical power in addition to a short exercise stimulus may have also precluded the detection of a training-induced adaptation in the VT. Finally, the data in the current study support previously reported findings that the less fit are more responsive to exercise training than those who are initially more fit.
Figure 5.1: Minute ventilation above and below the ventilatory threshold (HI and LO groups pooled)

Figure 5.1: Minute ventilation of all subjects below the VT and above the VT before training (Time 1) and after training (Time 2). Error bars denote means ± SEM.

a : $\dot{V}_E$ decreased significantly ($p = 0.08$) at the work rate above the VT. No change in the $\dot{V}_E$ was demonstrated below the VT.
Table 5.2: Effects of training on the anaerobic threshold and $\dot{VO}_{2\text{peak}}$ in CAD patients and the elderly

<table>
<thead>
<tr>
<th>Author</th>
<th>Subject Characteristics</th>
<th>Training Stimulus</th>
<th>Training Outcome</th>
<th>Δ Anaerobic Threshold (%)</th>
<th>Δ $\dot{VO}_{2\text{peak}}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belman, 1991</td>
<td>69 17 elderly (8 female)</td>
<td>2 mos. 4 30</td>
<td>LO group: 35% HRR</td>
<td>LT: + 12*</td>
<td>+ 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HI group: 75% HRR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blumenthal, 1989</td>
<td>67 33 healthy elderly (16 female)</td>
<td>4 mos. 3 60</td>
<td>70% HRR</td>
<td>not reported</td>
<td>VT: + 13*</td>
</tr>
<tr>
<td>Fabre, 1997</td>
<td>63 16 elderly (10 female)</td>
<td>3 mos. 2 60</td>
<td>Group A: 50% HRR</td>
<td>VT: + 13*</td>
<td>+ 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group B: HVT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jensen, 1996</td>
<td>54 186 men with CAD 6 mos. 3 45</td>
<td>LO group: 50% $\dot{VO}_{2\text{peak}}$</td>
<td>VT: + 3*</td>
<td>+ 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HI group: 85% $\dot{VO}_{2\text{peak}}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kleinman, 1997</td>
<td>53 10 1-vessel disease 9 mos. 2-3 30-40</td>
<td>100% HVT</td>
<td>VT: + 9%*</td>
<td>+ 25*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100% HVT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koyal, 1985</td>
<td>52 9 CAD (1 female) 4 mos. 3 30-40</td>
<td>75-85% peak HR</td>
<td>VT: + 30*</td>
<td>+ 24*</td>
<td></td>
</tr>
<tr>
<td>Sullivan, 1985</td>
<td>53 19 CAD 1 year 2 30-45</td>
<td>60-85% $\dot{VO}_{2\text{peak}}$</td>
<td>VT: - 3</td>
<td>+ 1</td>
<td></td>
</tr>
<tr>
<td>Thomas, 1985</td>
<td>62 45 elderly men 1 year 3 30</td>
<td>65-80% $\dot{VO}_{2\text{peak}}$</td>
<td>VT: + 6</td>
<td>+ 18*</td>
<td></td>
</tr>
<tr>
<td>Cayen, 1999 (current study)</td>
<td>62 35 elderly, CAD (3 female) 3 mos. 4 35</td>
<td>LO group: 91% HVT</td>
<td>VT: + 2</td>
<td>+ 8*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HI group: 107% HVT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary of reviewed studies examining the effects of exercise training on the VT and $\dot{VO}_{2\text{peak}}$ in the elderly and in patients with CAD.

NOTES: * denotes significant change between pre- and post-training. † denotes significant difference between groups. ‡Klainman, 1997 only reported changes in the VT as a percentage of the $\dot{VO}_{2\text{peak}}$. HRR denotes the "heart rate reserve". HVT denotes the heart rate at the ventilatory threshold. LT and VT denote the lactate and ventilatory thresholds, respectively.
5.3 Peak oxygen consumption

