Hemorheology and Cardiovascular Disease

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1. Introduction

Although the science of viscosity has existed for almost two centuries and its basic principles and theories are well established, the medical community at large has not recognized whole blood viscosity as a significant physiologic parameter. Fortunately, in recent years physicians and researchers have shown an increased interest in the role of whole blood viscosity in the pathogenesis of cardiovascular diseases. Clinical studies are confirming whole blood viscosity and its determinants as some of the most important parameters in assessing a person's risk for atherosclerosis-related diseases (heart attacks and strokes). The determinants of whole blood viscosity include hematocrit, red blood cell (RBC) deformability, RBC aggregation, and plasma viscosity (influenced to a large degree by fibrinogen).

The comprehensive overview and discussion of whole blood viscosity in this paper reveal the potential promise that viscosity holds in diagnosis, prediction, prevention, and treatment of cardiovascular diseases—and perhaps all diseases. Widespread understanding of whole blood viscosity may usher in a new era of research and patient management in cardiology and vascular science. A solid understanding of viscosity and an ability to measure it in the clinical setting can make this hope a reality.

2. Characteristics of Blood

Blood is a unique fluid. From a biologic perspective, it is a dynamic and living medium, which interacts with everything it comes in contact with (e.g., air, endothelium, drugs, foreign materials, changes in temperature, movement). Its innumerable tasks include maintaining a myriad of homeostatic functions essential to daily living. Blood transports nutrients and oxygen to various tissues, removes waste materials, regulates acid-base balance and salt, and clots when we cut ourselves.

In terms of fluid mechanics, blood is a highly complex fluid. Very few fluids can even begin to emulate its motion and flow properties. To appreciate the validity of these statements, consider one small drop of blood. Within that drop are millions of cellular constituents, which are constantly changing and adapting to their circumstances while being continuously circulated through the vascular system. One characteristic of particular relevance to fluid mechanics is that blood goes through capillary beds whose diameters are approximately 4 to 9 micrometers, barely large enough for erythrocytes (8 micrometers) and other cells to squeeze through.

Blood constitutes approximately 7% to 9% of normal body weight and is a suspension or slurry of cellular elements in an aqueous solution of plasma. Plasma itself, also a complex fluid, is a mixture of water, proteins, lipids, carbohydrates, enzymes, and other substances. Water constitutes the bulk of plasma volume, with solutes accounting for about 8%. The most important constituents in plasma are the proteins. They include albumin, fibrinogen, and globulin. These proteins are important in maintaining osmotic balance in the blood and in affecting both plasma viscosity and whole blood viscosity.

About 45% of blood volume is made up of cellular components, which include erythrocytes (RBCs), leukocytes (white blood cells), and platelets. RBCs

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make up most of the cellular content and therefore account for almost 50% of the blood volume. The most important constituent of the RBC is hemoglobin, which is responsible for carrying oxygen to the various parts of the body. The life span of an RBC is 90 to 120 days. Old RBCs are less deformable than new RBCs.

The presence of such a high volume of RBCs makes blood a non-Newtonian fluid whose viscosity varies with shear rate. The *shear rate* is the rate of change of velocity along the radial direction in a lumen. Specifically, whole blood viscosity decreases as shear rate increases, a phenomenon called "shear-thinning characteristics." In other words, when blood moves slowly as in diastole, its viscosity is high; when it speeds up as in systole, it becomes thinner and its viscosity is lower. The fact that whole blood viscosity increases at low shear is one of the key factors for the initiation of atherosclerosis at specific sites.

In its simplest definition, viscosity represents stickiness and thickness of blood. It is a frictional resistance to blood flow. In a nutshell, when whole blood viscosity increases, blood flow decreases, assuming that the heart maintains the same systolic pressure. Conversely, in order for heart to maintain the same cardiac output, the systolic pressure must increase as whole blood viscosity increases.

3. Clinical Significance of Blood Viscosity

3.1 Atherosclerosis

Atherosclerosis is a focal disease with predictable regions and sites of development. The predilection of atherosclerotic lesions to form on outer walls of vessel bifurcations, on the inlets of branches, and on the inner walls of curvatures of the arteries suggests that hemodynamic forces (i.e., injurious pulsatile flow) contribute to the initiation and progression of the disease.

Clinical and epidemiologic studies provide compelling evidence that whole blood viscosity may be a significant causal determinant of atherosclerosis. Lowe and Forbes (1988) reported that the rheologic changes of blood within the complex arterial geometries initiated flow-induced changes, which were followed by biochemical and pathologic mechanisms. Resch et al. (1991) investigated the prognostic relevance of blood rheologic variables in patients with arteriosclerotic diseases and found that those who experienced a second stroke or MI or cardiovascular death within two years of their first examination had significantly higher blood viscosity, RBC aggregation, serum viscosity, fibrinogen, and cholesterol levels than those who did not experience one of these events. Craveri et al. (1987) studied patients with peripheral atherosclerosis and found an increase in blood viscosity, which was attributed to the increased plasma viscosity and fibrinogen.

In the Edinburgh Artery Study, Lee et al. (1998) studied whether or not several hemostatic and rheological factors were associated with incident cardiovascular events. The researchers examined 1106 men and women 60 to 80 years old over 5 years and measured carotid intima-media thickness, blood and plasma viscosities, fibrinogen, and hematocrit. They found that whole blood viscosity and its major determinants (plasma viscosity, fibrinogen, and hematocrit) were linearly related to intima-media thickness in men. Correcting whole blood viscosity to a standard hematocrit of 45% had little effect on its association. In men, the increase in whole blood viscosity and fibrinogen significantly increased the risk of elevated intima-media thickness. No significant associations were reported between any of the hemorheologic factors and intima-media thickness in women. Therefore, Lee et al. concluded that, in men, whole blood viscosity and its major determinants are associated not only with incident cardiovascular events but also with the early stages of atherosclerosis.

3.2 Myocardial Infarction

Myocardial infarction (MI) is damage to an area of heart muscle caused by an inadequate supply of oxygen to that area; it is also known as heart attack. MI is the leading cause of death in the United States and industrialized nations and is the most important form of ischemic heart disease. In the United States, about 1.5 million people per year suffer an acute MI, and approximately one third of these die. At least 250,000 people per year die of heart attack before they reach the hospital (Cotran et al, 1999).

Jan et al. (1975) measured whole blood viscosity in patients with acute MI on the day of hospital admission, and 3 and 21 days after acute MI. They found that the patients with higher whole blood viscosity on admission had a significantly higher incidence of complications, namely, shock, thromboembolism, and left ventricular failure. They also found that whole blood viscosity remained high when measured 21 days

after an acute MI in spite of a fall in hematocrit. The high whole blood viscosity after acute MI was attributed to the increased plasma viscosity.

Malkun Paz et al. (1987) also measured venous and arterial blood viscosities in 25 patients with ischemic heart disease. They found that both venous and arterial blood viscosities were elevated independently of the hematocrit, and they proposed that this elevation might be due to increased plasma viscosity and platelet aggregation.

Ischemic heart disease is attributed to insufficient blood flow, which in turn is caused by increased blood viscosity. Hence, a number of clinical studies have investigated the relationship between MI and blood viscosity. Schabitz et al (1977) and Schabitz and Krosch (1979) compared the whole blood viscosity of 63 patients with chronic ischemic heart disease after myocardial infarction with the whole blood viscosity of healthy controls. The whole blood viscosity of the patients with MI was significantly higher for all degrees of severity than the whole blood viscosity of the healthy persons, and whole blood viscosity was positively correlated with hematocrit value, fibrinogen level, and total lipid and cholesterol levels. These researchers concluded that increased whole blood viscosity can be regarded as a risk factor for MI.

Koenig et al. (1998) examined the relation association of plasma viscosity with the incidence of a first major coronary heart disease (CHD) in the form of MI in 933 men 45 to 64 years old at the Augsburg, Germany, site of a study known as the MONICA (MONItoring trends and determinants in CArdiovascular disease) project. They found that patients with high (in the top 20%) viscosity had approximately a three times greater risk for CHD events than those with low (the bottom 20%) viscosity. This suggested that elevated plasma viscosity might be used to identify subjects at risk for CHD events. In addition, Junker et al. (1998) examined 1142 male MI patients to determine whether or not there was a significant relationship between plasma viscosity and the severity of CHD. They found a positive correlation between the two, which supported the hypothesis that plasma viscosity may be the mechanism linking cardiovascular risk factors to CHD.

