

THE EFFECT OF A CARDIAC REHABILITATION EXERCISE PROGRAM ON PLASMA
VISCOSITY, FIBRINOGEN CONCENTRATION, HEMATOCRIT, BLOOD LIPIDS AND
EXERCISE CAPACITY

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ABSTRACT

Hemorheological variables are strong predictors of coronary heart disease. Several cross-sectional and longitudinal training studies on healthy populations suggest that physical activity improves hemorheological profile through a decrease in whole blood viscosity, plasma viscosity (VIS), hematocrit (HCT), and fibrinogen (FIB). Although cardiac rehabilitation programs (CRP) have proven to be effective at reducing mortality, morbidity and improving cardiac risk factors, it is unclear whether CRPs improve hemorheological profile in secondary prevention patients. The purpose of this study was to determine if CRP improves plasma rheology, HDL cholesterol, triglyceride levels and exercise capacity. Fifteen subjects enrolled in a three month CRP program had HCT, FIB, and VIS measured on three occasions: twice before the CRP intervention, and once at the end of the CRP intervention. Changes in HDL, triglycerides, and exercise capacity were measured before and after the CRP intervention. There were no significant differences in any of the hemorheological variables over time [HCT ($p=0.330$); FIB ($p=0.275$); VIS ($p=0.533$)]. There was a modest, but statistically significant correlation between fibrinogen and plasma viscosity ($p=0.035$, $r = 0.319$). Exercise capacity, as measured by time completed on the Bruce treadmill protocol, improved significantly ($p<0.001$). HDL cholesterol levels and triglyceride levels just failed to reach significance ($p=0.08$ and $p = 0.123$ respectively). This study suggests that CRP provides enough exercise stimulus to increase exercise capacity; however, CRP does not provide adequate stimulus to bring about the hemorheological changes observed in other studies.

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CHAPTER 1

1.0 Introduction

Cardiovascular disease remains as the number one cause of mortality in North America, Western Europe and in many parts of Asia. Heart disease costs the Canadian economy more than \$18 billion in medical services, hospital expenses and loss of income and productivity each year (Canadian Heart & Stroke Foundation, 1995).

Numerous traditional risk factors have proven to be strong predictors of coronary artery disease (CAD). These include, but are not limited to: smoking, hypertension, hyperlipidemia, diabetes mellitus, male sex, obesity, stress, physical inactivity, family history and age (Ross, 1986). In addition to these traditional risk factors, there is an abundance of data demonstrating an association between CAD and such emerging risk factors such as homocysteine, C-reactive protein (CRP), fibrinogen and hemorheology (e.g., Baker, 2002; Benderly et al., 1996; Danesh, 2000, Koenig et al., 1998).

Recently, the flow properties of blood (hemorheology) have been gaining increasing attention by researchers because of their potential role in the pathogenesis of cardiovascular disease. Hemorheological properties such as blood viscosity may play an important role in oxygen delivery and blood pressure regulation, especially in pathological states such as atherosclerosis and hypertension (Letcher et al., 1981). The flow properties of blood may also be important in the initiation of atherosclerosis through endothelial injury (Koenig & Ernst, 1992). Blood viscosity has been shown to be linked to nearly all the major cardiovascular disease risk factors (Koenig, 1992; Lowe, 1992; Letcher, 1981; Barnes et al., 1977; Elwood, 1993; Ernest, 1995; Rankinen, 1993; Smith, 1998; Junker, 1998); furthermore, blood viscosity and some of its constituents have been shown to be independent predictors of cardiovascular disease (Sweetnam et al., 1996;

Yarnell et al., 1991; Koenig & Ernst, 1992; Elwood et al., 1993; Junker et al., 1998). In light of these facts, therapeutically reducing blood viscosity seems a reasonable strategy in combating the initiation and progression of cardiovascular disease.

Fibrinogen also has been tightly linked to CAD primarily as a marker of coagulation and inflammation (Baker et al., 2002; Benderly et al., 1996; Cook & Ubben, 1990; Dekker, 1996; Ross, 1993; Woodward, 1998; Elwood et al., 1993). In addition to its role in the extrinsic coagulation pathway, fibrinogen concentration is the primary determinant of plasma viscosity (Baker et al., 2002; Koenig et al., 1998; Lowe et al., 1991). As such, elevated levels of fibrinogen may be linked to CAD through its hemorheological properties.

An considerable amount of evidence suggests that regular aerobic exercise may protect against the incidence and progression of cardiovascular disease. Several mechanisms for this phenomenon have been proposed primarily with reference to improved myocardial function, normalization of blood lipid profile, and changes in body composition. Recognition of the health benefits and cost effectiveness of exercise against cardiovascular disease has resulted in the development of cardiac rehabilitation programs in hospitals and other health facilities (Balady et al., 2000). These programs range from structured, supervised dietary and exercise programs within hospitals to community-based, socially orientated programs.

Regular aerobic exercise training has been shown to improve some components of blood viscosity in several different populations, however results are equivocal. Cross sectional studies indicate that active individuals have a lower blood viscosity when compared to sedentary or less active individuals (Elwood et al., 1993). Longitudinal studies, however, have failed to consistently demonstrate a training effect on blood viscosity or some of its constituent

parameters. Discrepancies in results may be due to differences in the exercise intervention (frequency, intensity, type, time) or subject sample (age, fitness level, health status etc.)

1.1 Statement of the problem

In light of the debate and discrepancies in the area of exercise and its effects on hemorheology, this study proposes to investigate the effects of a level II-III cardiac rehabilitation program on several constituents of whole blood viscosity (plasma fibrinogen concentration, plasma viscosity, and hematocrit). This investigation will help determine if cardiac rehabilitation improves the rheological profile of patients recovering from conditions related to the progression of coronary atherosclerosis.

Secondly, this study will attempt to quantify the effect of a level II-III cardiac rehabilitation program on three traditional risk factors for heart disease: serum high-density lipoprotein cholesterol (HDL) concentration, serum triglyceride (TG) concentration and exercise capacity.

1.2 Definitions

1. Hemorheology: the study of the flow properties of whole blood and its constituent parts
2. Plasma Viscosity (PV): blood plasma's internal resistance to flow as measured in milli-Pascals seconds (mPaS)
3. Fibrinogen (FIB): a large, asymmetrical plasma protein that plays a key role in the coagulation cascade. Fibrinogen is also thought to be the primary determinant of plasma viscosity.
4. Hematocrit (HCT): the volume percentage of erythrocytes in whole blood.

5. Exercise capacity (EC): for this study, exercise capacity is defined as the time completed on a standard Bruce treadmill protocol measure in minutes and seconds.
6. Phase II/III cardiac rehabilitation program (CRP): a hospital or community based program designed to return cardiac patients to their optimum level of function following an acute coronary event and/or cardiovascular surgery. The cornerstone of these types of programs is typically directed and supervised exercise, although more integrated programs also include dietary counseling, smoking cessation, stress management and other educational components.

1.3 Delimitations

1. Subjects must have non-smoking status for 1 year or more.
2. Admission to the Lions Gate Hospital's Cardiac Rehabilitation Program due to a history of ischemic heart disease secondary to coronary atherosclerosis. This may have included: myocardial infarction, coronary artery bypass grafting, coronary angioplasty, or documented coronary atherosclerosis.
3. No other injuries or conditions that may prevent exercise participation.
4. No major changes in drug therapy program during the investigation.
5. Willing and able to regularly attend the cardiac rehabilitation classes (the exercise and counseling sessions).

1.4 Limitations

1. Sensitivity and reliability of standard laboratory protocols for measurement of fibrinogen, hematocrit, plasma viscosity and lipids.

2. Subject's effort level during measurement of exercise capacity.
3. Subject's compliance with suggested exercise, dietary, and pharmacological practices.

1.5 Assumptions

1. Subjects followed all instructed pretest instructions including overnight fast, abstinence from alcohol and caffeine 12 hours prior to the test, and abstinence from vigorous physical activity 24 hours prior to blood sampling.
2. Subjects reported all changes in pharmacological therapy.
3. Subjects did not participate in any organized exercise class between testing session one and testing session two.

1.6 Hypotheses:

1. Cardiac rehabilitation will improve hemorheological properties as indicated by:
 - a) A decrease in plasma viscosity
 - b) A decrease in plasma fibrinogen concentration
 - c) A decrease in hematocrit.
2. A significant relationship exists between plasma viscosity and plasma fibrinogen concentration.
3. Cardiac rehabilitation will increase HDL cholesterol and reduce triglyceride levels.
4. Cardiac rehabilitation will increase exercise capacity (EC) as determined time completed on Bruce treadmill protocol.

Specific null and alternate hypotheses are:

$H_0: \sigma_{VIS}^2 = 0$	$H_1: \sigma_{VIS}^2 > 0$
$H_0: \sigma_{FIB}^2 = 0$	$H_1: \sigma_{FIB}^2 > 0$
$H_0: \sigma_{HCT}^2 = 0$	$H_1: \sigma_{HCT}^2 > 0$
$H_0: \rho = 0$	$H_1: \rho \neq 0$
$H_0: \mu_{HDL1} \geq \mu_{HDL3}$	$H_1: \mu_{HDL1} < \mu_{HDL3}$
$H_0: \mu_{TG1} \leq \mu_{TG3}$	$H_1: \mu_{TG1} > \mu_{TG3}$
$H_0: \mu_{EC} \geq \mu_{EC3}$	$H_1: \mu_{EC1} < \mu_{EC3}$

1.7 Significance

This study will help determine if cardiac rehabilitation positively influences blood rheology for people who are recovering from recent heart surgery or acute coronary event. Therefore, this study may be important in revealing another beneficial effect of exercise for cardiac patients. Furthermore, this study will help determine if the hemorheological training effects commonly observed in healthy adult humans also occur in patients participating in a structured cardiac rehabilitation programs.

CHAPTER 2

2.0 Review of the Literature

This chapter will review the relevant literature and concepts surrounding heart disease, hemorheology, lipids, cardiac rehabilitation and the interrelationship between these factors.

2.1 A Brief and Targeted Explanation of Heart Disease

2.1.1 Gravity and Economic Impact of Heart Disease

According to the Heart and Stroke Foundation of Canada, one third of all deaths in Canada were due to heart disease in 1998. Due to advances in medicine, the death rate from heart disease has decreased by about 56% in the last 30 years; however, the absolute number of deaths has remained relatively constant over the same period. Heart disease and stroke cost the Canadian economy an estimated 18.5 billion dollars in 1994. Internationally, heart disease is the number one cause of mortality in North America, most Western European nations, and some Asian Countries (Canadian Heart & Stroke Foundation, 1995).