Although the VT was not affected by the exercise training in the current study, patients in both the HI and LO groups enjoyed an increase in the $\dot{V}O_{2\text{peak}}$. When measured in ml·kg$^{-1}$·min$^{-1}$ ("relative" to body weight), the LO group showed an increase in the $\dot{V}O_{2\text{peak}}$ of $8.3 \pm 3.1\%$ while the HI group demonstrated a $14.6 \pm 3.7\%$ increase in the $\dot{V}O_{2\text{peak}}$. In "absolute" terms (measured in L·min$^{-1}$), the $\dot{V}O_{2\text{peak}}$ increased $11.1 \pm 2.8\%$ in the LO group and $15.0 \pm 4.2\%$ in the HI group. Increases in both groups were statistically significant ($p < 0.05$) however the changes were not different between groups. The power to detect differences between the groups in the relative and absolute changes in $\dot{V}O_{2\text{peak}}$ was 0.057 and 0.288, respectively. It is therefore possible that a true difference between groups was not detected due to low statistical power. Changes in the $\dot{V}O_{2\text{peak}}$ could not be explained by training heart rate when expressed in absolute terms or in relation to the $HR_{vt}$ or HRR. Correlations between these heart rate indices and the change in $\dot{V}O_{2\text{peak}}$, expressed in relative or absolute terms, were not significant ($p > 0.05$). Correlations between the absolute training heart rate (bpm) and the change in the absolute and relative $\dot{V}O_{2\text{peak}}$ were weak (absolute $\dot{V}O_{2\text{peak}}$: $r = 0.354$, $p = 0.034$; relative $\dot{V}O_{2\text{peak}}$: $r = 0.204$, $p = 0.240$). However, some studies have shown that higher intensity exercise training elicits greater changes in the $\dot{V}O_{2\text{peak}}$ than low intensity exercise$^{55,147}$. Other studies involving patients with CAD and the elderly have demonstrated similar changes in $\dot{V}O_{2\text{peak}}$ after high and low intensity exercise training$^{7,87}$. Therefore, the increased risk of high intensity exercise$^{14}$ may not need to be incurred in CAD patients due to the equivocal extra benefit demonstrated.
The maximum work rate reached on the GXT increased significantly due to training in the HI group (+8%, \( p = 0.025 \)) and in the LO group (+16%, \( p < 0.001 \)). Since the GXT protocol between T1 and T2 were identical, the time to fatigue during the GXT increased after training in a similar fashion to the improvements in peak work rate. Thus the increase in the \( \dot{V}O_{2\text{peak}} \) did indeed translate to improved exercise tolerance. Positive correlations existed between the changes in the \( \dot{V}O_{2\text{peak}} \) (measured both in absolute and relative terms) and the increases in work rate achieved after training (\( r = 0.572 \) and \( r = 0.547 \) respectively, \( p < 0.001 \)). There were no significant differences between groups in the improvement of maximum work rate achieved. These findings demonstrate that exercise training above and below the VT increased functional capacity in our subjects however no one intensity yielded an advantage.

Decreases in the VT/\( \dot{V}O_{2\text{peak}} \) from 62% to 59%, \( p = 0.026 \) were only found when the two exercise groups were analyzed together. The decreases in the VT/\( \dot{V}O_{2\text{peak}} \) were due to improvements in the \( \dot{V}O_{2\text{peak}} \) and not due to a depression in the VT. These results agree with a study by Thomas et al.\(^{163} \) and point to an increased tolerance for exercise above the VT in those who undergo exercise training. It is interesting to note that when the two groups were considered separately in the current study, the decrease in the VT/\( \dot{V}O_{2\text{peak}} \) approached significance in the HI group (from 61 to 57% of the \( \dot{V}O_{2\text{peak}} \), \( p = 0.052 \)) but not in the LO group (from 63% to 60% of the \( \dot{V}O_{2\text{peak}} \), \( p = 0.155 \)) despite the lower sample size in the HI group. Changes in the VT/\( \dot{V}O_{2\text{peak}} \) however were not different between groups (\( p = 0.836 \)). These results allude to a marginally larger increase in the \( \dot{V}O_{2\text{peak}} \) after training above the VT versus training below the VT. Although the VT corresponds to endurance performance \(^{4} \) and theoretically to the tolerable intensities
of activities of daily living, increases in the \( \dot{V}O_{2\text{peak}} \) have its advantages as well. The \( \dot{V}O_{2\text{peak}} \) is positively correlated with overall survival in heart disease patients \(^{108}\).