Yarnell et al. (1991) studied the effects of plasma viscosity, fibrinogen, and white cell counts on ischemic heart disease in 4860 middle-aged men from the general population and calculated the age-adjusted relative odds of having a major event (MI or death) attributable to ischemic heart disease. Compared with the relative odds of the men with viscosity measurements in the lowest 20%, the relative odds were 4.5 for men with viscosity measurements in the highest 20%.

Kiesewetter et al. (1988) investigated classic risk factors and hemorheologic profiles in patients with arterial vascular disease. The rheological parameters included plasma viscosity, RBC and platelet aggregation, RBC rigidity, and hematocrit. The researchers found that 57% of the patients, compared with only 14% of the healthy control subjects, showed two or more elevated rheological parameters.

A premise of Leschke et al. (1988) was that whole blood viscosity is one of the most important factors in the microcirculation, for example, in patients with unstable angina pectoris. They measured plasma viscosity and erythrocyte aggregation together with fibrinogen. They found that patients with unstable angina showed significantly higher viscosity and fibrinogen levels, even before an infarction manifested, than the patients with stable angina. Leschke et al. explained that the abnormal viscosity in unstable angina plays a part in increasing myocardial ischemia, because oxygen delivery is already diminished and capillary flow slows down, thus contributing to the progression of the angina.

Rainer et al. (1987) investigated several rheologic variables in 17 patients (11 men and 6 women, mean age 52 years) with chronic stable angina. Rheologic measurements included whole blood and plasma viscosities (at shear rates of 750 and 1500 s^{-1}), hematocrit, and RBC aggregation. Compared with a normal control group, the patients showed significant increases (14% and 16%) in whole blood viscosity at both shear rates, a 9% increase in plasma viscosity, a 6% increase in hematocrit, and a 28% increase in the rate of RBC aggregation. Since RBC aggregation is closely related to low shear viscosity, one might expect a substantial increase in whole blood viscosity at low shear (i.e., 1 s^{-1}) among the patients with angina. Rainer et al. concluded that the rheologic abnormalities in patients with angina "are compatible with disturbed blood flow and an enhanced tendency for coronary arterial thrombosis."

3.3 Peripheral Arterial Diseases

Blood viscosity is considered one of the major factors in disorders of the peripheral circulation (Di Perri et al.1978). Ciuffetti et al. (1989) reported that whole blood viscosity (corrected for hematocrit at both

high and low shear rates) was significantly higher in patients with peripheral vascular disease than whole blood viscosity in healthy controls. Forconi et al. (1979) measured blood and plasma viscosity, packed RBC volume, and fibrinogen in 13 patients suffering from peripheral obliterative arterial disease of the lower limbs (stage III or IV) who were awaiting surgery. They compared these measurements with those of nine healthy control subjects. Blood samples were collected from the antecubital vein, femoral vein, and femoral artery. Whole blood viscosity was decidedly higher in the patients than in the control subjects. In the patients, venous blood viscosity was significantly higher than arterial blood viscosity, whereas no statistically significant differences in blood viscosity were found between artery and vein in the control subjects. Ciuffetti et al. concluded that there is a relation between hyperviscosity syndrome and vascular ischemia-inducing diseases.

Turczynski et al. (1991) studied the effect of increased blood and plasma viscosity on the claudication distance in 53 patients with obliterative atherosclerosis of the lower limbs and compared this with a control group of 100 healthy persons. A significant increase in blood and plasma viscosity was found among the patients, together with increases in total lipids, fibrinogen, triglycerides, total cholesterol, and free fatty acids. The claudication distance significantly decreased with increasing blood and plasma viscosity in patients with obliterative atherosclerosis.

Poredos and Zizek (1996) investigated the role of plasma viscosity on arterial wall deterioration in patients with different stages of arterial disease of the lower limbs. Arterial wall deterioration is one of the most important determinants of clinical manifestation and prognosis of the disease. The researchers examined four groups: 18 patients with intermittent claudication up to 200 meters, 15 patients with critical ischemia of the lower limbs (stage III and IV), 16 patients with recanalization procedures on peripheral arteries, and 19 healthy volunteers. Plasma viscosity was 1.78 mPa in the patients with critical ischemia, 1.68 mPa in those with intermittent claudication, and 1.58 mPa in the healthy subjects. Whole blood viscosity was significantly higher in the critical ischemia patients than in the intermittent claudication patients, and in the intermittent claudication patients than in the healthy subjects. Thus, Poredos and Zizek concluded that in patients with peripheral arterial disease plasma viscosity increases with the progression of the atherosclerotic process and correlates with the clinical stages of the disease.

Lowe et al. (1993) investigated the role of blood and plasma viscosity, fibrinogen, and activation of coagulation and leukocytes in a random sample of 1581 men and women aged 55 to 74 years in Edinburgh, Scotland, with symptomatic and asymptomatic peripheral arterial disease. On multivariate analysis, whole blood viscosity and fibrinogen were independently associated with peripheral arterial narrowing. Plasma viscosity was also associated with claudication. The risk of claudication for people within the top 20% plasma viscosity group was 3.4 times greater than the risk for those within the bottom 20% plasma viscosity group. The researchers concluded that blood rheologic factors and leukocyte activation are associated with lower limb ischemia in the general population and may be implicated in its pathogenesis.

3.4 Stroke

An estimated 158,000 Americans die of stroke every year, making it the number 3 overall killer in the United States. Recently, Edward Sondik, director of the National Center for Health Statistics at the Centers for Disease Control and Prevention in Atlanta, said that "death from stroke has gone from a fairly steep decline into essentially a flat mode, and it is hardly going down at all now" (WebMD, 1999). In other parts of the world, it is no different. For example, an epidemiologic study from China confirmed that stroke is the most common cause of death in that country, with an incidence of 219 in 100,000 people—more than five times that of MI (Shi et al. 1989). These researchers reported that traditional herbal medicine used in China might modify whole blood viscosity and platelet aggregation.

Autoregulation of the cerebral circulation attempts to protect the brain from stresses caused by hemorrhage and severe anemia. (Dormandy 1987). However, various clinical studies appear to indicate that the autoregulation does not work when an abnormally high blood viscosity, hematocrit, or fibrinogen level reduces blood flow in the brain (Di Perri 1981, Humphrey et al. 1981). On the other hand, the opposite view says that viscosity changes result in compensatory readjustment in vessel diameter, which is called "blood viscosity autoregulation of cerebral blood flow." (Muizelaar et al. 1986) The autoregulation maintains normal cerebral blood flow and oxygen transport despite increased blood viscosity (Brown and Marshall 1985). In general, high fibrinogen

levels have been observed in cerebrovascular disease, with a direct relation to both whole blood and plasma viscosity as well as to cerebral blood flow (Walzl et al. 1993).

Di Perri et al. (1985) evaluated hemorheologic factors in 106 patients suffering from acute and chronic cerebrovascular diseases. Blood samples were drawn within 6 hours of the onset of the vascular syndrome. The researchers observed that the onset of the vascular storm was associated with a marked increase in plasma fibrinogen and in blood/plasma viscosity. Whole blood filterability was significantly decreased. Acute stroke regressed with the progressive reduction of rheological abnormality, confirming the existence of an association between cerebrovascular disease and hemorheologic alterations.

Resch et al. (1992) investigated whether or not abnormalities in whole blood viscosity predict a poor prognosis for subsequent cardiovascular events in stroke survivors. For an average of 2 years, they followed 625 survivors of a first stroke. Eighty-five patients (13.6%) had a second stroke or MI, or died as a result of a cardiovascular event. Patients with re-events had higher whole blood viscosity and fibrinogen levels than those who did not have such events. Resch et al. concluded that hyperfibrinogenemia is an independent risk factor for cardiovascular events in stroke survivors, and they proposed intervention trials with fibrinogen-lowering measures, which also reduce blood viscosity.