2.1.2 Defining atherothrombotic coronary disease and consequential disorders

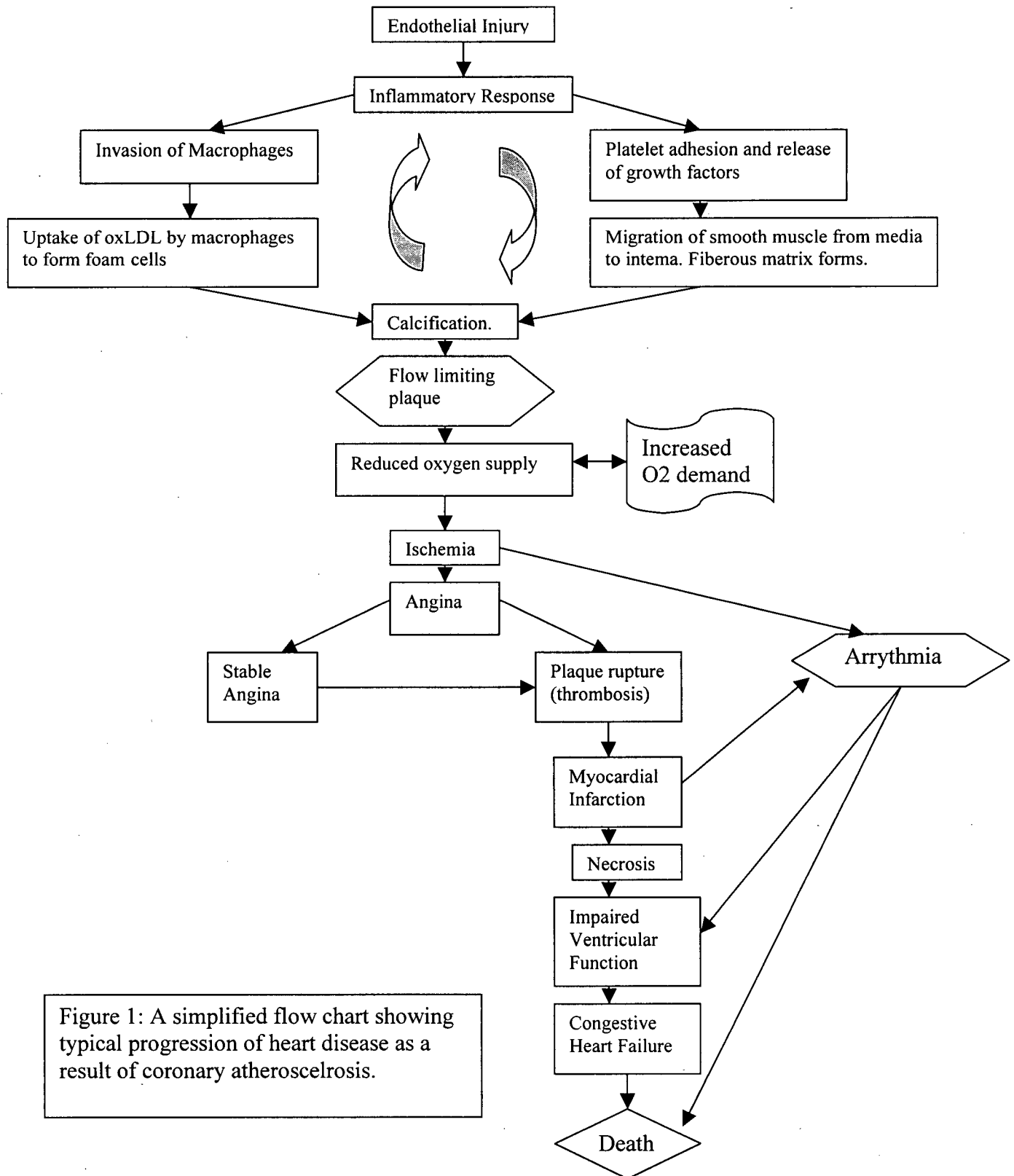
Cardiovascular disease is a broad term that encompasses all types of diseases that affect this system. However, the most prevalent cardiovascular diseases are those that are either directly related to, or a consequence of, partial or complete coronary artery occlusion. This includes: myocardial infarction, stroke, angina, peripheral vascular disease, heart failure, and some myocardial arrhythmias. Thus most cardiovascular disease stems from atherogenesis and/or thrombogenesis; therefore, discussion of cardiovascular disease will be restricted to these disease states.

2.1.3 Pathogenesis of atherothrombotic heart disease

The exact mechanism of atherosclerosis is unknown, but currently the *response to injury hypothesis* is most popular. The original theory was proposed in 1973 by Ross and Glomset and has been modified several times over the past 26 years (Ross, 1993).

According to this theory atherosclerosis begins with an injury to the endothelium of an artery. Injury can be caused by a number of factors: hypertension, elevated homocysteine levels, elevated level of free radicals from smoking, modified low density lipoproteins, diabetes mellitus, infectious micro-organisms, and/or combinations of these factors. Following endothelial injury there is an "inflammatory like" response resulting in endothelial release of vasoactive molecules, cytokines, and growth factors. This is accompanied by the adhesion of platelets and leukocytes, a change in the permeability of the endothelium, and the development of a procoagulant state. Furthermore, this immune cascade leads to the movement and proliferation of vascular smooth muscle from the media to the intima, and also increases the permeability of the arterial endothelium to low density lipoproteins (LDL). This LDL is available for oxidization by nitric oxide or other free radicals and is taken up by monocyte-derived macrophages. These fat filled macrophages (called foam cells) form the fatty streak, the first stage in the progression of atherosclerosis. Continued inflammation results in the progression of the lesion leading to the deposition of a fibrous cap, which surrounds a core of lipid and necrotic tissue, sometimes referred to as an advanced, or complicated lesion. The fibrous cap serves to stabilize the lesion; however, over time the cap erodes, becomes unstable and may allow the plaque to rupture and form a thrombus. This thrombus may circulate downstream of the lesion and result in infarction possibly leading to ischemia and necrosis. Myocardial damage ultimately impacts the pumping

ability of the heart and may eventually lead to failure of the ventricles to pump sufficient blood to sustain metabolic demand, a condition known as congestive heart failure. Figure 1 presents a highly simplified representation of the progression of atherothrombotic heart disease.



2.1.4 Risk Factors for atherothrombotic heart disease

Extensive research has identified numerous risk factors that are associated with heart disease. All “traditional” risk factors have been strongly linked to heart disease through multiple large-scale epidemiological studies such as the Framingham Heart Study (Kannel et al., 1964). In addition to traditional risk factors, countless “emerging” risk factors are proposed in the scientific literature. The validity, predictive strength and clinical application of these emerging risk factors have yet to be established. Amongst this class of risk factors are fibrinogen, plasma viscosity and hematocrit. Table 1 outlines some traditional and emerging risk factors.

<i>Traditional Risk Factors</i>	<i>Selected Emerging Risk Factors</i>
Age	C-reactive protein
Male Sex	Homocysteine
Cholesterol	Fibrinogen
Hypertension	Blood and plasma viscosity
Diabetes Mellitus	Various pathogens
Obesity	History of certain infectious diseases
Physical Inactivity	Dietary pattern
Smoking	Various lipid sub fractions
Family history	Metabolic syndrome

Table 1: Traditional and selected emerging risk factors.

2.2 Hemorheology

2.2.1 Defining hemorheology and viscosity.

Hemorheology comes from the Greek words haema meaning “blood”, and rheos meaning “stream”. Hemorheology is, therefore, the study of the flow and deformation of whole blood or its constituent parts. When a simple liquid flows in a straight tube it exhibits streamline flow where concentric cylindrical layers of fluid shear past each other in a predictable manner.

Laminar flow exhibits a velocity profile such that particles near the walls of the tube move slowest, while particles near the center of the tube move the fastest (fig 2). Laminar flow will exist provided the fluid's flow rate does not exceed its Reynolds number, beyond which turbulent flow prevails.

Viscosity is a parameter of rheology, and is defined as a fluid's resistance to laminar flow,

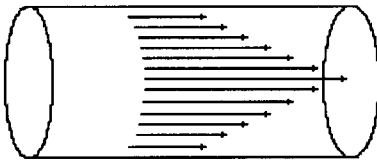


Figure 2: laminar flow through a tube illustrating higher flow velocity close to the center.

or as the internal friction of a fluid created by atoms, molecules, and/or larger particles sliding or shearing past one another. Therefore, viscosity (at a constant temperature) depends on two factors: the amount of friction between particles, and the rate at which the molecules flow past one another. Hence, we can

calculate viscosity as the ratio of shear stress (mPa) to shear rate (s^{-1}):

$$\text{Viscosity (mPa} \times s^{-1}) = \frac{\text{Shear Stress (mPa)}}{\text{shear rate (s}^{-1})}$$

Viscosity and flow through a circular tube can be related by the Hagen-Poiseuille equation:

$$Q = \frac{\Delta P \times \pi \times r^4}{8 \times L \times \eta}$$

Where: Q: flow

ΔP : driving pressure

r: radius of the tube

L: length of the tube

η : viscosity of the blood

A simple comparison can be made to Ohm's law, which states that flow is equal to the ratio of the driving pressure to resistance:

$$Q = \frac{\Delta P}{R}$$

2.2.2 Determinants of Whole Blood Viscosity

Blood viscosity is primarily determined by plasma viscosity, hematocrit, erythrocyte deformability, and erythrocyte aggregation (Koenig & Ernst, 1992; Lowe, 1992; Lowe, 1986).

The following section will define the various constituents of viscosity and also discuss its relation to heart disease.

2.2.2.a.i Plasma Viscosity

Unlike whole blood, plasma is a Newtonian fluid; therefore, as shear rate increases the shear force decreases such that viscosity remains constant for a given temperature. The viscosity of water at 37 °C is 0.69 mPa s; the addition of small molecules and electrolytes has minimal effect on viscosity, but the addition of large plasma proteins doubles viscosity (1.33 mPa s) (Lowe, 1986). The effect of individual proteins depends on size, asymmetry and concentration; thus fibrinogen has a stronger effect than do serum globulins (immunoglobins, lipoproteins) which have a larger effect than albumin (Lowe, 1992).

2.2.2.a.ii Plasma Viscosity and Heart Disease

Epidemiological studies have revealed that all major risk factors for cardiovascular disease have been correlated with blood and/or plasma viscosity. Age (Lowe et al., 1980), smoking habits (Benderly et al., 1996; Smith et al., 1998; Junker et al., 1998), hypertension

(Bonithon-Kopp et al., 1996; Letcher et al., 1981), hyperlipidemia (Lowe et al., 1982), diabetes (Barnes et al., 1977), and use of oral contraceptives (Ernst et al., 1989; Lowe et al., 1980) have all been shown to be highly correlated with blood and/or plasma viscosity. Although causal relationships have not been established, the flow properties of blood offer an interesting common pathway for many risk factors. This is not surprising given that rheology probably plays a significant role in the initial injury of the vessel wall and the genesis of atherosclerotic plaques (Lowe, 1992).

Plasma viscosity has also been directly associated with cardiovascular disease. The collaborative Caerphilly and Speedwell studies (Sweetnam et al., 1996; Yarnell et al., 1991; Elwood et al., 1993) and the MONICA (Koenig et al., 1992) project both have indicated plasma (and therefore blood viscosity) as an independent and predictive indicator of coronary artery disease. A meta-analysis in 2000 that compared people in the top third with the bottom third scores for plasma viscosity revealed a risk ratio of 1.57 (Danesh et al., 1998). Other studies have indicated a relationship between viscosity and acute myocardial infarction (Fuchs et al., 1984). Recently Junker et al. (1998) found a positive relationship between plasma viscosity and the extent of coronary artery disease after correcting for age, fibrinogen and use of diuretics.