Percentage changes in the \( \dot{V}O_{2\text{peak}} \) correlated positively with percentage changes in the VT (\( r = 0.572, p < 0.001 \)). This demonstrates that those people who show increases in the \( \dot{V}O_{2\text{peak}} \) with training will also likely show increases in the VT. Although this relationship does not necessarily imply cause and effect, one could speculate that some of the mechanisms responsible for increasing the VT may be some of the same that increase the \( \dot{V}O_{2\text{peak}} \).

Training-induced increases in the \( \dot{V}O_{2\text{peak}} \) in the elderly have been associated with an augmented a-vO\(_2\) difference at maximal exercise and not an increase in maximal cardiac output \(^{144}\). Increased peripheral muscle capillarization, aerobic enzyme activity, mitochondrial density, muscular recruitment and aerobic fibre-type characteristics can all increase the a-vO\(_2\) difference and thus cause an increase in the \( \dot{V}O_{2\text{peak}} \)^{23}. These same adaptations have also been postulated to delay the onset of significant anaerobiosis^{33} and thus the VT, as described in section 5.2. On the other hand, increased pain tolerance to metabolic acidosis or increased confidence to perform strenuous exercise may contribute to an improved \( \dot{V}O_{2\text{peak}} \) after training, without increasing the VT.

A previous study by Denis et al. \(^{41}\) reported that the \( \dot{V}O_{2\text{peak}} \) improved faster than the VT in response to training. Exercise tests were performed every 10 weeks during a 40-week training study and subjects demonstrated increases in the VT and the LT at week 20 while increases in the \( \dot{V}O_{2\text{peak}} \) occurred by week 10. Thus it is possible that the length of the training program in the current study was too short to elicit improvements in the VT but was sufficiently long to improve the \( \dot{V}O_{2\text{peak}} \). Interestingly, the time course of central adaptations to training \(^{157}\) (likely responsible for increases in the \( \dot{V}O_{2\text{peak}} \)) seems to
be slower than peripheral enzymatic adaptations to training \(^{122}\) (partly responsible for substrate utilization and the VT) \(^{33}\). Thus, increases in the VT may not be solely dependent on peripheral enzyme activity and may also depend on other, more slowly adapting mechanisms, as described in Section 2.4.4. In addition, improvements in the \(\dot{V}O_2\text{peak}\) may not be solely due to central haemodynamic augmentation and may be strongly affected by some more quickly adapting peripheral mechanisms such as increased enzymatic activity or increased tolerance to metabolic acidosis.

The change in the VT correlated negatively with the initial VT in the current study \((r = -0.574, p < 0.001)\). These findings agree with epidemiological data demonstrating that deconditioned subjects benefit more than able-bodied individuals from low intensity exercise \(^{71}\).

In summary, both the HI and LO groups demonstrated increases in the \(\dot{V}O_2\text{peak}\) with training. Although the increases in \(\dot{V}O_2\text{peak}\) between the groups was not statistically different, the HI group demonstrated a slightly higher increase than the LO group in the \(\dot{V}O_2\text{peak}\). There was however no correlation between the training heart rate and the change in \(\dot{V}O_2\text{peak}\). In addition, the correlation between the changes in VT and \(\dot{V}O_2\text{peak}\) demonstrate the possibility that some peripheral adaptations to endurance training may increase both the VT and \(\dot{V}O_2\text{peak}\). In other studies however, the \(\dot{V}O_2\text{peak}\) has been shown to respond faster than the VT to training, which may explain the significant increases in the \(\dot{V}O_2\text{peak}\) without concomitant increases in the VT in this study.
5.4 Acute exercise responses above and below the VT

The $\dot{V}O_2$ at the work rates above and below the VT did not change with training in either group. These results demonstrate that increases in cycling efficiency did not occur as a result of the training stimulus. This outcome was expected since most patients' aerobic training was accomplished by walking. Cycling was chosen to be the modality of the GXT in order to avoid the possible confounding results of improved cycling efficiency with training. One can therefore attribute the demonstrated increases in maximal work rate achieved to the improvement in cardiovascular function and not to increased cycling efficiency.

The RER above the VT decreased significantly in the HI group but not in the LO group, despite a lower sample size in the HI group. Since neither the VT, nor the elapsed time of the GXT to the occurrence of the VT changed in the HI group, the physiological basis of this finding must be explained by a mechanism that is specific to events occurring after the VT.