Fong and Chia (1990) studied the whole blood viscosity in 42 patients with nonembolic cerebral infarction. Whole blood viscosity and fibrinogen, cholesterol, and triglyceride levels were significantly higher than those of healthy persons, whereas high-density lipoprotein cholesterol (HDL-c) levels in the patients were significantly lower. Whole blood viscosity was found to have a positive correlation with hematocrit and fibrinogen, a negative correlation with HDL-c, and no correlation with cholesterol and triglycerides.

Coull et al. (1991) reported chronic blood hyperviscosity in 769 subjects with acute stroke, transient ischemic attack, or recognized risk factors for stroke. Whole blood viscosity at low shear rates was significantly elevated in stroke patients compared with whole blood viscosity in healthy persons. Among patient groups, patients with acute stroke had the highest blood viscosity, those with transient ischemic attack had the second highest viscosity, and those with recognized risk factors for stroke had the lowest blood viscosity. Increased whole blood viscosity was associated with an elevated plasma fibrinogen level and with a decreased albumin/globulin ratio. Coull et al. concluded that among stroke patients the abnormality of whole blood viscosity is, to a considerable degree, chronic. Fisher and Meiselman (1991) reported similar findings. They found significant acute increases in whole blood viscosity (at high shear of 1500 s^{-1}) and in plasma viscosity and fibrinogen level among severe stroke patients, but less specific hemorheologic abnormality among cerebral ischemia patients.

Grotta et al. (1982) examined the relation between hemorheologic parameters and cerebral blood flow in 53 patients and concluded that increased whole blood viscosity correlates with decreased cerebral blood flow, particularly in regions of low flow, and that both fibrinogen and hematocrit must be taken into consideration in viscosity determinations.

Ernst et al. (1988) investigated whether a complete ischemic stroke is due to significant hemorheologic abnormalities, leading to a rise of the peripheral resistance, or simply to ischemia. To clarify this question, they measured several hemorheologic parameters in 26 patients suffering from transient ischemic attacks. They found significant impairment of blood fluidity, blood filterability, and erythrocyte aggregation, suggesting that the flow properties of blood in patients are jeopardized even before an acute stroke. The researchers speculated that the hemorheologic abnormality predisposes to stroke by decreasing cerebral blood flow. Ernst et al. (1991) reported that pathologic blood flow properties and hyperviscosity lead to deterioration in the prognosis of patients with arteriosclerotic diseases, especially after a stroke. They concluded that in patients who survived a first stroke, elevated whole blood viscosity is a risk factor that is independent of other accepted risk factors.

3.5 Diabetes

In people with diabetes, whole blood viscosity, plasma viscosity, and hematocrit are elevated, whereas RBC deformability is decreased and RBC aggregation is increased The increase in low-shear-rate viscosity is attributed to increases in fibrinogen and globulin (Hoare et al 1976, Dintenfass 1977). Solerte and Fioravanti (1987) studied 22 patients with insulin-dependent diabetes and overt nephropathy and 24 diabetic patients without renal changes. Whole blood viscosity and plasma viscosity were higher and RBC

deformability was lower in the patients with nephropathy than in the patients without nephropathy. In addition, increased whole blood viscosity and plasma viscosity and decreased RBC deformability were correlated with impairments in glomerular filtration rate and renal plasma flow in patients with overt nephropathy. Linderkamp et al. (1999) compared whole blood viscosity parameters in two groups of children with type 1 diabetes and a control group of healthy children. One group of patients was studied before treatment and after 4 to 6 weeks of insulin; the other group was studied after being treated with insulin for 5 to 8 years. In both groups of diabetic children, whole blood viscosity and hematocrit were higher and RBC deformability was lower than in the control group.

Associations with whole blood viscosity and plasma viscosity also have been documented for risk factors for diabetes like the insulin sensitivity index and markers for the metabolic syndrome. Nordby et al. (1995) found that in 14 hypertensive and 12 normotensive premenopausal women whole blood viscosity and hematocrit were negatively correlated with the insulin sensitivity index (Nordby et al. 1995). Using HDL-c, triglycerides, glucose, and diastolic blood pressure measurements as risk markers for the metabolic syndrome, Carroll et al. (2000b) studied 561 nonsmoking, nondiabetic men. As the number of risk markers increased from 0 to 3 plasma viscosity levels increased When the metabolic syndrome was present (4 markers), plasma viscosity was significantly higher than when the metabolic syndrome was not present.

4. Risk Factors for Cardiovascular Diseases

Approximately 300 risk factors have been identified for atherosclerosis (Hopkins and Williams 1981, Hopkins and Williams 1986). In spite of this impressive figure, conventional risk factors can predict and account for only about 30% to 50% of incidental cases of cardiac and vascular diseases.

Consider the classic profile of a person who is likely to have a heart attack: someone who smokes, has high levels of low-density lipoprotein cholesterol (LDL-c), eats a diet high in animal fat, is overweight, and does not exercise. It may surprise you to know that up to 50% of people who have heart attacks do not fit this description. They don't smoke, are not overweight, have normal cholesterol and blood pressure levels, and exercise regularly. Unfortunately, there are few, if any, warning signs to alert these persons to future heart problems (*Harvard Health Letter*, 1999). The main reason for this dismal situation is that the mechanisms of interaction of these risk factors with atherogenesis are poorly understood. The problem stems from the fact that all of these conventional risk factors relate to systemic abnormalities or characteristics.

Elevated whole blood viscosity may be the parameter or mechanism by which other conventional risk factors influence atherosclerosis development. In other words, whole blood viscosity can be considered the common denominator. An examination of several studies that have correlated whole blood viscosity and conventional risk factors for cardiovascular disease can provide a sound basis for evaluating the validity of this statement.

The risk factors discussed in this section are the most significant ones: hypertension, hyperlipidemia, smoking, exercise, obesity, age, and gender.

4.1 Hypertension

According to *Robbins Pathologic Basis of Disease* (Cotran et al. 1999), elevated blood pressure (hypertension) is a major risk factor for atherosclerosis in all age groups, but in people over 45 years hypertension is a stronger risk factor than high cholesterol. Hypertension affects both the function and the structure of blood vessels, largely small muscular arteries and arterioles. People with hypertension remain asymptomatic until late in the course of the disease. Hypertension is one of the most important risk factors for both coronary heart disease and cerebrovascular accidents, and it may also lead to cardiac hypertrophy with heart failure, aortic dissection, and renal failure.

The systemic arterial blood pressure depends on two fundamental hemodynamic variables: cardiac output and total peripheral resistance. Cardiac output is determined by the functional characteristics of the heart. It is well known that the cardiac output is proportional to blood pressure (BP) and inversely proportional to the total peripheral resistance (TPR), as shown in Eq. 1:

$$Cardiac\ output = \frac{BP}{TPR}. \tag{1}$$

The balance between cardiac output and blood pressure involves two critical physiologic variables: lumen diameter and whole blood viscosity, as qualitatively manifested in Eq. (2), the Poiseuille equation for laminar flow:

$$BP = CO \bullet [TPR] = CO \bullet \left[\frac{128(WBV)L}{\pi d^4} \right] \qquad (2)$$

where CO is cardiac output, WBV is whole blood viscosity and d and L are the characteristic lumen diameter and length, respectively.

This equation demonstrates that whole blood viscosity directly contributes to the total peripheral resistance. Although modern medicine has paid much attention to total peripheral resistance, our understanding of the clinical significance of whole blood viscosity in atherosclerotic disease is still in its infancy. Equation 2 indicates that when a normally functioning heart is faced with an increased peripheral resistance because of hyperviscous blood, the normal cardiac output can be maintained only by increasing the perfusion pressure (Stoltz et al.1999).

Clearly, whole blood viscosity is a cause of hypertension. In patients diagnosed with hypertension, whole blood viscosity has been observed to be elevated and the degree of elevation to be correlated with both systolic and diastolic pressure levels in general. Whole blood viscosity affects peripheral resistance to blood flow, and peripheral resistance affects diastolic blood pressure (Sharp et al. 1996). Hence, increased whole blood viscosity can be a cause of increased diastolic blood pressure.