It would seem logical that blood viscosity and blood pressure are tightly linked since a rise in viscosity increases total peripheral resistance and should therefore increase blood pressure. Diastolic and mean arterial pressure, as well as left ventricular hypertrophy all have been highly correlated with increased blood viscosity and other rheological variables (Bonithon-Kopp et al., 1993). Furthermore, Devereux et al. found that myocardial hypertrophy is more closely related to increased blood viscosity than to blood pressure values (Devereux et al., 1984). Jung et al. found that mean plasma viscosity was significantly higher in hypertensive patients when compared to

healthy controls (1986). They pointed out that this was probably related to an increase in plasma protein and/or fibrinogen concentration. In a study of 67 patients with hypertension, Leschke et al. (1987) determined that patients with renal hypertension had the highest blood viscosity when compared to patients with essential hypertension and healthy controls. They attributed the increase to an elevated fibrinogen level associated with renal failure.

2.2.2.b.i Fibrinogen

Fibrinogen is a large, asymmetrical protein that disrupts laminar flow and thus is a primary contributor to plasma viscosity (Somer & Meiselman, 1993). Correlations between plasma viscosity and fibrinogen concentration have varied between 0.2 to 0.7 in large epidemiological studies (Koenig et al., 1998; Yarnell et al., 1991). An increased level of circulating plasma fibrinogen is considered a risk factor for cardiovascular disease primarily due to its role in the clotting mechanism; however, it might also be pathogenic due to its tendency to increase plasma viscosity (Lowe, 1986).

Fibrinogen is a key protein in the clotting cascade (Fig 3). Following endothelial injury, various clotting factors are activated in a cascading pattern ending with the cleaving of fibrinogen to fibrin. Activated fibrin then forms a clotting matrix through covalent cross bridge formation between adjacent fibrin molecules and also with aggregated platelets.

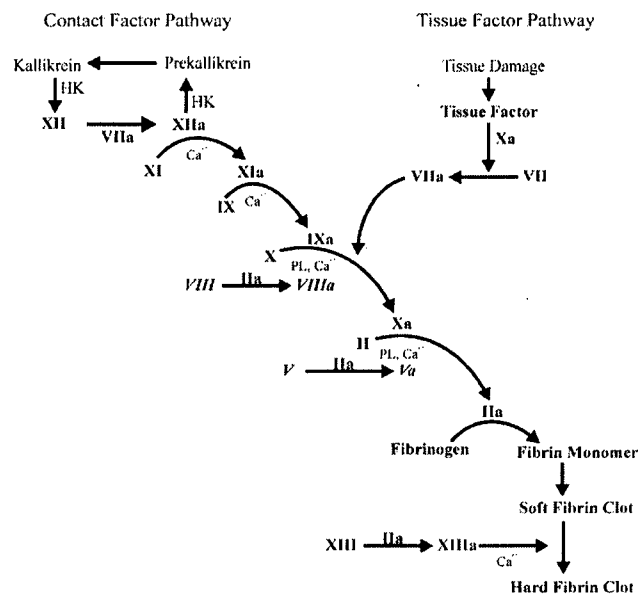


Figure 3: The complex clotting cascade that terminates in the cleaving of fibrinogen to fibrin (source: <http://facstaff.bloomu.edu/tbel2/research.htm>)

2.2.2.b.ii Fibrinogen and heart disease

Since fibrinogen is a key protein in the formation of potentially thrombotic clots, it has been hypothesized that elevated levels of fibrinogen are associated with an increase risk of acute coronary syndrome secondary to coronary atherosclerosis. Danesh et al. (1998) published a meta-analysis of fibrinogen's relation to coronary heart disease. They pooled data from 18 prospective studies (most of which controlled for traditional risk factors) involving a total of 4018 subjects both with and without documented CHD. Comparison of individuals with fibrinogen levels in the top one third with individuals in the bottom one third yielded a combined risk ratio for CHD of 1.8 (95% CI, 1.6-2.0). The investigators pointed to fibrinogen's role in coagulation, blood viscosity, and platelet aggregation as an apparent plausible mechanism by which fibrinogen is related to CHD.

Not only does fibrinogen concentration act as a strong predictor of the incidence of CAD; it also correlates well with the extent of the disease. Several studies have demonstrated that fibrinogen level increases as the extent of stenosis increases from 0-100% determined through coronary angiography (Bolibar et al., 1993).

Fibrinogen concentration also correlates with other established risk factors. Age, smoking, LDL, physical inactivity, social class, and alcohol abstinence have all been found to be correlates of fibrinogen concentration (Danesh et al., 1998). Even after accounting for the relationship between various "classic" risk factors and fibrinogen concentration, a strong relationship still exists between fibrinogen and CAD risk.

Using data from 1238 subjects enrolled in the MONICA trial, Woodward et al. (1998) found that fibrinogen concentration predicted mortality from cardiovascular events even after adjustment for major risk factors.

Despite the strong link between elevated fibrinogen levels and cardiovascular disease, there is no current therapy that significantly reduces fibrinogen levels to decrease incidence of heart disease. It has been suggested that statin's cardioprotective mechanism is at least partly linked to reducing inflammation; however, a review by Krysiak et al. (2003) suggests that this relationship is not well established.

2.2.2.c Erythrocytes

The following section will discuss how red cells impact whole blood viscosity through their concentration (hematocrit), deformability, and tendency to stick together (aggregation). The association between hematocrit and heart disease is then discussed.

2.2.2.c.i Hematocrit

The volume percentage of erythrocytes in whole blood is termed hematocrit. Normal hematocrit is between 37-51% for healthy humans (Lowe, 1986); however, certain conditions such as polythycemia and various forms of anemia result in a hematocrit outside the normal range (Somer & Meiselman, 1993). Certain drugs and procedures such as recombinant erythropoeitin, diuretics, and blood doping may also result in an abnormally high hematocrit either by altering the number of red cells or volume of plasma.

A linear logarithmic relationship exists between hematocrit and whole blood viscosity, but this relationship only exists for a hematocrit between 20 to 60%, which is well within the normal physiological range (Lowe, 1986). Beyond a hematocrit of 60%, viscosity increases exponentially.

Red blood cells drastically increase viscosity because their large size disrupts smooth laminar flow. Furthermore, due to their deformable nature and tendency to aggregate together at low shear rates, erythrocytes cause blood to behave in a non-Newtonian fashion such that whole blood viscosity is dependent on shear rate (Lowe, 1992). At high shear rates viscosity is at a minimum because the red cells deform into an efficient ellipsoid shape, and migrate towards the center of the blood vessel. At low shear rates, viscosity is at a maximum because red cells are in their natural disc shape, and tend to aggregate by forming inter-cellular bonds through the action of plasma proteins such as fibrinogen. At the very low shear rates, which occur in capillaries, red cells stack upon one another in an orderly fashion forming rouleaux, which markedly increase whole blood viscosity (Fahraeus, 1958).

Whole blood viscosity is also sensitive to blood vessel diameter. As vessel diameter decreases below 500 μm , viscosity decreases due to the axial migration of red blood cells leading to the formation of a cell rich core surrounded by a marginal layer primarily containing plasma. As vessel diameter approaches the smallest diameter through which red blood cells can pass (2.7 μm), viscosity sharply increases because the width of the lubricating plasma layer is minimized (Gaehtgens & Duhrrssen, 1980). This effect is known as the Fahraeus-Lindqvist effect, named after the first scientist to observe this phenomenon (Fahraeus, 1958).

2.2.2.c.ii Erythrocyte Deformability

If red blood cells were rigid cells, blood at high hematocrit values would be solid and stiff (El-Sayed, 1998); therefore, erythrocyte deformability (filterability) allows blood to remain fluid. At high shear rates red blood cells deform into fluid-dynamically-efficient ellipsoids and align themselves longitudinally with the direction of flow thus reducing viscosity. Erythrocyte deformability also allows red cells to traverse nutritive capillaries whose diameter of 5 μm is smaller than the red cell's resting diameter of 7.5 μm (Lowe, 1986). Erythrocyte deformability depends on the cell's surface area to volume ratio, membrane fluidity, cell shape, the cytoskeleton, and internal viscosity (which is primarily a function of hemoglobin concentration) (Lowe, 1986). Red cell deformability is also dependent on plasma osmolality, pH, and oxygen partial pressure (Chien, 1981). Erythrocyte deformability is altered in sickle cell disease, and other cardiovascular diseases (Somer & Meiselman, 1993).

2.2.2.c.iii Erythrocyte Aggregation

At low shear rates erythrocytes aggregate in plasma through the formation of fibrinogen cross bridges between adjacent red cells resulting in rouleaux (Fahraeus, 1958). There is a strong correlation between viscosity and red cell aggregation but this relationship disappears beyond shear rates of 100 s^{-1} . An increase in fibrinogen concentration also increases the rate of aggregation, and thus markedly increases whole blood viscosity and flow (Lowe, 1986). When blood flow ceases, a particular yield stress is required to disrupt aggregation and restart flow. This yield stress is highly dependent on fibrinogen concentration and hematocrit.

2.2.2.c.iv Erythrocytes and Heart Disease

Nineteen prospective studies investigating the relationship between hematocrit and heart disease were recently review and analyzed by Danesh et al. (2000). These researchers pooled data on 9182 subjects and compared the top third versus the bottom third and found a risk ratio of 1.13. The researchers also mentioned that when data only from subjects with pre-existing heart diseased was used the risk ratio for a secondary event was “somewhat” higher. Taken together, there seems to be a significant evidence to suggest that some relationship exists between hematocrit and incidence of heart disease. Considering that hematocrit accounts for the majority of the variance in whole blood viscosity, the relationship between blood viscosity and heart disease should be discussed in this section. As mentioned in Chapter 1, whole blood viscosity is strongly associated with heart disease (Fuchs et al., 1984; Koenig et al., 1998; Sweetnam et al., 1996; Yarnell et al., 1991; Elwood et al., 1993; Yarnell et al., 1987; Junker et al., 1998). Danesh et al. pooled data from 657 subjects and compared people in the top third of blood viscosity scores with the bottom third and calculated a risk ratio of 1.24 (Danesh et al., 1998).

2.2.2.d Effect of Drugs on Hemorheology

Over the past three decades there have been over 50 investigations into the effects of various drugs on hemorheology; however, this body of literature has for the most part been inconclusive. In a review of the literature, Ehrly concludes that only a few drug treatments have been consistently shown to improve blood viscosity; these include: hemodilution, drugs that reduce plasma fibrinogen, and drugs that improve red cell deformability (Ehrly, 1990). There is some evidence to suggest that statins reduce fibrinogen concentration; however, a review by Krysiak et al. suggest that this relationship is not well established (Krysiak, Okopien & Herman, 2003).

2.3 A Brief Review of Lipids

There is an abundance of research on the study of cholesterol and its association with heart disease. The following text serves to briefly summarize this large body of knowledge with particular reference to facts most relevant to this study. A more exhaustive review on cholesterol can be found in *The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* (2002).