If some of the mechanisms responsible for the VT are independent of blood lactate concentration (i.e., a shift in fibre-type recruitment or a catecholamine surge), it is possible for substrate metabolism (and thus RER) to change without a concomitant change in the VT. One explanation for the decreased RER above the VT in the HI group is that exercise training above the VT leads to decreased lactate production or improved lactate removal. This would in turn decrease the amount of lactic acid buffered by bicarbonate and thus lower the amount of "non-metabolic" CO$_2$ expired. A possible mechanism for augmented lactate removal is a greater capacity for lactate metabolism by
the heart, liver or skeletal muscle. It can be argued that the augmentation in Cori cycle enzymes in response to training \(^{45}\) may be stimulated by chronic exposure to lactic acid through training above the VT. An increase in hematocrit due to training could potentially augment the buffering of lactic acid by hemoglobin. Attenuated lactate production due to a training-induced increase in muscle mitochondrial content or aerobic enzymes may also decrease lactate accumulation \(^{76}\) and lower the RER above the VT. Exercise below the VT may not provide enough lactic acid exposure to stimulate such an adaptation.

It is known that metabolic acidosis decreases hormone-sensitive lipase activity\(^{18}\) thereby decreasing the release of free fatty acids for metabolism. It can be hypothesized that training-induced improvements in lactate removal at a given workload above the VT decreases lipase inhibition, thereby enhancing fat metabolism. Indeed, increased total fat oxidation has been demonstrated due to training in individuals exercising at intensities as high as 75 to 80% of \(\text{VO}_{2\text{peak}}\)^{33,78}. 
5.5 Heart rate and oxygen pulse

Training-induced bradycardia at a given work rate or $\dot{V}O_2$ has especially great importance in patients with CAD. A decreased heart rate at a given systolic blood pressure decreases the cardiac work rate and thus the oxygen demand of the heart. In addition, a slower heart rate allows a longer time for coronary perfusion during diastole, thus increasing myocardial oxygen supply\textsuperscript{145}. Since patients with CAD may have compromised myocardial perfusion, a decrease in heart rate at a given work rate may decrease the potential for myocardial ischemia and angina.

Heart rates at the workloads above and below the VT decreased significantly in the LO group. Statistically significant changes in HR were not seen in the HI group, likely due to the low number of subjects in this group. The statistical power to detect a change in the HI group was 0.06 for the work rate below the VT and 0.16 for the work rate above the VT ($\alpha = 0.05$). It is possible therefore that a type II error existed when analyzing the data in the HI group. When the data for both the HI and LO groups were combined, significant decreases in heart rates above ($p = 0.022$) and below the VT ($p = 0.031$) were found after training. The changes in heart rate between T1 and T2 were not significantly different between groups at either work rate. Resting heart rates on the other hand, did not decrease significantly due to training. This result is in agreement with previous findings that older individuals show little change in training-induced resting heart rate, in contrast to the training-induced resting bradycardia seen in younger individuals\textsuperscript{12}. 
The O₂ pulse increased significantly at work rates above and below the VT in the LO group. Increases in this parameter did not reach statistical significance in the HI group likely because of the smaller sample size in this group. Changes in the O₂ pulse were not significant between groups at the work rates above or below the VT. Likewise, the maximal O₂ pulse increased significantly due to training in both groups however such changes reached statistical significance only in the LO group, despite similar relative changes within each group (+7.0% in the LO group versus +8.5% in the HI group).

The O₂ pulse data demonstrate that O₂ consumption per heart beat increased as a result of training. According to the Fick equation, VO₂ per heart beat can increase due to a larger stroke volume (central adaptation) or a larger a-vO₂ difference (peripheral adaptation). Niinimaa and Shephard reported no significant increase in either stroke volume or the a-vO₂ difference in elderly patients that trained for 11 months. However, both of these parameters have been improved in subjects who trained in longer studies. Paterson et al. demonstrated in post-MI patients that submaximal a-vO₂ difference was augmented without an increase in stroke volume after the first 6 months of training. After 6 to 12 months of training however, stroke volume did increase. Therefore, it is possible that the increased O₂ pulse in this study was due to peripheral adaptations causing an augmented a-vO₂ difference, since only three months of training were provided. Regardless of the mechanism, the lower HR at a given work rate or VO₂ demonstrates an exercise training effect in this study. The data demonstrate that exercise training slightly above or below the VT does not confer differential decreases in HR or improvements in O₂ pulse during acute exercise above or below the VT.
5.6 Compliance