Letcher et al. (1981) measured whole blood viscosity at six different shear rates, which significantly correlated with blood pressure. The increase in whole blood viscosity was attributed to high plasma viscosity, high hematocrit, and increased levels of fibrinogen and globulin. Letcher et al. (1983) focused on the fact that in patients with borderline hypertension, total peripheral resistance is either elevated or abnormally related to cardiac output. They hypothesized that it may be due to elevated whole blood viscosity. The researchers measured various components of whole blood viscosity in 25 patients with borderline hypertension and compared these with components of whole blood viscosity in 25 normal subjects. They found that whole blood viscosity directly correlated with both systolic and diastolic pressures and was greater in the hypertensive patients than in normal subjects. Letcher et al. explained that at low shear rates, increased RBC aggregation accounted for the higher whole blood viscosity, whereas at high shear rates, increased hematocrit and plasma viscosity increased whole blood viscosity. In general, they concluded that the increased whole blood viscosity is a consequence of increased hematocrit, plasma viscosity, and RBC aggregation, all of which are instrumental in the pathogenesis of cardiovascular disease.

Tsuda et al. (1997) reported that both whole blood viscosity (normalized to a hematocrit of 45%) and plasma viscosity were significantly raised (at low and middle shear rates) in patients with essential hypertension. Toth et al. (1999) also studied hemorheologic parameters in patients with essential hypertension and found that whole blood and plasma viscosity and fibrinogen levels were in the pathologic range (i.e., WBV = 5.18 mPa at 90 s^{-1}) and significantly higher than in healthy controls (i.e., WBV = 4.18 mPa at 90 s^{-1}). The researchers concluded that hemorheologic factors might play a role in the pathogenesis and the development of organ damage in hypertension.

Koenig et al. (1989, 1991) studied the association between plasma viscosity and blood pressure in a large (over 5000) population sample 25 to 64 years old at the Augsburg site of the MONICA project. After adjustment for all confounders, plasma viscosity had the strongest association with high blood pressure next to body mass index. In other words, plasma viscosity showed a stronger association with hypertension than other well-known risk factors, such as smoking, total serum cholesterol, and alcohol consumption. If whole blood viscosity had been measured, it might have shown a much stronger association than plasma viscosity at low shear rates (e.g., 1 s^{-1}). Koenig et al. pointed out that increased plasma viscosity (mainly due to increased fibrinogen level) might contribute to persistently increased resistance to blood flow on the microcirculatory level in hypertensive patients. Acknowledging the prognostic relevance of blood viscosity, they recommended that the influence of antihypertensive drugs on whole blood viscosity should be taken into account. In this regard, although diuretic-type drugs are extremely effective in reducing blood pressure, they may increase blood viscosity, thus impairing circulation in microvessels.

Fossum et al. (1997) measured whole blood viscosity in 105 healthy subjects to study whether or not it is a risk factor for cardiovascular disease. Whole blood viscosity was found to correlate with systolic blood pressure, total cholesterol, total cholesterol/HDL-c ratio, triglycerides, body mass index, and waist-hip ratio. Subjects with a systolic blood pressure (SBP) greater than 130 mm Hg had higher whole blood viscosity than those with a lower SBP. The researchers concluded that

even in a population of healthy normotensive subjects of a wide age range and of both genders, there are positive correlations between whole blood viscosity and a number of cardiovascular factors, including SBP.

Persson et al. (1991) studied rheologic properties of blood in 6 patients with primary pulmonary hypertension and compared them with the rheologic properties in 10 healthy subjects. Whole blood viscosity was found to increase at all shear rates both before and after being normalized to a hematocrit of 45%. Plasma viscosity and fibrinogen concentration in patients did not significantly differ from the values found in the healthy group. The researchers concluded that patients with primary pulmonary hypertension have impaired whole blood viscosity, which may have hemodynamic significance.

4.2 Cholesterol

The most widely recognized risk factor for cardiovascular disease may be abnormal cholesterol levels. According to results from clinical studies, whole blood viscosity is positively related to total cholesterol and LDL-c and negatively related to HDL-c (Crowley et al. 1994, Lowe 1992, Rosenson et al. 1996, Sloop and Garber 1997). These positive and negative relationships between whole blood viscosity and cholesterol (and LDL-c and HDL-c) also hold true for the components of whole blood viscosity.

Wannamethee and Shaper (1994) reported a positive association between hematocrit and cholesterol and a negative association with HDL-c in a large prospective study (n = 5497) in middle-aged British men who had no evidence of ischemic heart disease. In another study of healthy, middle-aged British men designed to evaluate whole blood viscosity in terms of participants' physical activity and cardiorespiratory fitness, cholesterol was positively correlated with hematocrit and plasma viscosity (Carroll et al. 2000a). Bonithon-Kopp et al (1993) showed that changes in plasma viscosity were positively associated with changes in total cholesterol and LDL-c in a 2-year study of middle-aged healthy French men (n = 637) and women (n = 431), and Koenig et al. (1992) found that plasma viscosity was positively correlated with cholesterol and negatively correlated with HDL-c in participants in the World Health Organization's MONICA project (Augsburg site).

Stoltz and his colleagues (Stoltz et al. 1981, Gaillard et al. 1982) studied rheologic factors in the genesis of thrombosis and atherosclerosis by measuring whole blood and plasma viscosity in a rat model with modifications in plasma lipids. Increases in biochemical parameters such as blood glucose, cholesterol, and triglycerides were accompanied by a considerable increase in whole blood viscosity, particularly at low shear rates below 20 s^{-1}.

4.3 Smoking

Dintenfass (1975) reported more than 25 years ago that significant increases in whole blood viscosity, hematocrit, RBC aggregation, plasma viscosity, and fibrinogen were observed in male smokers 45 to 55 years of age. Since then, a number of researchers examined the effect of smoking on vascular diseases by studying hemorheologic changes. In a study of apparently healthy male smokers (n = 45) and nonsmokers (n = 45), the former had higher whole blood viscosity, hematocrit, fibrinogen, and plasma viscosity than the latter (Lowe et al. 1980). A comparison of smoking and nonsmoking blood donors (86 men and 66 women) revealed that those who smoked more than 21 cigarettes a day had significantly higher whole blood viscosity and plasma viscosity and higher hematocrit and fibrinogen than those who did not smoke (Gudmundsson and Bjelle 1993). When male blood donors were divided into groups according to their daily cigarette consumption (never smoked, ex-smoker, 10–20/day, 21–40/day, and >40/day), whole blood viscosity and its determinants were seen to increase in a dose-related manner (Ernst et al. 1987).

Smoking is now considered an indisputable risk factor for cardiovascular disease; research into the effect of smoking on whole blood viscosity parameters, and the relationship of these parameters to cardiovascular disease, continues (Ernst 1995, Yarnell et al. 2000). Ernst (1995) explained the changes that chronic smoking exerts on the flow properties of blood. Chronic smoking leads to a rise in hematocrit. It also alters the rheologic behavior of RBCs and increases plasma viscosity. The cause of increased plasma viscosity is attributed to the elevated plasma fibrinogen levels among male smokers. Finally, smoking increases the total white cell count and modifies leukocyte function. Together these changes result in a significant deterioration of the flow properties of blood, as evidenced by a steep increase in whole blood viscosity of 10% to 20%. Accordingly, blood fluidity is jeopardized in smokers, reducing blood flow and hindering microcirculatory function (Ernst et al. 1988a). Summarizing the findings

of this and other studies, Ernst (1995) noted that the increased blood rheology might be one mechanism by which smoking increases the risk of vascular diseases.

Rothwell et al. (1991) studied hemorheologic changes in men and women immediately after they stopped smoking cigarettes. Within 2 days, there were "substantial and persistent reductions in blood viscosity." At high shear rate the reduction was about 8%; at low shear rate it was approximately twice that. Rothwell et al. attributed the changes to reductions in packed cell volume, total plasma protein, and fibrinogen, with resulting reductions plasma viscosity and rouleaux formation. The changes related to plasma proteins were not as great in women as in men. These results indicate that heavy smokers can experience substantial improvement in hemorheologic parameters almost as soon as they stop smoking.