2.3.1 Cholesterol Subfractions and Heart Disease

Serum cholesterol can be broken down into several subfractions based on particle density. The most commonly measured and reported subfractions of a typical clinical lipid panel are: total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglycerides (TG). Various other subfractions and ratios are sometimes reported and

are emerging as important clinical markers for the treatment and prevention of heart disease. It is well established the TC, LDL and TG are all positively associated with the incidence of CAD; whereas HDL is negatively associated with CAD (Third Report of NCEP, 2002). The landmark Framingham study was key in objectively determining the risk associated with elevated total and LDL and depressed HDL cholesterol levels (Kannel et al., 1961; Kannel et al., 1964). More recent research has indicated that elevated triglyceride levels are also a risk factor for CAD (Third Report of NCEP, 2002).

2.3.2 Management of Dyslipidemia

Not only have cholesterol levels been associated with the incidence of heart disease, but therapeutically improving cholesterol levels has also been shown to decrease morbidity and mortality in numerous populations. It is well documented that numerous lifestyle factors impact cholesterol levels. Regular aerobic exercise, a diet low in fat, smoking cessation, weight loss, better glycemic control in diabetics and moderate alcohol consumption all impact cholesterol levels, and these lifestyle factors should be targeted before or in conjunction with any pharmacological therapy.

It is well established that regular cardiovascular exercise is associated with a higher level of HDL cholesterol and a lower triglyceride level (Kokkinos & Fernhall, 1999; Goldberg & Elliot, 1985). As a result of the evidence in support of exercise to improve cholesterol profile, all major health organizations, medical boards, and individual clinicians recommend regular exercise as a means for treating dyslipidemia (Third Report of NCEP, 2002).

A well balanced diet that is low in saturated and trans-fatty acids and high in fibre is associated with a lower level of total and LDL cholesterol. More recent research has also

suggested that a diet which is high in omega 3 fatty acids (particularly those from cold water fish) and other monounsaturated fats can significantly reduce triglyceride levels (Din, Newby & Flapan, 2004). As such, it is universally agreed that diet has a significant effect on serum cholesterol and a diet such as the AHA Step I Diet is recommended for the treatment of dyslipidemia (Third Report of NCEP, 2002; Balady et al., 2000).

In conjunction with lifestyle management, dyslipidemia can be treated quite effectively with various drugs such as statins, fibrates, niacin, and bile acid sequestrants. Again, the reader is directed to the NCEP III guidelines for more in-depth discussion on pharmacological management of dyslipidemia (Third Report of NCEP, 2002).

2.4 A Brief Explanation of Cardiac Rehabilitation

The 1970s marked the beginning of structured cardiac rehabilitation programs (CRP), but current rehabilitative care has become more comprehensive than the clinical trials undertaken in Europe three decades ago. Initial trials of the program were limited to exercise training and were restricted to patients who had been hospitalized after acute MI; however, the CRP now has a wider patient base and the focus is on both prevention and recovery. The CRP aims to improve patients' health and to enable them to have a more active lifestyle for people who have a chronic problem or people who have experienced a major cardiac event. In order to achieve these goals, rehabilitative services have also expanded to encompass pharmacological therapy, smoking cessation, diet, education, and behavioral counseling for patients in primary or secondary prevention. Despite documented benefits of CRP, only 11% to 34% of patients in the United States who have experienced a MI or heart surgery take part in a rehabilitative program after being discharged from the hospital (Taylor et al., 2004).

Several research studies have confirmed the benefit of CRP on mortality, morbidity and numerous cardiac risk factors. This information is best summarized by a 2004 review and meta-analysis of nearly 9,000 subjects (Taylor et al., 2004) that found reductions in:

- ❑ All-cause mortality
- ❑ Cardiac mortality
- ❑ Total cholesterol level
- ❑ Triglyceride level
- ❑ Systolic blood pressure
- ❑ Rates of self-reported smoking.

Other studies have found positive changes in HDL cholesterol (Warner et al., 1995) and psychosocial measures (Grace et al., 2002), although the recent meta-analysis by Taylor et al. failed to confirm these findings (Taylor et al., 2004). Regardless, CRP has proven to be an effective and cost effective treatment for the cardiac patient.

2.4.1 Effect of CRP / exercise on hemorheology

Table 2 outlines previous research on the effect (or relationship between) exercise training and various hemorheological variables including VIS, FIB and HCT. Previous research can be divided into cross-sectional studies vs. longitudinal studies and can further categorized by population type: those with atherosclerosis and healthy populations.

Investigators	Sample	Dependent variable	Intervention	Conclusion
Church et. al, 2002	23 subject with CAD, reference group of 10 healthy subjects	Plasma viscosity, blood viscosity, hematocrit	Phase II cardiac Rehab, 60 min of exercise 3d/w for 12 weeks	Significant reduction in plasma viscosity and blood viscosity, no change in hematocrit.
Reinhart et. al, 1998	25 subjects with EF<40% randomized to control or experimental group	Plasma viscosity, blood viscosity	Walking 1-hour 1d/w plus 40 min, 4d/w of bicycle ergometry at 70-80% peak exercise capacity.	No significant change in measure variables. Significant change in MVO ₂ .
Levine et. al,	15 subjects with CAD	Plasma viscosity,	Phase II cardiac rehab,	No significant changes in

1995		fibrinogen, hematocrit	30-40 min 3d/w for 10w.	blood markers. Significant improvement in exercise capacity
Milani et. al, 2004	277 Phase II cardiac rehab patients. 42 control patients	C-Reactive Protein	Phase II Cardiac Rehab. Exercise and dietary consultation	Significant reduction in CRP levels independent of statin use and weight loss.
Dumortier et. al, 2002	32 obese, insulin resistant subjects (21 experimental group, 11 in control group)	Plasma viscosity, hematocrit	45 min 3d/w for 2 months aerobic exercise.	Significant decrease in plasma viscosity but not hematocrit
Ernst and Matrai, 1987	44 patients with PAD (22 experimental, 22 control)	Blood and plasma viscosity	"Standardized treadmill exercise" 5d/w for 2 months	Significant decreases in plasma and blood viscosity
El-Sayed and Davies, 1995	25 young and healthy men and women randomized and controlled study.	Fibrinogen, hematocrit	30 min, 3d/w for 12w at 70-80% MHR	Decrease in fibrinogen concentration (6%) did not reach significance. Possible type II error
De Paz et. al, 1992	23 young and healthy middle distance runners and matched sedentary control subjects	Several thrombotic and thrombolytic markers	Cross sectional comparison of middle distance runners and sedentary controls	Difference in fibrinogen levels did not reach statistical significance. Small sample size
Suzuki et al., 1992	86 post MI patients (56 experimental, 30 control)	Several thrombotic and thrombolytic markers	Aerobic exercise training 60 minutes 2d/w for one month	Significant decrease in fibrinogen concentration
Worsornu et al, 1992	56 post CABG men assigned to three groups: aerobic training, power training, and control	Fibrinogen, hematocrit	Power training or aerobic treadmill training for 6 months	Fibrinogen levels were lowest in aerobic group followed by power group followed by control group.
Wannamethee et. al., 2002	3810 men with and without CAD	Plasma and blood viscosity, fibrinogen, hematocrit and numerous other hemostatic markers	Cross sectional comparison of active versus inactive subjects	Inverse relationship between activity level and plasma viscosity, fibrinogen. No relationship with hematocrit.
Connelly et al, 1992	3967 men without CAD	Fibrinogen, Factor VII	Cross sectional survey	Men who reported high levels of physical activity had lower fibrinogen concentration
Carroll et. al., 2000	590 healthy middle aged men.	Plasma viscosity, hematocrit	Cross sectional comparison between low and high levels of self reported physical activity	Inverse relationship between both plasma viscosity and hematocrit with physical activity.

Table 2: research conducted on CRP (or exercise) on hemorheology.

2.4.1.i Cross Sectional Studies.

Three large scale, epidemiological studies have investigated the relationship between fibrinogen and physical activity in a cross sectional, retrospective fashion. Connelly et al. (1992) used intake data from the thrombosis prevention trial, which investigated the effects of low dose aspirin versus anticoagulation on thrombosis prevention. 3967 middle aged men free of

documented coronary artery disease were classified into three levels of self reported physical activity during leisure time: no physical activity, mild physical activity and strenuous physical activity. The investigators found a significant difference in fibrinogen concentration between the strenuous group versus the other two groups, and no difference between the mild and no physical activity group. This effect was demonstrated in both smokers and non-smokers.

Carroll et al. (2000) also used middle-aged men without heart disease to investigate the relationship between physical activity and hemorheology. These investigators measured self-reported physical activity using a validated Physical Activity Index, additionally they estimated maximal oxygen consumption (MVO₂) using a sub maximal cycle-ergometer test. A significant inverse relationship was found between physical activity level/ MVO₂ and both plasma viscosity and hematocrit. The researchers suggested that physical activity may reduce both viscosity and hematocrit through the hemodilution effect of regular cardiovascular exercise conditioning.

Recently Wannamethee et al. (2002) reported updated results from the British Regional Heart Study. The 4252 men who had entered the study twenty years prior were re-examined for numerous hemostatic and hemorheological variables were measured including fibrinogen, and hematocrit. Physical activity was quantified using a validated index similar to that used by Carol et al. Unlike the studies by Carroll et al. and Connelly et al., this study used men with and without heart disease. Similar to the previously mentioned studies, the researchers found a significant inverse relationship between fibrinogen (and other inflammatory markers) and self reported physical activity. Furthermore, those men who had taken up exercise during the 20-year follow up period had fibrinogen levels similar to those who remained exercisers. Conversely, those who had become inactive over the follow up period had fibrinogen levels similar to those who had remained inactive. No relationship was found between hematocrit and physical activity.

In a smaller study, De Paz et al. (1992) found that 13 young competitive middle distance runners had similar resting fibrinogen levels as age and size-matched sedentary controls. Although limited by a very small sample size, it is interesting to note that higher levels of physical activity/fitness do not seem to have as strong an effect on fibrinogen concentration when compared to older adults.

2.4.1.ii Longitudinal, Interventional Studies.

Only a handful of smaller studies have investigated the effect of exercise training on various hemorheological variables. Review of these studies reveals no consistent effect of exercise training on hemorheology. Most of the research in this area is characterized by small sample size, non-randomized design and limited control of confounding variables. Comparison of these studies is difficult primarily because of the different target populations: young versus old, healthy versus heart disease versus insulin resistant etc. Furthermore, the exercise intervention varies to some degree between studies from phase II cardiac rehab to interval training for competitive middle distance running. These studies can be roughly divided into those studying subjects with documented heart disease and those without.

2.4.1.ii.a Studies on Heart Disease Patients

Church et al. (2002) investigated the effects of a 12-week phase II cardiac rehabilitation program on plasma viscosity, whole blood viscosity, and hematocrit on 23 subjects. They also compared results to a reference group of 10 healthy, age-matched subjects. They found a significant improvement in both plasma and blood viscosity after the completion of the rehabilitation program; however, there was no change in hematocrit. Furthermore, they found

that both plasma and blood viscosity remained higher in the rehab group than in the healthy reference group. The main limitation of this study is the lack of a true control group.