Out of the 57 patients who passed the screening criteria and were originally included in the study, 61% did not remain in their randomized group or dropped out of the study. Of the remaining 35 patients who were tested at T2, 18 patients in the LO group and 9 patients in the HI group exercised more than 3 times per week for 7 weeks according to the exercise logs that were submitted. This is in response to the exercise prescription of 5 days per week for 13 weeks. Because of the high dropout rate, the “low compliers” were not excluded from the data analysis. The low compliance was likely due to a series of very large snow storms during the winter in which this study took place (Nov. 1998- Mar. 1999). It became very difficult for patients to complete their exercise prescriptions outdoors. It is also possible that some subjects failed to submit all of their exercise diaries and in fact exercised more often than what was recorded.

Some patients who did not exercise at their prescribed training intensities “crossed over” into opposite groups for the purpose of the data analysis. The decision to include these patients in the study was made in order to preserve the sample size, but at the expense of keeping the group assignments random.
5.7 Limitations to the current study

5.7.1 Sample size

Low statistical power for most measures was demonstrated in the HI group likely because of a low sample size ($n = 12$). Of the 30 people originally assigned at random to the HI group, 21 were subsequently either excluded from the study (for reasons outlined in section 4.2, $n = 11$) or crossed over into the LO group ($n = 10$). Only 3 patients however, crossed over from the LO group to the HI group. Evidence from prior studies at the TRI led the investigators of this study to expect only a 40% dropout or non-compliance, instead of the 70% that was demonstrated. It is possible that the low sample size increased the chance of a type II error in discovering a true difference between the HI and LO groups in response to training.

5.7.2 Exercise stimulus and compliance

Controlling the exercise stimulus experienced by each patient was the most challenging aspect to this study. The procedures of the TRI involved an exercise prescription consisting of one day per week of supervised exercise at the TRI and four days of home-based exercise. Thus, trained staff did not monitor the exercise intensity for 80% of the training sessions. Although all patients were instructed on how to monitor their heart rates by radial artery palpation and were tested periodically on these skills at the TRI, the degree of accuracy achieved by the patients was uncertain. In addition, the information recorded by the patients on their exercise diaries could not be confirmed. It
was assumed that the patients would be honest in recording their walking routines. It was possible that patients could have failed to record their exercise sessions or on occasion, neglected to hand in their weekly diaries. It was equally possible that patients could have recorded exercise sessions that never occurred. The resources however, to run a fully supervised exercise program were not available.

Assuming that all the exercise diaries were true representations of the actual training achieved, compliance to the 13-week program was still sub-optimal. Eight of the 35 patients in the final analysis recorded exercising either less than 3 times per week or for fewer than 7 weeks. The exercise stimulus gained by such infrequent exercise would likely be minimal.

Patients originally assigned to the LO group who, on average, reported training at heart rates corresponding to a $\dot{V}O_2$ above their VT were included in the HI group for the final data analysis. The opposite was done for people assigned to the HI group who reported training at heart rates below their VT. Manipulation of the groups in this manner was carried out in order to maintain adequate statistical power. It was possible that the patients in the LO group tending to exercise above their VT were those who were more fit and therefore more able to exercise at high intensities. The opposite was possible for those that crossed over from the HI group. Upon further statistical analysis however, the initial $\dot{V}O_2peak$ or VT, measured in absolute or relative terms was not different between the 3 people that crossed over into the HI group and the 10 patients that crossed over to the LO group. The original random assignment however was obliterated.
5.7.3 $\dot{V}O_2\text{peak}$

According to the criteria outlined in section 3.3.2, 23% and 31% of patients did not attain a "maximal $\dot{V}O_2$" during testing at T1 and T2, respectively. Thus peripheral or central haemodynamic mechanisms may not have been the limiting factors to the $\dot{V}O_2$ attained in some of the exercise tests. Differential degrees of patient motivation or confidence on the part of the attending physician may have added variability to the $\dot{V}O_2\text{peak}$ measures. Heart rate was not used as a criteria for the $\dot{V}O_2\text{max}$ since maximal heart rates were within 10 bpm of the age-predicted maximal heart rate (220 bpm − age) 17% of the time (12 out of 70 tests). Beta-blockade therapy in 27 of the 35 patients (77%) in the current study likely attenuated maximal heart rates.