4.4 Exercise

A number of researchers have reported that physical activity reduces blood and plasma viscosity (Koenig 1997, Carroll et al. 2000a). Charm et al. (1979) reported reduced plasma viscosity among joggers compared with non-joggers, which was attributed to a lowered γ-globulin concentration. Realizing that the life-extending effects of regular exercise are related to a decrease in both coronary and peripheral vascular morbidity, associated with some improvements in cardiovascular risk factors, Brun et al. (1998) investigated whether blood rheology, which is markedly affected by exercise, could be a possible link between the beneficial metabolic and hemodynamic effects of exercise. They reported that short-term effects of exercise are an increase in whole blood viscosity resulting from both fluid shifts and alterations of erythrocyte rheological properties (rigidity and aggregability). The long-term effect of exercise has improved blood fluidity, which is seen in parallel with the classical training-induced hormonal and metabolic alterations. While body composition, blood lipid pattern, and fibrinogen improve (thus decreasing plasma viscosity), the metabolic and rheologic properties of erythrocytes are modified, with a reduction in aggregability and rigidity. Thus, Brun et al. concluded that the hemorheologic effects of exercise can be hypothesized to be a mechanism (or at least a marker) of risk reversal and that blood fluidity is a physiological determinant of fitness.

Ernst and Matrai (1987) studied the effect of standardized treadmill exercise on hemorheology for the treatment of intermittent claudication. Forty-two stable patients with claudication were assigned to two groups. Group I (n = 22) was submitted to regular standardized treadmill exercise for 2 months. During this time the maximal and pain-free walking distances increased significantly (more than 100%). Group II (n = 20) patients did not exercise over the same period of time, and their walking distances remained essentially unchanged. No drugs or other forms of treatment were given in either group. The rheology of blood—as quantified by blood and plasma viscosity, hematocrit, blood filterability, and RBC aggregation—was initially abnormal in patients compared with matched controls. Blood and plasma viscosity, blood cell filterability, and RBC aggregation normalized significantly in group I, but remained pathologic in group II. The hemorheologic values of patients after 2 months of exercise no longer differed significantly from those of healthy controls. The "fluidification" of blood induced by regular exercise was qualitatively and quantitatively similar to that obtainable by hemorheologically active medications. The results suggest that training may be looked on as a form of hemorheologic therapy suitable for increasing the fluidity of blood in patients with ischemic diseases.

Reinhart et al. (1998) analyzed the influence of exercise training on blood viscosity. Twenty-five patients with chronic heart failure (ejection fraction < 40%) after MI were randomly assigned to either an 8-week intensive exercise program at a residential rehabilitation center or 8 weeks of sedentary life at home. Exercise training, which significantly increased maximal cardiac output and oxygen uptake, did not change plasma viscosity or whole blood viscosity. Reinhart et al. concluded that the improvement of whole blood viscosity remains an interesting therapeutic option for the symptoms of these patients, but that it must be achieved by methods other than exercise training.

Martin et al. (1985) studied whether or not the rheologic properties of blood in healthy people might be altered by exercise. They measured whole blood and plasma viscosity in 47 healthy female subjects before, immediately after, and 1 hour after maximal upright exercise. Whole blood viscosity increased an average of 12.6% with exercise, whereas plasma viscosity did not rise to the degree expected, which was attributed to a disproportionate observed loss of fibrinogen from the protein pool. Martin et al. concluded that there appears to be no adaptive adjustment in females to physical conditioning that results in changes in blood viscosity.

Wood et al. (1991) found that endurance-trained subjects had significantly higher pre-race whole blood viscosity than control subjects but similar plasma viscosity and hematocrit. Similarly, elite athletes have a higher blood viscosity, which is explained by higher values in both plasma viscosity and hematocrit. By contrast, there was no difference in RBC deformability and aggregation (Benhaddad et al.1999). Benhaddad et al. suggested that this might be due to some degree of reversal of the autohemodilution associated with fitness in athletes.

4.5 Obesity

An early examination of the relation between excess weight and increased whole blood viscosity parameters showed higher levels of whole blood viscosity, plasma viscosity, and RBC aggregation in a group of 14 obese people than in an age- and gender-matched control group (Ernst et al. 1986). Subsequent reports have confirmed the relationships between obesity or body mass index and whole blood viscosity, hematocrit, plasma viscosity, and fibrinogen (Carroll et al. 2000b, de Simone et al. 1990, Fossum et al. 1997, Yarnell et al. 2000). Comparative studies have shown that obese adults had significantly higher whole blood viscosity and plasma viscosity and obese children had significantly higher fibrinogen levels than did control groups (Rillaerts et al. 1989, Valle et al. 2000).

In a 2-year longitudinal study , Bonithon-Kopp et al. (1993) found that changes in the body mass index of men were positively associated with changes in plasma viscosity. A 1-month, reduced-calorie diet in 20 obese teenagers resulted in significant decreases in body mass index, plasma viscosity, fibrinogen, and RBC aggregation. Before the study, plasma viscosity and whole blood viscosity at low shear rates were significantly higher in the obese teenagers than in a control group of non-obese teenagers. At the end of the study plasma viscosity, but not whole blood viscosity, was reduced in the obese teenagers (Fanari et al. 1993). Solerte et al. (1997) reported that body fat distribution was related to whole blood viscosity, plasma viscosity, fibrinogen, and RBC aggregability in obese adult patients and that those who had central obesity showed significantly higher levels of these parameters than did those with peripheral obesity.

Parenti et al. (1988) evaluated slimming effects on certain metabolic (cholesterol, triglycerides, basal insulinaemia) and hemorheologic (hematocrit, fibrinogen, whole blood viscosity and plasma viscosity) rates. They studied 24 obese subjects (15 female and nine male) aged 25-58, with body mass index ranging from 35.5 to 67, before and after a hypocaloric diet period involving a 20-kg weight loss. The study showed no significant changes in plasma proteins, serum HDL-c, hematocrit, fibrinogen, or whole blood viscosity at high and low shear rate, while basal insulinemia, total cholesterol, triglycerides, whole blood viscosity at low shear rate corrected to 45% hematocrit, and plasma viscosity were significantly reduced.

4.6 Gender

Jousilahti's abstract also says that CHD incidence in men compared with women was approximately 3 times higher and mortality was approximately 5 times higher. There is a distinct gender gap with regard to cardiovascular diseases: Women of reproductive age are less likely than men of the same age to develop these conditions. Not surprisingly, then, studies have found that some cardiovascular risk factors, including whole blood viscosity, hematocrit, fibrinogen, and RBC aggregation, are significantly higher in men than in women (de Simone et al. 1990, Fossum et al. 1997, Gudmundsson and Bjelle 1993, Rosenson et al. 1996, Woodward et al. 1999). In the Edinburgh Artery Study Fowkes et al. (1994), using the ankle-brachial pressure index as an indicator of peripheral atherosclerosis, found that whole blood viscosity, plasma viscosity, and fibrinogen had significantly higher correlations with the ankle-brachial pressure index in men than in women. Kameneva et al. (1998) assessed the mechanical qualities of blood for gender differences and demonstrated that blood from men had higher whole blood viscosity, hematocrit, and RBC rigidity index (and therefore lower RBC deformability) than blood from premenopausal women.

Morbidity and mortality from cardiac diseases and especially from MI in premenopausal women are significantly less than in age-matched men. Regarding the nature of this phenomenon, Kameneva et al. (1999) hypothesized that the regular monthly bleeding of premenopausal women enhances the rheologic properties of their blood and is responsible for the fact that their risk of cardiovascular diseases is lower than that of men at any age. Kameneva et al. speculated that the reduced concentration of RBCs, the higher proportion of younger RBCs, and the lower proportion of older RBCs in

women's blood are responsible for the gender difference in the mechanical properties of blood. Their study of blood from 47 premenopausal women and 50 age-matched men showed that male blood had higher viscosity and RBC aggregation and lower RBC deformability and oxygen delivery index (the ratio of hematocrit to blood viscosity) than female blood. Kameneva et al. concluded that these differences between male and female blood may contribute to men's higher risk for cardiovascular diseases and suggested that, because blood donation increases the proportion of young RBCs while decreasing the proportion of old RBCs, regular blood donation by men might reduce their susceptibility to cardiovascular diseases.

Woodward et al. (1999) found that postmenopausal women had higher levels than premenopausal women of blood viscosity, hematocrit, corrected blood viscosity, plasma viscosity and fibrinogen, and that each of these differences was completely or partly abolished by use of hormone replacement therapy. Gelmini et al. (1987) reported that whole blood filterability was significantly lower in postmenopausal than in premenopausal women. Blood concentrations of total cholesterol, triglycerides, uric acid, fasting glucose, and fibrinogen were higher after menopause, and HDL-c was lower. These authors concluded that the changes might be partly responsible for the increased incidence of cardiovascular diseases in postmenopausal women.