Suzuki et al. (1992) compared various hematological and hemostatic markers in 56 post MI patients and thirty control patients. After one month of conditioning, these researchers found a significant decrease in fibrinogen concentration as well as several other markers of coagulability. Worsornu et al. (1992) also found greater reduction in fibrinogen levels in 56 post bypass men who were either trained with power exercises or aerobic exercises when compared to a control group. Changes were greater for aerobic group versus the power group at three months and at six months.

Levine et al. (1995) conducted a similar study in subjects attending a 10 week cardiac rehabilitation program; however, they did not find any significant change in hematocrit, fibrinogen, plasma viscosity and blood viscosity. This study is again limited by the lack of a control group and the small sample size of 15 subjects.

Similar to the result of Levine, Reinhart et al. (1998) did not find any significant change in plasma viscosity, blood viscosity and hematocrit in CHF patients who exercised every day for 8 weeks. Unlike the studies of Levine and Church, subjects were randomized to either a control or exercise group; however, sample size was still relatively low at 25.

2.4.1.ii.b Other Intervention Studies

Dumortier et al. (2002) investigated the effect of an exercise training program on obese, insulin resistant subjects. Twenty-one subjects exercised 45 minutes three times per week for two months, and eleven subjects served as controls. The researchers found a significant change in plasma viscosity, but not in hematocrit.

El-Sayed and Davies (1995) found no difference in fibrinogen concentration after 12 weeks of conditioning in young, healthy volunteers. This study did utilize a control group; however, sample size was noted to be small and the authors mentioned the likelihood of type II error.

CHAPTER 3

3.0 Methods

3.1 Ethics

The ethical review boards of the University of British Columbia, and Lion's Gate Hospital granted approval for this study. Study purpose, design, risk, and confidentiality were explained to each subject during recruitment. Informed consent was received from each subject before they entered the study.

3.2 Subject Recruitment

Ten male and five female subjects were recruited during the intake clinic for the Lions Gate hospital (LGH) cardiac rehab program (CRP). At this time, a detailed medical history was taken as part of normal patient care for the CRP and also served as pre-screening for potential recruitment into the study. The following criteria were required for participation in the study:

- ❑ Non-smoking status for 1 year
- ❑ Admission to the LGH CRP due to a history of ischemic heart disease secondary to coronary atherosclerosis. This may have included: myocardial infarction, coronary artery bypass grafting, coronary angioplasty, or documented coronary atherosclerosis.
- ❑ No other injuries or conditions that may prevent exercise participation.
- ❑ No major changes in drug therapy program during the investigation.
- ❑ Willing and able to regularly attend the cardiac rehabilitation classes (the exercise and counseling sessions).

3.3 Study Design

Data was collected in a serial fashion as illustrated in Figure 4.

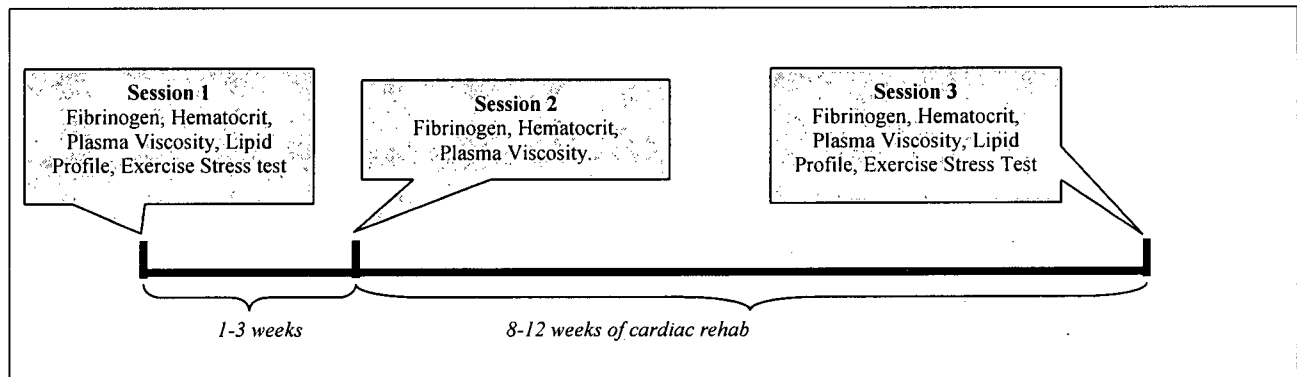


Figure 4: Planned study design showing timing of data collection for sessions 1, 2 and 3.

The stability and reliability of the hemorheological variables (fibrinogen, hematocrit, plasma viscosity) were measured through changes between the preadmission clinic and the admission clinic. No intervention was introduced during this time as subjects waited to start formal exercise class. This period was designed to serve as a “control interval”. Changes to hemorheological variables between the admission clinic and the exit clinic are hypothesized to be a result of the intervention. This period was designed to serve as the intervention interval.

No control period exists for lipids, and exercise capacity as these variables have been studied extensively previously, and there is no reason to expect significant change over the roughly 10-day control interval.

3.3.1 Session 1

After consent to participate in the study was received, subjects were given requisitions for required blood work. Subjects were asked to fast overnight and abstain from alcohol and caffeine

for 24 hours prior to all blood sampling. All blood samples were drawn at LGH laboratory in the morning between 8:00am and 9:30am. Lipids (total cholesterol, HDL cholesterol, triglycerides and LDL cholesterol), hematocrit and fibrinogen were analyzed at the LGH laboratory as per standard assay techniques. If a full lipid panel had been completed within 30 days of recruitment independent of this study, then this data was used for analysis. Plasma viscosity was sent to Vancouver General Hospital for analysis using the capillary tube micro-viscometer. Plasma viscosity is determined by measuring plasma density and efflux time through a capillary tube of known diameter. Plasma density and efflux time is then compared to the density, efflux time, and viscosity of distilled water at a constant temperature of 37 degrees Celsius. The relationship between viscosity, density and efflux time is demonstrated with the following formula:

$$\frac{\eta_s}{\eta_w} = \frac{t_s \rho_s}{t_w \rho_w}$$

Where:

n_s = plasma viscosity at 37 °C

n_w = water viscosity at 37 °C = 0.6915

t_s = plasma efflux time

t_w = water efflux time

p_s = density of plasma at 37 °C

p_w = density of water at 37 °C = 0.99777

Therefore:

$$\eta_s = 0.6930 \frac{t_s \rho_w}{t_w}$$

Fibrinogen was measured at LGH laboratory using a high sensitivity thromboplastin reagent based on recombinant rabbit tissue factor for the determination of prothrombin time and fibrinogen.

If an exercise stress test was not completed within 30 days of recruitment then an exercise stress test was carried out either at the LGH cardiac stress lab or at the cardiologist office. If no recent stress test was available, and the probability of myocardial ischemia or arrhythmia was low then an exercise tolerance test was performed by the exercise specialist in the hospital gym with the emergency department within 100m of the gym. All graded exercise testing followed the standard Bruce protocol. Briefly, the Bruce protocol is a stepped treadmill protocol that employs 3 minute stages of increasing intensity. Table 3 summarizes the standard Bruce treadmill stages. Ionotropic (blood pressure) and chronotropic (heart rate) response was recorded pre-exercise, through out the test and post exercise. Testing was terminated as per standard published clinical guidelines (Balady et al., 2000) and the total time completed on the Bruce Protocol was recorded.

Treadmill		METS	Cumulative Time (min)
Speed (mph)	Incline (%)		
1.7	10	5	3:00
2.5	12	7	6:00
3.4	14	10	9:00
4.2	16	13	12:00
5	18	18	15:00

Table 3: Exercise stages for the standard Bruce treadmill protocol used for quantifying exercise capacity.

3.3.2 Session 2

9.5 \pm 2.5(mean \pm S.D.) days after completing the first round of blood work and just prior to starting formal exercise classes, subjects had plasma viscosity and plasma fibrinogen measured again in the same fashion as mentioned in the pre-admission clinic. During the interval between session one and session two, subjects were instructed to continue with their normal physical activity and dietary habits.

3.3.3 Cardiac Rehab Intervention

CRP classes were held three times per week at LGH, although a few occurred in the community due to labor action that prevented the class from using the hospital gymnasium. A typical class first involves pre-exercise blood pressure and pulse measurement. All subjects wore a heart rate watch for constant monitoring during exercise. Subjects would then engage in 10 minutes of warm up exercise, which usually included stationary cycling and stretching exercises. This was then followed by 30-40 minutes of cardiovascular exercise at a target heart rate that represented approximately 70-85% of heart rate reserve. Exercise intensity and duration was periodically adjusted to reflect increasing fitness levels. Exercise blood pressures were recorded periodically to ensure proper inotropic response. Subjects then participated in resistance training using a combination of dumbbells, pulleys, therabands, and floor exercises for a period of 10-15 minutes. Resistance exercises were targeted to major muscle groups and areas of particular weakness (for example, pectoralis major for subjects who had open heart surgery). Once again, resistance and the number of exercises were increased as fitness levels improved. Stretching and cool down exercises occurred during the last 5-10 minutes of class. Post exercise blood pressure and pulse was also measured before subjects left class.

3.3.4 Session 3

After completing an average of 69.4 ± 23.3 days in the CRP, subjects were tested for plasma viscosity, plasma fibrinogen, hematocrit, lipids, and exercise capacity in the same manner as discussed in section 3.3.1.

3.4 Data Analysis

All data was analyzed using SPSS v.12.0 software. Repeated measures ANOVA were used to see if significant differences existed in HCT, FIB and PV between sessions one, two and three. Repeated measures ANOVA were also used to see if there were significant changes to lipids, exercise capacity, between session one and session three. A Pearson product moment correlation was used to determine the relationship between plasma fibrinogen concentration and plasma viscosity.

CHAPTER 4

4.0 Results

4.1 Subjects

Fifteen complete data sets were collected and analyzed. Ten males with an average age of 67.2 ± 7.02 and five females with an average age of 67 ± 7.31 completed this study. Most subjects entered the rehabilitation program as a result of multiple cardiovascular diagnoses; for example, a subject with pre-existing diabetes may have had a heart attack revealing three-vessel disease that was treated with coronary by-pass surgery. Other co-morbidities such as osteoarthritis and joint arthroplasty were also considerations during exercise prescription. Table 4 summarizes the characteristics of the subjects:

	Males	Females	Total
Sample size	10	5	15
Average age \pm S.D. (years)	67.2 ± 7.02	67 ± 7.31	67.1 ± 6.85
Age Range (years)	50-75	56-73	50-75
Myocardial Infarction	8	5	13
Coronary Bypass Surgery	7	3	11
Angioplasty and Stent	4	2	6
Peripheral Artery Disease	1	0	1
Diabetes Mellitus	3	2	5
Stable Angina	1	0	1
Pacemaker / ICD	0	2	2

Table 4: summary of subject data including age, and cardiovascular diagnoses.

The subjects' pharmacological regime remained relatively constant. Subjects with minor changes in prescriptions that were not thought to influence any outcome measures were not disqualified from the study. Management of drug therapy was controlled by the subject's own physician independent of this study as part of normal patient care. All subjects remained on constant dose of statin and ASA through the entire length of the study, and no subjects were taking warfarin.