5.7.4 Study duration

Lastly, more significant improvements in the VT may have been demonstrated if the exercise stimulus lasted for 6 months, similar to the TLC study\textsuperscript{87}. It is possible that larger changes in the VT and the $\dot{V}O_2\text{peak}$ may have precipitated further separation of these parameters between the groups.
5.8 Conclusions

The present investigation sought to examine the differences in prescribing exercise training above and below the ventilatory threshold in patients with CAD.

The following statements can be made with regard to the hypotheses stated in section 1.4:

1) *Training above or below the ventilatory threshold does not necessarily increase the VO₂ at the ventilatory threshold.*

It was hypothesized that training above the VT would confer a greater increase in the VT than training below the VT. This hypothesis was rejected. A change in the ventilatory threshold was not detected in either the HI or LO groups in this investigation. All patients in the current study exercised at heart rates below 100 bpm, with the HI group training at 107% of the HR vt and the LO group training at 91% of the HR vt. Other studies have demonstrated increases in the VT while training at similar percentages of the HR vt but at absolute heart rates much greater than 100 bpm. Thus it is possible that variations in *absolute* training heart rate, rather than in the heart rate *relative* to the VT provides a stronger effect on improvements in the VT. It is possible that a low training heart rate does not provide adequate blood flow at the periphery to elicit the adaptations necessary for increases in the VT.
2) Training above the ventilatory threshold does not elicit a greater increase in the \( \dot{V}O_{2peak} \) than training below the ventilatory threshold.

It was hypothesized that training above the VT would increase the \( \dot{V}O_{2peak} \) to a greater extent than training below the VT. This hypothesis was rejected. Increases in the \( \dot{V}O_{2peak} \) were demonstrated for both the HI and LO groups however these changes were not statistically different between groups. Thus, training slightly above the ventilatory threshold does not confer a greater advantage than training below the ventilatory threshold. Such a message has strong implications for exercise prescriptions in high-risk patients such as those with CAD. The increased risk of exercising at higher intensities need not be taken in order to reap the benefit of an augmented \( \dot{V}O_{2peak} \). The increase in the \( \dot{V}O_{2peak} \) without a concomitant increase in the VT suggests that different mechanisms are responsible for the augmentation of these variables.
5.9 Recommendations for Future Work

The results of this study combined with those in the literature, suggest that improvements in the VT are more responsive to differences in the absolute training heart rate rather than differences in the heart rate relative to the VT. The mechanisms for improvement in the VT however are thought to be peripheral in nature. It is therefore plausible that the absolute heart rate is the root of a “peripheral blood flow threshold”, above which improvements in the VT occur. Thus it would be interesting to elucidate the training blood flow threshold below which improvements in the VT do not occur.

According to the results of the current study, a good starting point for “low intensity training” would be at training heart rates below 100 bpm. It would be interesting to determine if there is a correlation between peripheral blood flow during the training sessions and changes in the VT. It is suggested that the exercise training stimulus endure for at least 6 months.

As a corollary to the above proposal, the effects of chronic exposure to high and low blood lactate concentrations through differential training intensities can also be explored. Such a study would require patients to undergo blood lactate testing during each of the first few training sessions, in order to establish a training target heart rate. Blood lactate determination would be required often throughout the length of the study in order to control for concurrent training adaptations. New techniques to determine blood lactate concentrations through salivary samples may make such a study less uncomfortable for patients and contribute to increased compliance. Central, peripheral
and cardiopulmonary adaptations can be compared in response to the differential training stimuli.

The mechanism for exercise-induced improvements in the VT has not been elucidated in patients with CAD. Although metabolic adaptations at the periphery seem to be responsible for changes in the VT in healthy subjects, the effects of coronary artery disease on peripheral adaptations and their relation to the VT is not known. CAD may alter the contributions of increased capillarization, mitochondrial content, aerobic enzyme activity or fibre-type conversion to the increase in a-vO$_2$ difference compared to healthy volunteers.