4.7 Age

A report on the relative importance of cardiovascular risk factors states that age is the strongest risk factor for cardiovascular disease (Hopkins and Williams 1986), and results from clinical studies indicate that whole blood viscosity and its determinants are positively related to age. In 45 apparently healthy male nonsmokers increases in whole blood viscosity, plasma viscosity, and fibrinogen were associated with increased age (Lowe et al. 1980). In 128 apparently healthy adults, age correlated weakly with whole blood viscosity at a low shear rate, plasma viscosity, and RBC aggregability at a moderate shear rate, and in 110 normotensive adults whole blood viscosity increased with age in men but not in women (de Simone et al. 1990, de Simone et al. 1991). Yarnell et al. (2000) reported that plasma viscosity and fibrinogen increased with increasing age in a population sample of 49- to 65-year-old men.

Armani et al. (1990) studied whether or not reduced microvascular blood flow associated with hemorheology might contribute to age-related increases in the incidence of ischemic vascular disease. They measured blood and plasma viscosity and fibrinogen in 10 healthy elderly subjects, aged between 88 and 96 years, compared with 15 healthy young subjects (mean age 37 years). Elderly subjects showed a significant increase in plasma fibrinogen and a trend to an increase in plasma viscosity, whereas no difference was present in whole blood viscosity. Armani et al. concluded that aging is associated with a number of thrombotic risk factors, the most important of which seems to be fibrinogen. Similarly, Coppola et al. (2000) reported that plasma fibrinogen concentration significantly increases with age, whereas whole blood viscosity shows no significant difference among age groups. On the contrary, hemoglobin, RBC count and platelet count are significantly lower in aged group. In men, whole blood viscosity at higher shear rate of 450 s^{-1} negatively correlates with advancing age.

Bowdler et al. (1987) investigated the relationship between whole blood viscosity and age using heparinized blood samples obtained from 50 normal male blood donors between the ages of 20 and 65 years. Plasma viscosity showed no significant variation with donor age. The age-related trend to a higher viscosity was present at shear rates below 46 s^{-1}, but not at higher shear rates. The tendency for the viscosity trend to be greater at lower shear rates indicates increased shear thinning in blood obtained from older subjects, the cause of which may be either diminished RBC deformability in these subjects, or an increased tendency to form aggregates at low shear rates.

Reinhart et al. (1985) measured rheological parameters in 10 pairs of mothers and newborns. Whole blood viscosity was similar despite a higher fetal hematocrit (47.0 versus 35.5%). When the hematocrit of the suspension of RBCs in plasma was adjusted to 45%, the viscosity was significantly lower in the fetal blood over a wide range of shear rates (0.52-208 s^{-1}). The main reason for the lower viscosity in the fetal blood was that plasma viscosity was lower than in the maternal blood (1.08 versus 1.37 centipoises).

5. Summary

Hemorheology plays an important role in atherosclerosis. Hemorheologic properties of blood include whole blood viscosity, plasma viscosity, hematocrit, RBC

deformability and aggregation, and fibrinogen concentration in plasma. Blood flow is determined by three parameters (pressure, lumen diameter, and whole blood viscosity), whole blood viscosity is one of the key physiological variables. However, the significance of whole blood viscosity has not yet been fully appreciated.

Whole blood viscosity has a unique property, non-Newtonian shear-thinning characteristics, which is primarily due to the presence of RBCs. Hence, RBC deformability and aggregation directly affect the magnitude of blood viscosity, and any factors or diseases affecting RBC characteristics influence blood viscosity.

Therefore, one can see that whole blood viscosity is the causal mechanism by which traditional risk factors such as hypertension, hyperlipidemia, smoking, exercise, obesity, age, and gender are related to atherogenesis. In this regard, we included whole blood viscosity in the three key determinants of injurious pulsatile flow that results in mechanical injury and protective adaptation in the arterial system.

Because whole blood viscosity is a potential predictor of cardiovascular diseases, it should be measured in routine cardiovascular profiles. Incorporating whole blood viscosity measurements into a standard clinical protocol could improve our ability to identify patients at risk for cardiovascular disease and its complications.

References

(1) Armani U, Piana A, Cella A, Gastaldi S, Del Nero E, Evaluation of various hemorheological parameters in nonagenarians: evidence of an increase of fibrinogen, *Boll Soc Ital Biol Sper* 1990 Oct;66 (10):961-7

(2) Aronson HB, Horne T, Blondheim SH, Davidson JT, Blondheim DS, Effect of a 24-hour food-and-water fast on viscosity of whole blood and plasma, *Isr J Med Sci* 1979 Oct;15(10):833-5

(3) Benhaddad A, Bouix D, Khaled S, Micallef JP, Mercier J, Bringer J, Brun JF, Early hemorheologic aspects of overtraining in elite athletes, *Clin Hemorheol Microcirc* 1999;20(2):117-25

(4) Better Nutrition. March 1999; 61(3)

(5) Bonithon-Kopp C, Levenson J, Scarabin PY, et al. Longitudinal associations between plasma viscosity and cardiovascular risk factors in a middle-aged French population. *Atherosclerosis* 1993;104:173–182.

(6) Bowdler AJ, Foster AM, The effect of donor age on the flow properties of blood. Part I: Plasma and whole blood viscosity in adult males, *Exp Gerontol* 1987;22(3):155-64

(7) Brown MM and Marshall J, Regulation of cerebral blood flow in response to changes in blood viscosity, The Lancet, 1985; 1:604-609.

(8) Brun JF, Khaled S, Raynaud E, Bouix D, Micallef JP, Orsetti A. The triphasic effects of exercise on blood rheology: which relevance to physiology and pathophysiology? Clin Hemorheol Microcirc 1998; 19(2):89-104.

(9) Carroll S, Cooke CB, Butterly RJ. Physical activity, cardiorespiratory fitness, and the primary components of blood viscosity. *Med Sci Sports Exerc* 2000;32:353–358.

(10) Carroll S, Cooke CB, Butterly RJ. Plasma viscosity, fibrinogen and the metabolic syndrome: effect of obesity and cardiorespiratory fitness. *Blood Coagul Fibrinolysis* 2000;11:71–78.

(11) Charm SE, Paz H, Kurland GS, Reduced plasma viscosity among joggers compared with non-joggers, Biorheology 1979;16:185-189.

(12) Ciuffetti G, Mercuri M, Mannarino E, et al. Peripheral vascular disease: rheologic variables during controlled ischemia. *Circulation* 1989;80: 348–352.

(13) Coppola L, Caserta F, De Lucia D, Guastafierro S, Grassia A, Coppola A, Marfella R, Varricchio M, blood viscosity and aging, *Arch Gerontol Geriatr* 2000 Aug 1;31(1):35-42

(14) Cotran RS, Kumar V, Collins T, Robbins Pathologic Basis of Disease, Sixth ed., W.B. Saunders, Philadelpia, 1999.

(15) Coull BM, Beamer N, de Garmo P, et al. Chronic blood hyperviscosity in subjects with acute stroke, transient ischemic attack, and risk factors for stroke. *Stroke* 1991;22:162–168.

(16) Craveri A, Tornaghi G, Paganardi L, et al. Hemorrheologic disorders in obese patients: study of the viscosity of the blood, erythrocytes, plasma, fibrinogen and the erythrocyte filtration index. *Minerva Med* 1987;78(13):899–906.

(17) Crowley JP, Metzger J, Assaf A, et al. Low density lipoprotein cholesterol and whole blood viscosity. *Ann Clin Lab Sci* 1994;24(6):533–541.