4.2 Timing of data collection

All subjects attended three data collection sessions as outlined in figure 5. The first two sessions were designed as a control interval to assess changes in HCT, FIB, and PV without any CRP intervention. The third data collection session occurred after completion of the CRP and was used to assess changes due to CRP. The interval between session one and session two (waiting period for the CRP) was $9.3 \text{ days} \pm 2.5 \text{ days}$, and the average length of time between session two and session three (days in CRP) was $69.5 \pm 23.3 \text{ days}$. It should be mentioned that most people completed the entire 12-week program; however, a three subjects requested to be fast tracked through the program, and only completed 4-8 weeks of the rehab program.

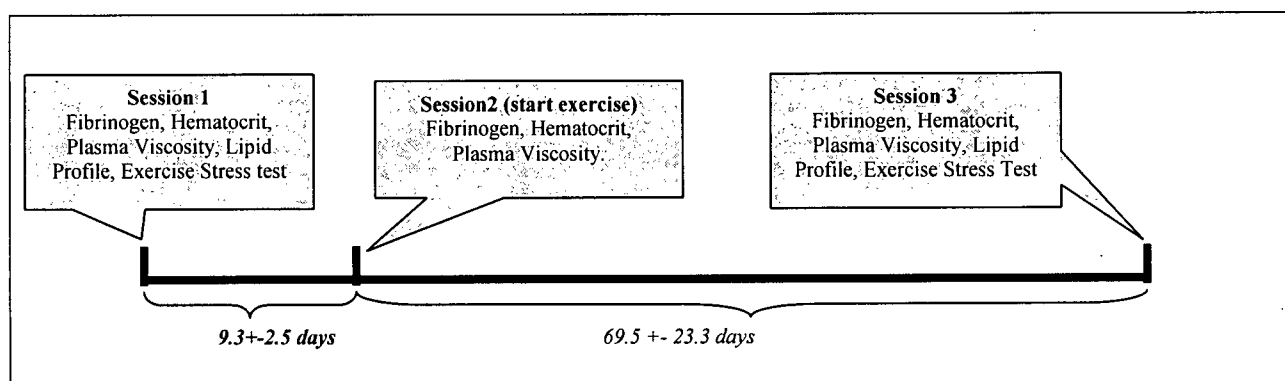


Figure 5: Actual timing of data collection showing time intervals between Sessions 1, 2 and 3.

4.3 Hemorheological Changes Over Time

Hematocrit (HCT), fibrinogen (FIB) and plasma viscosity (PV) were collected on all three sessions: twice before the rehabilitation program began and once after the CRP was completed. Although trends indicating a decrease in FIB and PV are observed, repeated measures ANOVA revealed no significant difference over time for HCT ($p=0.330$) FIB ($p = 0.275$) or PV ($p =$

0.533) (figures 6 and 7). It should be noted that one PV outlier was removed as it was over 8 standard deviations from the average PV and is thought to be a result of gross measurement error.

	Session 1	Session 2	Session 3
Hematocrit \pm SD	0.406 \pm 0.028	0.406 \pm 0.031	0.408 \pm 0.032
Fibrinogen (g/L) \pm SD	4.09 \pm .584	4.17 \pm .581	3.96 \pm .457
Plasma Viscosity (mmol/L) \pm SD	1.57 \pm 0.098	1.55 \pm 0.092	1.54 \pm 0.093
Total Cholesterol (mmol/L) \pm SD	4.20 \pm 0.92		4.47 \pm 0.85
LDL Cholesterol (mmol/L) \pm SD	2.03 \pm 0.62		2.31 \pm 0.67
HDL Cholesterol (mmol/L) \pm SD	1.41 \pm 0.42		1.5 \pm 0.37
Triglycerides (mmol/L) \pm SD	1.64 \pm 0.87		1.39 \pm .58
Exercise Capacity (min:sec) \pm SD	7:02 \pm 2:44		8:35 \pm 2:24

Table 5: Summary means \pm SD for all data

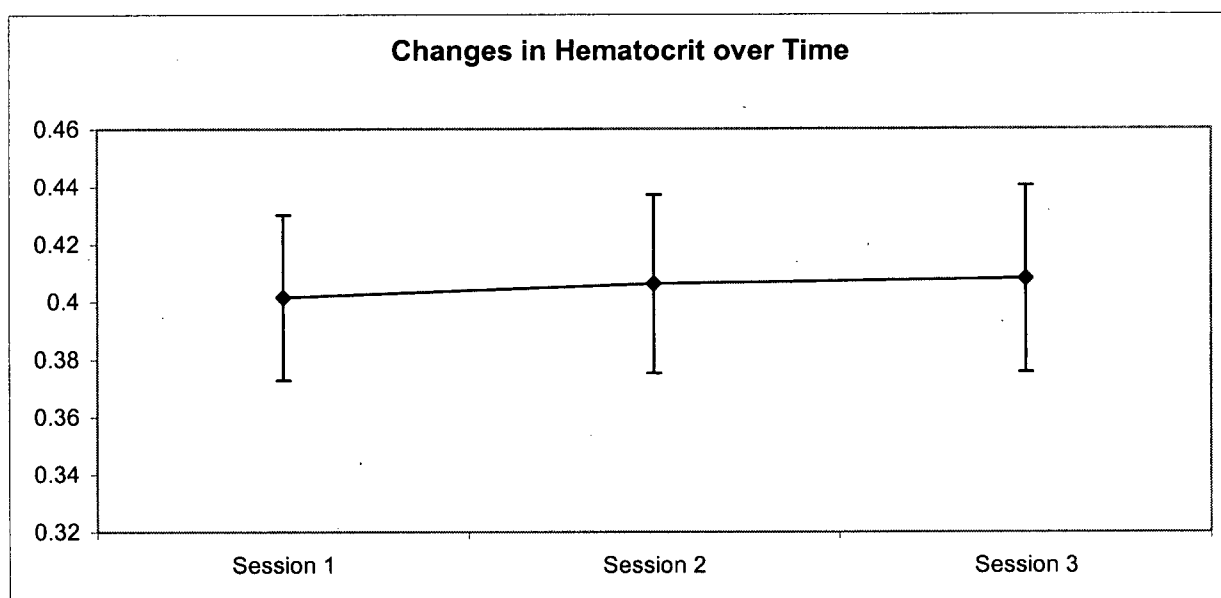


Figure 6: Graph illustrating non-significant change ($p=0.330$) in hematocrit over Sessions 1, 2 and 3. Error bars represent one standard deviation.

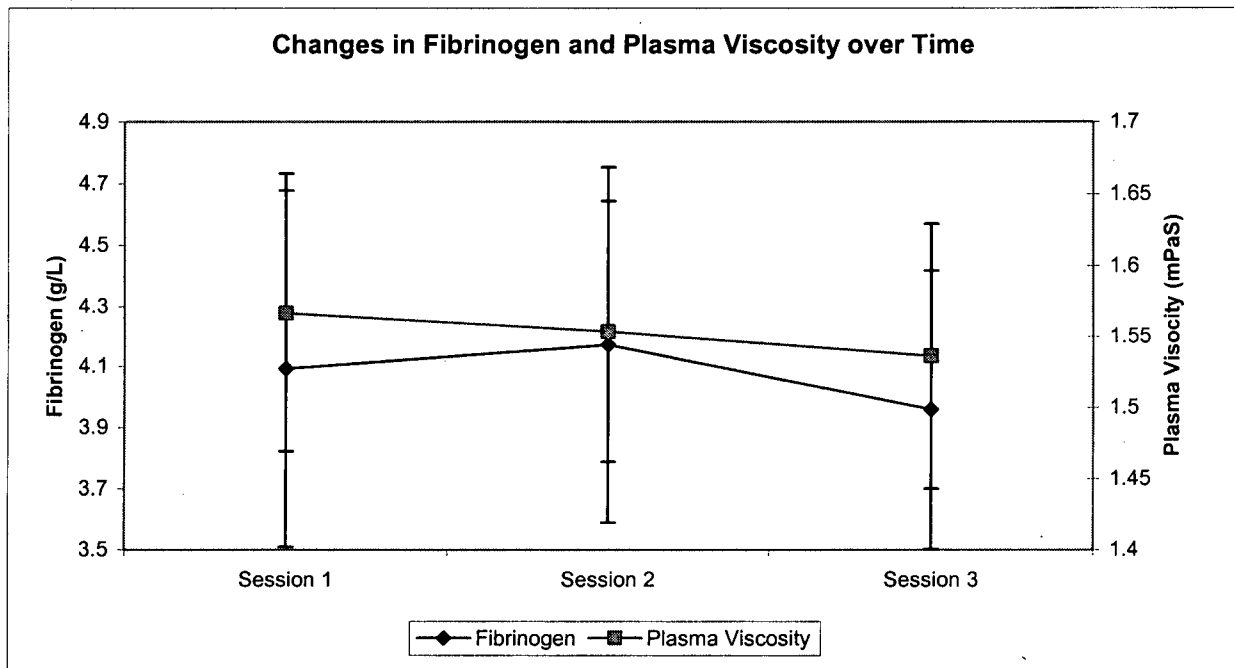


Figure 7: Graph illustrating non-significant change in fibrinogen concentration ($p=0.533$) and plasma viscosity ($p=0.275$) over Sessions 1, 2 and 3. Error bars represent one standard deviation.

4.4 Relation between fibrinogen and plasma viscosity:

A simple Pearson product-moment zero-order correlation between PV and FIB at all three testing session reveals a modest, but statistically significant correlation ($r=0.319$, $p=0.035$) (figure 8).

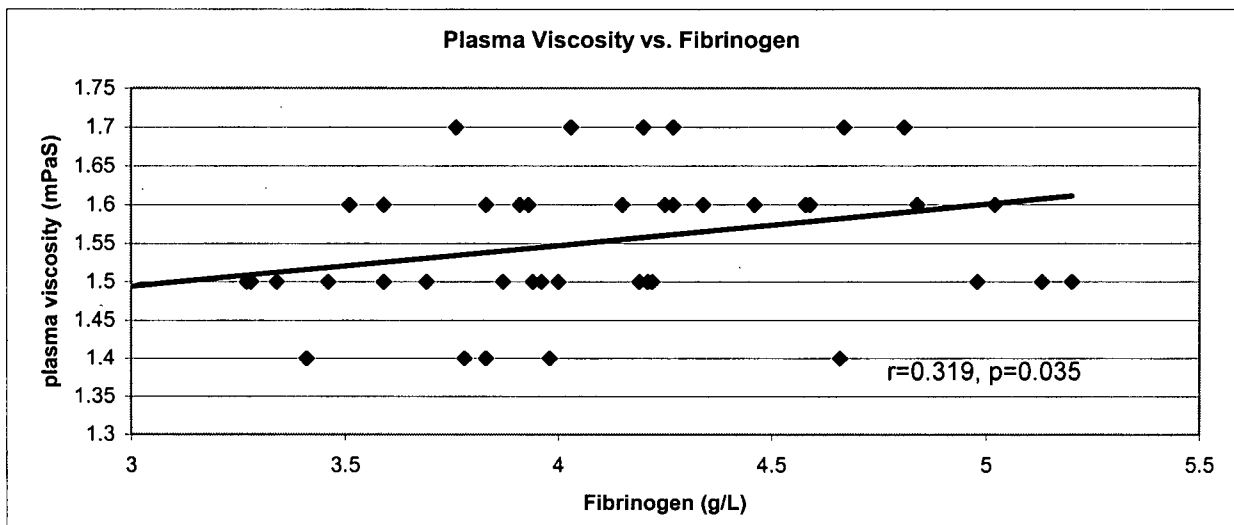


Figure 8: Scatter plot of plasma viscosity versus fibrinogen illustrating modest but significant Pearson product moment correlation coefficient ($r=0.319$, $p=0.035$)

4.5 Changes in Lipids and Exercise Capacity

Repeated measures ANOVA between pre and post HDL and TG levels just failed to reach significance ($p=0.08$ and $p=0.123$ respectively) although a boosting trend was observed for HDL and a lowering trend was observed for TG. Although not hypothesized, Repeated measures ANOVA between pre and post CRP lipid levels revealed a significant increase in both TC ($p=0.012$) and LDL ($p=0.001$) (figure 9).