Because a strong correlation between endurance running and the ventilatory threshold in athletes has been found, interest in the use of the VT as a measurement of functional capacity has grown since Wasserman's popularization of this parameter in the mid 1970's. Since functional capacity is hampered in many CAD patients, it would be interesting to determine if improving the VT does in fact relate to a concomitant increase in the quality of life in such patients. Disease-specific quality of life questionnaires, incorporating both physical and psychological measures, could be administered to a group of exercising CAD patients. Submaximal exercise tests could also be performed. Study designs can incorporate both the effects of differential training intensities and changes in the VT on the quality of life and the tolerance of activities of daily living.
References


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Appendices

Appendix 1: Consent form
Appendix 2: Example of weekly exercise diary
Appendix 3: Inter-observer agreement of VT determinations using the ventilatory equivalent method
Appendix 4: Intra-observer reproducibility of VT determinations using the ventilatory equivalent method
Appendix 5: Inter-method agreement of VT determinations
Appendix 1: Consent form

TORONTO REHABILITATION INSTITUTE CARDIAC PROGRAMME
INFORMED CONSENT FOR AN EXERCISE TRAINING STUDY

I, ______________________________ agree to participate in a very important cardiac rehabilitation study conducted at the Toronto Rehabilitation Institute. As a patient in this study, I will receive the same cardiac rehabilitation services as in the customary programme but will have one additional exercise assessment (after 12 weeks of exercise training). The risks of an exercise test include, but are not limited to irregular heart rhythms, abnormal blood pressure and very rarely, heart attack or stroke. This test carries the same risks as the exercise test that was previously performed on me. The exercise test will be conducted on a stationary cycle ergometer and simultaneous recording of heart rate, blood pressure, electrocardiogram and respiratory gases will be obtained as usual. I understand that I will be questioned and tested by a physician.

I desire such testing so that the Toronto Rehabilitation Institute can better advise me regarding my exercise programme. I understand that such tests do not entirely eliminate the risks of future events. I further understand that selection and supervision of my test is a matter of professional judgment.

The purpose of this study is to compare two methods prescribing exercise. I understand that I will be asked to participate in the regular rehabilitation programme, with slight changes in the way my exercise is prescribed. I will be randomly assigned to one of two exercise intensity groups. Neither of the exercise intensities exceed the current ACSM guidelines for exercise training and both are expected to improve my cardiovascular function. I will be asked to complete questionnaires relating to my quality of life.

I understand that all of my individual medical and scientific data are confidential and will not be disclosed by the Centre without my written permission. In any written reports or scientific publications, only group data will be reported. I have read the above and I understand it. My questions have been answered to my satisfaction and I understand that I can withdraw from this study at any time without prejudicing my participation in the rehabilitation programme.

No questions asked □ Subject Signature: ________________________________

Questions answered □ Witness Signature: ________________________________

Date: ________________________________
### Appendix 2: Example of Weekly Exercise Diary

**Toronto Rehabilitation Centre**
347 Rumsey Road, Toronto, Ontario M4G 1R7
MARINA CARDIAC WING (416) 425-1117

**Exercise Prescription:**
3.0 min 54 min

**FEB 01 1999**

**Please circle your class day**

<table>
<thead>
<tr>
<th>Date (mo/day)</th>
<th>Type of Exercise</th>
<th>Distance (miles)</th>
<th>Duration (min/sec.)</th>
<th>10 sec. pulse</th>
<th>Symptoms</th>
<th>Remarks</th>
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**COMMENTS:**

- Weight
- Resting Heart Rates (60 sec.) 3 mornings before arising
- Exercise clothes
Appendix 3: Inter-observer agreement of VT determinations using the ventilatory equivalent method

Independent determinations of the VT using the ventilatory equivalent graph were completed by Barry Cayen, B.Sc.H. (BC) and Donald Mertens, M.D. (DM). Discrepancies greater than 100 ml-min\(^{-1}\) were then discussed on an individual basis.
Appendix 4: Intra-observer reproducibility of VT determinations using the ventilatory equivalent method

BC determined the VT twice in twenty randomly-chosen ventilatory equivalent graphs. Determinations were made greater than one month apart.
Appendix 5: Inter-method agreement of VT determinations

**Ventilatory equivalent method versus V-Slope method**

![Graph showing the relationship between Ventilatory Equivalent Method and V-Slope Method. The equation $y = 0.92x - 0.09$ with a correlation coefficient $r = 0.929; p < 0.001$ is displayed, along with $n = 65$.]

All values were determined by BC.
Appendix 5: Inter-method agreement of VT determinations

Ventilatory equivalent method versus minute ventilation method

All values were determined by BC.