(18) de Simone G, Devereux RB, Chien S, et al. Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. *Circulation*

1990;81:107–117.
(19) de Simone G, Devereux RB, Roman MJ, et al. Gender differences in left ventricular anatomy, blood viscosity and volume regulatory hormones in normal adults. *Am J Cardiol* 1991;68:1704–1708.
(20) Di Perri T. The hyperviscous vicious cycle. *Viscositas* 1981;1:4-5.
(21) Di Perri T, Forconi S, Agnusdei D, et al. The effects of intravenous isoxsuprine on blood viscosity in patients with occlusive peripheral arterial disease. *Br J Clin Pharmacol* 1978;5(3): 255–260.
(22) Di Perri T, Guerrini M, Pasini FL, et al. Hemorheological factors in the pathophysiology of acute and chronic cerebrovascular disease. *Cephalalgia* 1985;5(suppl 2):71–77.
(23) Dintenfass L. Elevation of blood viscosity, aggregation of red cells, haematocrit values and fibrinogen levels with cigarette smokers. *Med J Aust* 1975;1:617–620.
(24) Dintenfass L. Blood viscosity factors in severe non-diabetic and diabetic retinopathy, Biorheology, 1977;14:151-157.
(25) Dormandy JA. Cardiovascular diseases. In: Chien S, et al, ed. *Clinical Hemorheology*. Boston: M. Nijhoff, 1987:165–194.
(26) Dupuy-Fons C, Brun JF, Quere I, et al. Rheology and occlusive arterial disease of the legs. *J Mal Vasc* 1996;21(3):165–170.
(27) Ernst E. Haemorheological consequences of chronic cigarette smoking. *J Cardiovasc Risk* 1995;2:435–439.
(28) Ernst E, Matrai A, Marshall M. Blood rheology in patients with transient ischemic attacks. *Stroke* 1988;19:634–636.
(29) Ernst E, Koenig W, Matrai A, Filipiak B, Stieber J, BLOOD rheology in healthy cigarette smokers. Results from the MONICA project, Augsburg, *Arteriosclerosis* 1988a Jul-Aug;8(4):385-8
(30) Ernst E and Matrai A, Intermittent claudication, exercise, and blood rheology, Circulation, Vol 76, 1110-1114
(31) Ernst E, Matrai A, Schmolzl C, Magyarosy I. Dose-effect relationship between smoking and blood rheology. *Br J Haematol* 1987;65:485–487.
(32) Ernst E, Resch KL, Matrai A, Paulsen HF. Hyperviscosity: an independent risk factor after a survived stroke. *Acta Med Austriaca* 1991;18 (suppl 1):32–36.
(33) Ernst E, Weihmayr T, Schmid M, et al. Cardiovascular risk factors and hemorheology. Physical fitness, stress and obesity. Atherosclerosis 1986;59:263–269.
(34) Fahey JL, Barth WF, Solomon A. Serum hyperviscosity syndrome. *JAMA* 1965;192:464–468.
(35) Fanari P, Somazzi R, Nasrawi F, et al. Haemorheological changes in obese adolescents after short-term diet. *Int J Obes Relat Metab Disord* 1993;17(9):487–494.
(36) Fisher M, Meiselman HJ. Hemorheological factors in cerebral ischemia. *Stroke* 1991;22:1164–1169.
(37) Fong CS, Chia LG. Blood viscosity and blood factors in non-embolic cerebral infarction. *J Formos Med Assoc* 1990;9(11):1015, 1031–1034.
(38) Forconi S, Guerrini M, Ravelli P, et al. Arterial and venous blood viscosity in ischemic lower limbs in patients affected by peripheral obliterative arterial disease. *J Cardiovasc Surg (Torino)* 1979; 20(4):379–384.
(39) Fossum E, Hoieggen A, Moan A, et al. Whole blood viscosity, blood pressure and cardiovascular risk factors in healthy blood donors. *Blood Press* 1997;6(3):161–165.
(40) Fowkes FG, Pell JP, Donnan PT, et al. Sex differences in susceptibility to etiologic factors for peripheral atherosclerosis. Importance of plasma fibrinogen and blood viscosity. *Arterioscler Thromb* 1994;14:862–868.
(41) Gaillard S, Delhon A, Laurresergues H, Stoltz JF. Hemorheological and biochemical parameters in the "fatty" rat. Biorheology 1982; 19(1/2):353-362.
(42) Gelmini G, Delsignore R, Coiro V, Evaluation of erythrocyte deformability in pre-menopausal and post-menopausal women, *Maturitas* 1987 Nov;9(3): 275-81
(43) Grotta J, Ackerman R, Correia J, et al. Whole blood viscosity parameters and cerebral blood flow. *Stroke* 1982;13:296–301.
(44) Gudmundsson M, Bjelle A. Plasma, serum and whole-blood viscosity variations with age, sex, and smoking habits. *Angiology* 1993;44:384–391.
(45) Harvard Health Letter. The Search for New Culprits, written by President and Fellows of Harvard College, 24(8), May 1999.
(46) Hoare EM, Barnes AJ, Dormandy JA, Abnormal

blood viscosity in diabetes and retinopathy, Biorheology, 1976; 13:21-25.

(47) Hopkins PN, Williams RR. Identification and relative weight of cardiovascular risk factors. *Cardiology Clinics* 1986;4:3–31.

(48) Huisman A, Aarnoudse JG, Heuvelmans JH, Goslinga H, Fidler V, Huisjes HJ, Zijlstra WG, Whole blood viscosity during normal pregnancy, *Br J Obstet Gynaecol* 1987 Dec;94(12):1143-9

(49) Humphrey PRD, Du Boulay GH, Marshall J, et al. Viscosity, cerebral flow and hematocrit in patient with paraproteinemia, Acta Neurol. Scand., 1980; 61:201-209.

(50) Jan KM, Chien S, Bigger JT Jr. Observations on blood viscosity changes after acute myocardial infarction. *Circulation* 1975;51:1079–1084.

(51) Jousilahti P, Vartiainen E, et al. Sex, age, cardiovascular risk factors, and coronary heart disease, Circulation, 1999;99:1165-1172.

(52) Junker R, Heinrich J, Ulbrich H, et al. Relationship between plasma viscosity and the severity of coronary heart disease. *Arterioscler Thromb Vasc Biol* 1998;18:870–875.

(53) Kameneva MV, Garrett KO, Watach MJ, Borovetz HS. Red blood cell aging and risk of cardiovascular diseases. *Clin Hemorheol Microcirc* 1998;18:67–74.

(54) Kameneva MV, Watach MJ, Borovetz HS, Gender difference in rheologic properties of blood and risk of cardiovascular diseases, *Clin Hemorheol Microcirc* 1999;21(3-4):357-63

(55) Kiesewetter H, Jung F, Kotitschke G, et al. Prevalence, risk factors and rheological profile of arterial vascular disease: first results of the Aachen study. *Folia Haematol Int Mag Klin Morphol Blutforsch* 1988;115(4):587–593.

(56) Koenig W, Sund M, Ernst E, et al. Association between plasma viscosity and blood pressure. Results from the MONICA-project Augsburg. *Am J Hypertens* 1991;4(6):529–536.

(57) Koenig W, Sund M, Ernst E, et al. Association between rheology and components of lipoproteins in human blood. Results from the MONICA project. *Circulation* 1992;85:2197–2204.

(58) Koenig W, Sund M, DoringA,Ernst E, Leisure-Time Physical Activity but Not Work-Related Physical Activity Is Associated With Decreased Plasma viscosity, *Circulation.* 1997;95:335-341

(59) Koenig W, Sund M, Ernst E, et al. Is increased plasma viscosity a risk factor for high blood pressure? *Angiology* 1989;40(3):153–163.

(60) Koenig W, Sund M, Filipiak B, et al. Plasma viscosity and the risk of coronary heart disease: Results from the MONICA-Augsburg Cohort Study, 1984 to 1992. *Arterioscler Thromb Vasc Biol* 1998;18:768–772.

(61) Lee AJ, Mowbray PI, Lowe GD, et al. Blood viscosity and elevated carotid intima-media thickness in men and women: the Edinburgh Artery Study. *Circulation* 1998;97(15):1467–1473.

(62) Leschke M, Blanke H, Stellwaag M, et al. Hyperfibrinogenemia and pathological plasma viscosity: pathogenetic factors in unstable angina pectoris. *Dtsch Med Wochenschr* 1988;113(30): 1175–1181.

(63) Letcher RL, Chien S, Pickering TG, et al. Elevated blood viscosity in patients with borderline essential hypertension. *Hypertension* 1983;5:757–762.

(64) Letcher RL, Chien S, Pickering TG, et al. Direct relationship between blood pressure and blood viscosity in normal and hypertensive subjects: role of fibrinogen and concentration. *Am J Med* 1981;70:1198–1202.