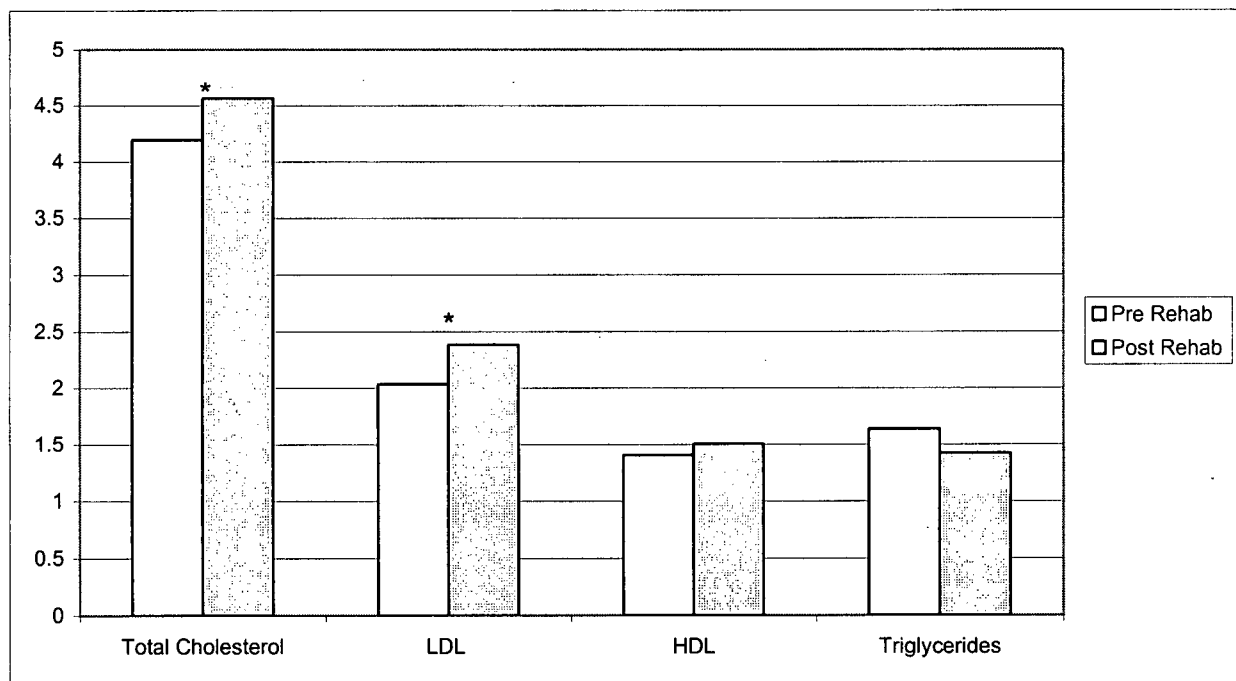


Figure 9: Lipids levels before and after CRP illustrating non- significant change in HDL ($p=0.08$) and triglycerides ($p=0.123$), and significant change in TC ($p=0.012$) and LDL ($p=0.001$).

The mean exercise time completed on the standard Bruce treadmill protocol was significantly higher after the CRP intervention ($p<0.001$) (figure 10).

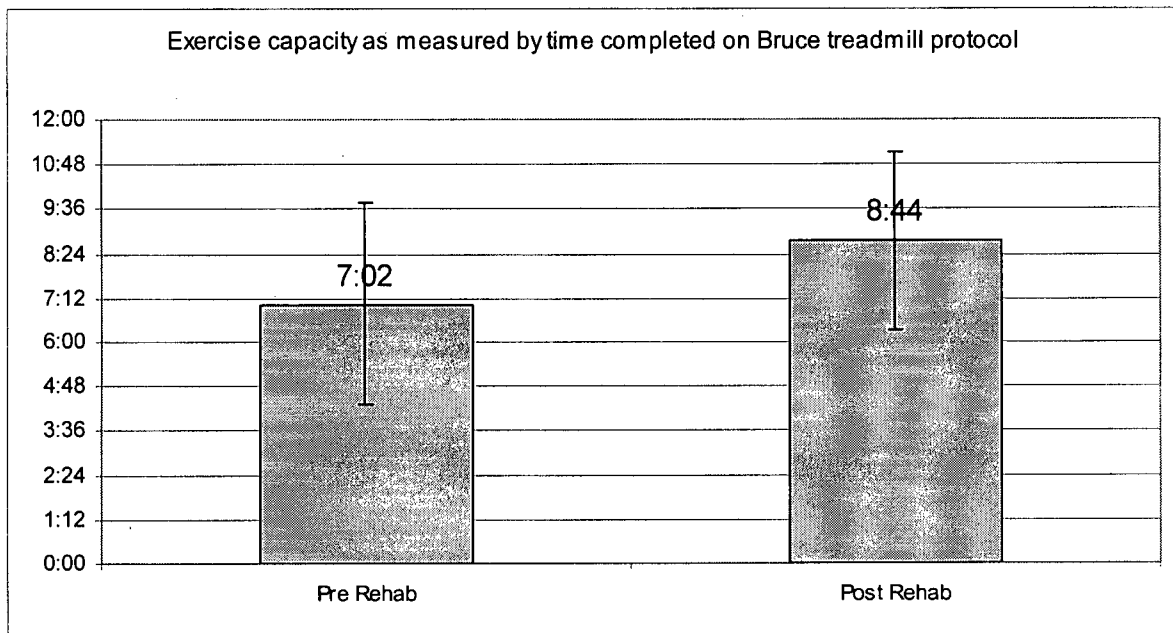


Figure 10: Bar graph illustrating significant ($p < 0.001$) change in exercise capacity measured as time completed on a standard Bruce treadmill protocol.

This study was not able to demonstrate any effect of the CRP on hemorheology. Although we were able to find a significant correlation between FIB and PV, the relationship was weaker than expected. Exercise capacity did improve significantly after the CRP. The data just failed to reach significance for HDL and TG. This study's initial hypotheses are summarized in table 6.

<i>Hypothesis</i>	<i>p</i>	<i>Conclusion</i>
CRP will reduce HCT	0.330	Fail to reject H_0 , no change
CRP will reduce PV	0.533	Fail to reject H_0 , no change
CRP will reduce FIB	0.275	Fail to reject H_0 , no change
Significant correlation between FIB and VIS	0.035	Reject H_0 , weak but sig. correlation
CRP will increase exercise capacity	<.001	Reject H_0 , significant improvement
CRP will reduce TG	0.123	Fail to reject H_0 , no change
CRP will increase HDL	0.08	Fail to reject H_0 , no change

Table 6: Hypothesis summary indicating initial hypothesis significance level and conclusion.

CHAPTER 5

5.0 Discussion

5.1 Changes in Hemorheology

5.1.1 Changes in Hematocrit

The primary purpose of this study was to investigate the effects of CRP on hemorheology. The most biologically significant measure of hemorheology is whole blood viscosity because it is this physical property that cardiovascular system must deal with *in vivo*. Unfortunately, blood viscosity is a very hard property to measure due to its non-Newtonian properties. Not only is whole blood viscosity more difficult to measure than its constituent parts, but it also requires expensive, specialized equipment if one wishes to measure across several different shear rates. As such, the researchers used hematocrit as a barometer of whole blood viscosity due to the fact that erythrocyte concentration (i.e: hematocrit) accounts for the majority of the variance in blood viscosity during bulk flow through arteries and arterioles (Somer & Meiselman, 1993). Measuring hematocrit is also a very simple, economical and reliable measure, further adding to its appeal as an indicator of whole blood viscosity.

This study was not able to find any significant difference in hematocrit over time; as such we can infer that the CRP had no effect at decreasing hematocrit levels and potentially lowering whole blood viscosity. These findings are consistent with most of the longitudinal research done on diseased populations; however, our findings do not agree with most of the cross sectional research.

The research of Church et al. (2002), Levine et al. (1995), and Dumortier et al. (2002) all found no change in hematocrit in response to exercise training programs. Church et al. and Levine et al. used cardiac patients whereas Dumortier et al. used obese, insulin resistant subjects,

both of which are likely to have similar levels of exercise capacity to the subjects used in this study. The exercise intervention in these studies was similar in frequency, intensity, and duration to the current study; furthermore, study designs were similar and sample sizes all were less than 40. Another small ($n=25$) training study using young healthy subjects randomly assigned to a exercise group or a control group also failed to find any change in hematocrit after 23 weeks of training (el-Sayed & Davies, 1995).

In contrast, several large cross-sectional studies that compared people who exercise with those that do not exercise find significantly lower hematocrit levels in people who are physically active (Danesh et al., 2000; Carroll, Cooke & Butterly, 2000). Furthermore, several longitudinal training studies on healthy subjects and athletes demonstrate that higher intensity training does result in a decreased hematocrit secondary to plasma volume expansion (Conventino, 1991; Fellman, 1992).

It would seem that exercise training may reduce hematocrit (and therefore whole blood viscosity); however, the training burden required to induce such changes may be too great for the average CRP participant. Perhaps some parameter of exercise, either the frequency, intensity, duration or time of exercise is not great enough to stimulate change. This hypothesis is supported by a review article on exercise induced plasma volume expansion which stated that "the intensity of exercise is probably the major stimulus for plasma volume expansion induced by training...the frequency of exercise training may also have a significant effect on plasma volume response" (Fellman, 1992). Conventino et al. also found that training two hours per day had a far more marked effect on plasma volume than training one hour (Conventino, 1991). Research into the phenomenon of plasma volume expansion secondary to relatively intense exercise training seems to explain the results of cross sectional studies that find physically active subjects having lower

HCT compared to sedentary subjects. It also suggests that CRP exercise training does not provide adequate stimulus to promote plasma volume expansion (reducing hematocrit and whole blood viscosity) thus accounting for the results of the longitudinal training studies.