(65) Linderkamp O, Ruef P, Zilow EP, Hoffmann GF. Impaired deformability of erythrocytes and neutrophils in children with newly diagnosed insulin-dependent diabetes mellitus. *Diabetologia* 1999;42(7):865–869.

(66) Lowe GD. Blood viscosity, lipoproteins, and cardiovascular risk. *Circulation* 1992;85(6):2329–2331.

(67) Lowe GD, Drummond MM, Forbes CD, Barbenel JC. The effects of age and cigarette-smoking on blood and plasma viscosity in men. *Scott Med J* 1980;25(1):13–17.

(68) Lowe GD, Forbes CD. Rheology of cardiovascular disease. In: Lowe GD, ed. *Clinical Blood Rheology*, vol. 2, Boca Raton, FL: CRC Press, 1988:114–140.

(69) Lowe GD, Fowkes FG, Dawes J, et al. Blood viscosity, fibrinogen, and activation of coagulation and leukocytes in peripheral arterial disease and the normal population in the Edinburgh Artery Study. *Circulation.* 1993;87:1915–1920.

(70) Malkun Paz C, Alvarado Molina M, Hurtado Figueroa R, et al. Blood viscosity in ischemic heart disease. *Arch Inst Cardiol Mex* 1987;57(2): 145–150.

(71) Martin DG, Ferguson EW, Wigutoff S, Gawne T, Schoomaker EB, blood viscosity responses to maximal exercise in endurance-trained and sedentary female subjects, *J Appl Physiol* 1985 Aug; 59(2):348-53

(72) Muizelaar JP, Wei EP, Kontos HA, et al. Cerebral blood flow is regulated by changes in blood pressure and in blood viscosity alike. *Stroke* 1986;17:44–48.

(73) Nordby G, Moan A, Kjeldsen SE, Os I. Relationship between hemorheological factors and insulin sensitivity in normotensive and hypertensive premenopausal women. *Am J Hypertens* 1995;8(5 Pt 1):439–444.

(74) Parenti M, Palareti G, Babini AC, Poggi M, Torricelli P, Melchionda N, Effect of slimming on metabolic and haemorheologic patterns in a group of obese subjects, *Int J Obes* 1988;12(2):179-84

(75) Persson SU, Gustavsson CG, Larsson H, Persson S. Studies on blood rheology in patients with primary pulmonary hypertension. *Angiology* 1991;42 (10):836–842.

(76) Poredos P, Zizek B. Plasma viscosity increase with progression of peripheral arterial atherosclerotic disease. *Angiology* 1996;47(3):253–259.

(77) Rainer C, Kawanishi DT, Chandraratna PA, et al. Changes in blood rheology in patients with stable angina pectoris as a result of coronary artery disease. *Circulation* 1987;76:15–20.

(78) Reinhart WH, Danoff SJ, King RG, Chien S, Rheology of fetal and maternal blood, *Pediatr Res* 1985 Jan;19(1):147-53

(79) Reinhart WH, Dziekan G, Goebbels U, Myers J, Dubach P. Influence of exercise training on blood viscosity in patients with coronary artery disease and impaired left ventricular function. Am Heart J 1998; 135(3):379-382

(80) Resch KL, Ernst E, Matrai A, et al. Can rheologic variables be of prognostic relevance in arteriosclerotic diseases? *Angiology* 1991;42(12):963–970.

(81) Resch KL, Ernst E, Matrai A, Paulsen HF. Fibrinogen and viscosity as risk factors for subsequent cardiovascular events in stroke survivors. *Ann Intern Med* 1992;117(5):371–375.

(82) Rillaerts E, van Gaal L, Xiang DZ, et al. Blood viscosity in human obesity: relation to glucose tolerance and insulin status. *Int J Obes* 1989;13: 739–745.

(83) Rosenson RS, McCormick A, Uretz EF. Distribution of blood viscosity values and biochemical correlates in healthy adults. *Clin Chem* 1996;42(8 Pt 1): 1189–1195.

(84) Rothwell M, Rampling MW, Cholerton S, Sever PS, Haemorheological changes in the very short term after abstention from tobacco by cigarette smokers, *Br J Haematol* 1991 Nov;79(3):500-3

(85) Sakai K, Maeda H, Tsukimori K, Nagata H, Koyanagi T, Nakano H, How blood viscosity influences changes in circulation during pregnancy? *Fukuoka Igaku Zasshi* 1992 Aug;83(8):328-32

(86) Schabitz J, Krosch H. The clinical significance of blood viscosity in degenerative angiopathies. *Z Gesamte Inn Med* 1979;34(9):107–109.

(87) Schabitz J, Krosch H. Haemorheological investigations in patients with chronic ischaemic heart disease and acute myocardial infarction. *Cor Vasa* 1983;25(3):161–167.

(88) Schabitz J, Kohlmann U, Muller G, blood viscosity measurements in coronary infarct patients, *Z Gesamte Inn Med* 1977 Jun 15;32(12):283-5

(89) Sharp DS, Curb JD, Schatz IJ, et al. Mean red cell volume as a correlate of blood pressure. *Circulation* 1996;93:1677–1684.

(90) Shi FL, Hart RG, Sherman DG, et al. Stroke in the People's Republic of China. *Stroke* 1989;20:1581–1585.

(91) Sloop GD, Garber DW. The effects of low-density lipoprotein and high-density lipoprotein on blood viscosity correlate with their association with risk of atherosclerosis in humans. *Clin Sci* (Colch) 1997;92:473–479.

(92) Solerte SB, Fioravanti M. Hemodynamic alterations in long-term insulin-dependent diabetic patients with overt nephropathy: role of blood hyperviscosity and plasma protein changes. *Clin Nephrol* 1987; 28(3):138–143.

(93) Solerte SB, Fioravanti M, Pezza N, et al. Hyperviscosity and microproteinuria in central obesity: relevance to cardiovascular risk. *Int J Obes Relat Metab Disord* 1997;21:417–423.

(94) Stoltz JF, Gaillard S, Dehlon A, et al. Plasma viscosity and biochemical parameters in the "fatty" rat. *Atherosclerosis* 1981;39:125–129.

(95) Toth K, Kesmarky G, Vekasi J, et al. Hemorheological and hemodynamic parameters in patients with essential hypertension and their modification

by alpha-1 inhibitor drug treatment. *Clin Hemorheol Microcirc* 1999;21(3-4):209–216.

(96) Tsuda Y, Satoh K, Kitadai M, et al. Chronic hemorheological effects of the calcium antagonist nilvadipine in essential hypertension. *Arzneimittelforschung* 1997;47(8):900–904.

(97) Turczynski B, Sroczynski J, Matyszczyk B, Szczesny S. Blood and plasma viscosity versus claudication distance in patients with obliterative atherosclerosis of the lower limbs. *Pol Arch Med Wewn* 1991;85:41–49

(98) Valle M, Gascon F, Martos R, et al. Infantile obesity: a situation of atherothrombotic risk? *Metabolism* 2000;49:672–675.

(99) Walzl M, Lechner H, Walzl B, et al. Improved neurological recovery of cerebral infarctions after plasmapheretic reduction of lipids and fibrinogen. *Stroke* 1993;24:1447–1451.

(100) Wannamethee G, Shaper AG. Haematocrit: relationships with blood lipids, blood pressure and other cardiovascular risk factors. *Thromb Haemost* 1994;72(1):58–64

(101) Wood SC, Doyle MP, Appenzeller O, Effects of endurance training and long distance running on blood viscosity, *Med Sci Sports Exerc* 1991 Nov;23(11):1265-9

(102) Woodward M, Rumley A, Tunstall-Pedoe H, Lowe GD, Associations of blood rheology and interleukin-6 with cardiovascular risk factors and prevalent cardiovascular disease, *Br J Haematol* 1999 Feb;104(2):246-57

(103) Yarnell JW, Baker IA, Sweetnam PM, et al. Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease. The Caerphilly and Speedwell collaborative heart disease studies. *Circulation* 1991;83:836–844.

(104) Yarnell JWG, Sweetnam PM, Rumley A, Lowe GDO. Lifestyle and hemostatic risk factors for ischemic heart disease: the Caerphilly Study. *Arterioscler Thromb Vasc Biol* 2000;20(1):271–279.