5.1.2 Changes in Fibrinogen

This study's inability to find a significant change in resting fibrinogen concentration following CRP is consistent with the longitudinal findings of Levine et al.(1995), Reinhart et al. (1998), De Paz et al. (1992) and El. Sayed and Davies (1995). All of these researchers failed to find a significant difference in fibrinogen levels following a training intervention that was similar to the one employed in this study. Levine et al. and Reinhart et al. both used heart disease patients as subjects whereas El Sayed and Davies and De Paz et. al. used young healthy volunteers.

These studies contrast with the finding of Suzuki et al. (1992) and Worsornu et al. (1992) who both found significant decreases in fibrinogen after a physical conditioning program. Suzuki et al. compared various hematological and hemostatic markers in 86 post MI patients versus thirty control patients. After one month of conditioning, these researchers found a significant decrease in fibrinogen concentration as well as several other markers of coagulability. Worsornu et al. also found significantly lower fibrinogen levels in 56 post bypass men who were divided into three groups: aerobic training, power training or control. Changes were greater for the aerobic group versus the power group at three months and at six months. It should be noted that the studies by Suzuki et al. and Worsornu et al. both employ larger sample sizes and compare to a true control group.

Large-scale epidemiological studies that compare physical activity levels with fibrinogen concentration consistently demonstrate lower fibrinogen levels in people who are more active (Wannamethee et. al., 2002; Connelly et al., 1992). In a 2003 review of fibrinogen and heart disease, Koenig states that numerous studies indicate that people who are more physically active have lower fibrinogen levels and that this relationship appears to have a dose-response relationship (Koenig, 2003).

Both fibrinogen and C-reactive protein are termed acute-phase inflammatory markers, and often studied in conjunction. Indeed, both fibrinogen and C-reactive protein are highly predictive of acute coronary events and both are considered emerging risk factors. As such, it is prudent to briefly mention a fairly well designed study that investigated the effect of CRP on C-reactive protein. In this study Milani et al. (2004) compared 277 consecutive CRP patients with 42 control patients who did not attend CRP. After controlling for statin use and weight loss, these researchers found a significant decrease in C-reactive protein following CRP. It would seem reasonable to predict that more robust study designs like the one used by Milani et. al. would also be able to detect significant changes in fibrinogen concentration following CRP. Unfortunately such studies have yet to be published.

5.1.3 Changes in Plasma Viscosity

Results from longitudinal training studies on plasma viscosity are mixed, with about half finding significant change as a result of exercise training. Both Church et al. (2002) and Ernst and Matrai (1987) found significant decreases in plasma viscosity after exercise training. Church et al. studied 23 patients passing through a phase II CRP program and compared them to a reference group of 11 healthy subjects. Interestingly, subgroup analysis revealed that only the subjects in

the top third in initial plasma viscosity significantly reduced their plasma viscosity. Ernst and Matrai found a significant decrease in plasma viscosity with treadmill training to exhaustion on subjects with intermittent claudication of the legs by comparing 22 experimental subjects with a true control group of 22 subjects.

Conversely, results from this study agree with those of Levine et al. (1995) and Reinhart et al. (1995) who both failed to find significant changes in plasma viscosity after exercise training despite significant increases in exercise capacity. As with the current study, both of these studies used a similar exercise training intervention on heart patients. Levine et al. suffered from small sample size and lack of a true control group, making the possibility of a type II error high. Reinhart et al. did employ a control group; however, sample size was also fairly small at $n=25$.

Church et al. suggests that differences in results between studies are possibly the result of different methods used to assess plasma viscosity: both Levine et al. and Reinhart et al. used rotary viscometers, whereas Church and Ernst used capillary tube viscometers (as was the case in this study).

Although longitudinal studies display mixed results, large-scale cross-sectional studies unequivocally demonstrate that higher levels of physical activity are associated with lower plasma viscosity. Analysis of 4252 subjects from the British Regional Heart Study reveals a significant inverse relationship between plasma viscosity and the amount of physical activity (Wannamethee et al., 2002). Furthermore, follow-up 20 years later showed that subjects who changed their activity patterns had plasma viscosity levels that resembled their current level of physical activity (i.e.: those who became inactive had viscosity levels similar to those who remained inactive, and those who became active had viscosity levels similar to those who remained active). These results were independent of age and smoking status. Similar results were

reported in the findings of Carroll et al. (2000) who cross-sectionally studied 740 asymptomatic middle aged men.

In summary, based upon large-scale observational studies it would appear that exercise does favorably impact hemorheology; however, results from interventional longitudinal studies fail consistently to confirm this hypothesis. Also, it is not clear whether a typical CRP provides adequate stimulus to promote change in hemorheology. Finally, methodological differences in measurement and exercise intervention between studies may account for the mixed results observed in the literature.

5.2 Relationship Between Plasma Viscosity and Fibrinogen Concentration

Fibrinogen is a large, asymmetrical protein that disrupts laminar flow and thus is the primary contributor to plasma viscosity. Correlations between plasma viscosity and fibrinogen concentration have varied between 0.2 to 0.7 in large epidemiological studies (Koenig et al., 1998; Yarnell et al., 1991). Other plasma borne proteins such as serum globulin and albumin also affect plasma viscosity, but to a lesser extent than fibrinogen (Lowe, 1992).

Data from this study reveal a modest but significant correlation between plasma viscosity and fibrinogen concentration ($r=0.319$, $p=0.035$), with fibrinogen accounting for about 10% of the variance in plasma viscosity. Although a higher correlation was expected, this result falls within the range of other published studies (Lowe, 1986). One must assume that other plasma proteins and measurement error can explain the remainder of the variance. Test sensitivity must be considered since all plasma viscosity measurements were reported to only one decimal place and only ranged from 1.4-1.7 mPaS. Additionally, viscosity measurements were often reported as being the same at both 25 and 37 degrees Celsius, when one would expect at least some

difference between these two temperature readings due to plasma viscosity's linear relationship with temperature.

5.3 Changes in Exercise Capacity

Exercise times on the standard Bruce Protocol were significantly longer post CRP versus pre CRP ($p < 0.001$). This physical conditioning phenomenon is consistent across almost all trials investigating the effectiveness of cardiac rehabilitation programs. The AHA's Scientific Statement on Secondary Prevention of Coronary Disease states that CRP result in improvements of 20-60% in functional capacity (Balady et al., 2000). This is consistent with results from this study, which demonstrated a 22% improvement in time completed on the Bruce treadmill protocol.

The improvement in exercise capacity is important in light of a recent study by Mora et al. (Mora et al., 2003) that found exercise capacity as measured during stress testing (and not ST segment changes) being highly prognostic of future cardiac events. It should be noted that this study was completed on 3000 asymptomatic women, which limits generalizability to the population that is currently being studied (i.e. cardiac patients). Regardless, Mora et al.'s study underlines the importance of improving fitness and exercise capacity to reduce chance of coronary disease.

5.4 Changes in Lipids

5.4.1 Changes in HDL Cholesterol and Triglycerides

Our data does not support that hypothesis that CRP significantly increases HDL ($p = 0.08$) and reduces triglyceride levels ($p = 0.123$). A very recent and extensive review on all randomized

control trials investigating the effects of cardiac rehabilitation on lipids found a significant decrease in triglyceride levels (weighted mean difference, -0.23 mmol/L; 95% CI: -0.39 to -0.07 mmol/L), but no significant change in HDL cholesterol (-0.05 mmol/L; 95% CI: -0.03 to 0.14 mmol/L) (Taylor et al., 2004).

This recent meta-analysis confirms the well-established opinion that exercise reduces triglyceride levels. Data from this study do show a decrease in mean TG concentration of 0.244 ± 0.57 mmol, which just fails to reach significance, probably due to a lack of power.

Surprisingly Talyor et al. found that CRP did not favorably influence HDL levels. This contradicts the long held opinion that exercise favorably influences HDL concentration. In a review of the effect of exercise on HDL concentration, Kokkinos and Fernhall (1999) concluded that exercise increases HDL concentration in a dose-response fashion. The reviewers also noted that statistical significance usually is reached after about 1200-1600 kcal of exercise per week, or 7-10 miles of walking. It is doubtful that most CRP programs elicit a weekly caloric expenditure of 1200-1600 kcal during class. Even when exercise is suggested to patients on days that they do not attend class, it is doubtful that total weekly caloric expenditure exceeds 1200kcal, owing primarily to the physical limitations of most cardiac patients. Therefore it can be suggested that the CRP intervention in this study (which is typical of most other CRP) does not provide adequate exercise stimulus to evoke statically significant changes in HDL cholesterol, although a modest increase was observed that nearly reached our a-priori alpha level of 0.05.

5.4.2 Changes in Total Cholesterol and LDL Cholesterol

No a-priori hypotheses were made in regards to TC and LDL levels; however, this data was available and so appropriate analysis was carried out. Surprisingly, the results indicated a

significant increase in both TC and LDL cholesterol. This result was unexpected, especially since all subjects remained on a constant dose of statin medication. Not only were these results unexpected, but they do not agree with the meta-analysis of Taylor et al. (2004) which indicated that CRP significantly reduces TC but not LDL.

Careful re-examination of each subject's chart reveals a potential cause of the increase in TC and LDL. Each subject had a personalized consultation with the dietitian shortly after admission to the CRP program. A summary sheet of recommendations was given to the researcher for each consultation. It is noted on several summary sheets that the diets of the subjects contained extremely low amounts of saturated and trans fatty acids, and it was often suggested that subjects could be less stringent in this regard. The dietitian's observations and recommendations were valid because 80% of subjects entered the study with LDL levels below clinical targets (mean LDL = $2.03 \pm .62$ mmol versus current guidelines which suggest an LDL >2.6 mmol). Mean post-CRP LDL levels were still within targets (mean LDL = 2.31 ± 0.67) although a few more subjects slipped above the 2.6 mmol target. This suggests that subjects were less strict in terms of fat restriction once they realized that they were within current guidelines for LDL. Casual discussion with subjects and the dietitian supports this observation.

5.5 Study Limitations

The researchers recognize several limitations of this study. First it must be recognized that sample size is very small, greatly reducing the power of the study and increasing the chance of type II error. Although the current design tried to incorporate a "control interval" when no CRP intervention occurred, this study would be more robust if it included a true control group that did not participate in any CRP.

All 45 samples of plasma viscosity measured as 1.4, 1.5, 1.6, or 1.7 mPaS indicating that the sensitivity of this test is very limited, further increasing the chance of type II error.

5.6 Conclusions and Suggestions for Further Research

Data from this study failed to demonstrate changes in hemorheology, HDL cholesterol, and triglycerides following CRP. Even with a larger sample size, it is unknown whether CRP will provide adequate stimulus to promote changes in some or all of these variables. Investigating therapeutic methods of altering blood viscosity, plasma viscosity, fibrinogen, HDL cholesterol and triglycerides is important because all of these variables are highly predictive of heart disease. At this time it is unclear whether current standard practices in cardiac programs favorably affect these variables. Future research in this area will require larger sample sizes and use of a true randomized design. Comparison between current standard CRP practices should be compared to more aggressive exercise protocols that require subjects to meet pre-established weekly threshold energy expenditure levels (for example 1500 kcal per week).

The CRP intervention did significantly improve exercise capacity, although the lack of a true control group limits strength of this statement. Regardless, increasing fitness has been shown to decrease risk of a heart event in some populations, and improves countless other health and quality of life measures.

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