

## Hemorheological Parameters and Fibrinogen in Atherosclerosis

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### ABSTRACT

Intrinsic blood hemorheology affects the initiation and the progression of atherosclerosis. The most important factors which determine whole blood viscosity are hematocrit and fibrinogen concentration. Red blood cell aggregability and deformability also play a key role. Hemorheological abnormalities and increased blood viscosity have been noticed in arterial hypertension as well as in diabetes, obesity, hypercholesterolemia and among cigarette smokers. This review discusses the emerging role of blood rheology in the context of atherosclerotic plaque formation and focuses on the fibrinogen concentration and hemodynamics.

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**Key words:** Fibrinogen; Blood viscosity; Atherosclerosis

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### INTRODUCTION

Atherosclerosis is a chronic-inflammatory, progressive disease that affects mainly the aorta and its branches. The etiology of atherosclerosis is multifactorial. Plaques formations are diffused, but not at random. Atherosclerotic lesions tend to form at the specific points at the coronary artery tree. The “hot spots” prone to atherosclerosis are situated on lateral wall of one or both daughter vessels bifurcation and internal curvatures<sup>[1]</sup>. At those risk points the complex, disturbed flow tends to occur, and endothelial shear stress (SS) becomes low or low and oscillatory promoting vessel infiltration by atherosclerotic blood borne particles<sup>[2]</sup>. Endothelial shear stress (SS) is known as the tangential force per unit area applied by blood flow upon the endothelial cells and is mathematically defined as the product of blood viscosity and shear rate, where the shear rate is the ratio of flow velocity to the internal vessel lumen diameter.

Disturbed flows cause endothelial dysfunction and impair endothelial cell barrier integrity. Russel Ross, regarded low grade systemic inflammation as the reason responsible for endothelial dysfunction but now we know that endothelial injury and inflammation at the “risk points” are induced by low and oscillatory SS<sup>[3]</sup>.

Hemorheology is the scientific field that deals with the flow and deformation behaviour of the blood and its formed elements. From a biological point of view the most important hemorheological properties of blood are: plasma viscosity and the whole blood viscosity attributed to hematocrit and red blood cell mechanical deformability and their tendency for reversible aggregation.

### NON-NEWTONIAN BLOOD PROPERTIES

According to rheological behaviour, the fluids are divided mainly into two groups: Newtonian and non-Newtonian. In the Newtonian fluid, while the temperature and pressure are constant, the relation between the shear stress and the shear rate is constant and meets Newton’s

equation  $\tau = \gamma \times \eta$ , where  $\tau$  - shear stress,  $\gamma$  - shear rate,  $\eta$  - viscosity. Non-Newtonian fluids do not conform to these conditions and their viscosity varies with shear rate and time.

From a biological point of view, blood can be considered as a suspension of red blood cells (RBC) in a liquid (blood plasma). The internal structure of blood causes that at the low shear rate the non-Newtonian properties appear. The RBC are considered to be the main determinant of blood viscosity. Thrombocytes, however numerous, are too small in size, and the number of leukocytes is too low to alter the rheological behaviour of blood. Above the shear rate of 100 s<sup>-1</sup> blood exhibits Newtonian properties but at lower shear rates the non-Newtonian properties are relevant, particularly at points where complex secondary flows occur (Figure 1).

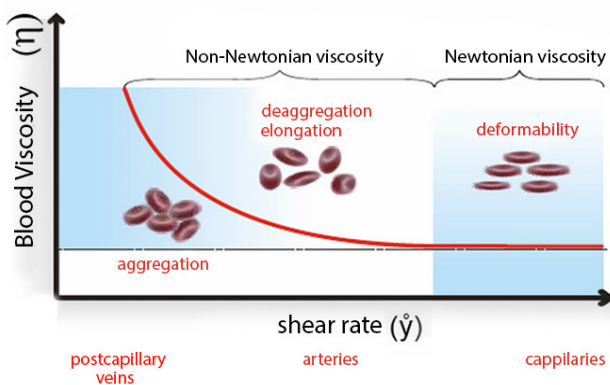


Figure 1 Shear-viscosity curve for blood.

Blood rheology has been reported to be altered by various classic risk factors of atherosclerosis. Patients with arterial hypertension, diabetes, obesity, hypercholesterolemia and smokers have an increased blood viscosity (vulnerable blood)<sup>[4-5]</sup>. We hypothesize that an increased blood viscosity and other hemorheological parameters contribute to prolonging of the residence time of morphological elements and lipids at the risk points in the vasculature tree with low and oscillatory SS, thereby facilitating intima infiltration and plaque formation.

## DETERMINANTS OF BLOOD VISCOSITY

The principal determinant of blood viscosity is hematocrit. Growth of hematocrit causes blood viscosity increase. RBCs aggregation (rouleaux formation) affects blood fluidity too, especially in the low-share regions with disturbed flow. In the high shear rates, the aggregates are broken down. They are formed in post-capillary venules, where the blood flow slows down.

In addition, blood viscosity correlates with plasma viscosity. Albumin and high density lipoprotein (HDL) concentration are negatively correlated with blood viscosity<sup>[6]</sup>.

The rheological properties of blood and plasma positively correlate with interleukin 6, von Willebrand factor, uric acid, C-reactive protein, alfa-2 macroglobulin, apolipoprotein B, whereas they are negatively correlated with the oxygen supply at the tissue level<sup>[7]</sup>.

## FIBRINOGEN AS A RISK FACTOR

Fibrinogen is a long asymmetrical acute phase protein with a large molecular weight (340,000 Daltons). It is a heterohexamer composed of 2 combinations of 3 different polypeptide chains: A  $\alpha$ , B  $\beta$  and  $\gamma$ ,

connected by disulfide bounds, encoded by separate genes localized on chromosome 4. Its synthesis takes place in hepatocytes and fibroblasts, as well as macrophages and the endothelium cells in response to the inflammation factors such as IL-6, LIF (Leukaemia Inhibitory Factor), OSM (Oncostatin M)<sup>[8]</sup>. Chronic inflammation and, for instance, cigarette smoking may lead to chronic IL-6 production and thus increased fibrinogen concentration<sup>[9]</sup>. OSM is the strongest factor of fibrinogens synthesis<sup>[10]</sup>. Moreover, OSM is also associated with the proliferation of smooth muscle cell<sup>[11]</sup>. IL-6 is synthesized under the influence of TNF-alpha which may also influence atherogenesis<sup>[12]</sup>. IL-4, IL-10 and IL-13 antagonize synthesis of fibrinogen<sup>[13]</sup>. In humans nearly all fibrinogen is present in plasma. Its concentration ranges from 2.0 g/L to 4.5 g/L on average.

## FIBRINOGEN POLYMORPHISMS

Fibrinogen concentration is genetically determined. In the human over 10 polymorphisms of fibrinogen's genes were reported<sup>[14-15]</sup>. The common genetic polymorphisms in  $\beta$ -fibrinogen, which lead to elevated plasma levels of fibrinogen, are the -148C/T (HindIII), -1420G/A and -455G/A (HaeIII) polymorphisms located in the 5'-flanking region, C448G/A in exon 8 and Bcl I allele in its downstream region of the  $\beta$ -chain fibrinogen gene. Plasma fibrinogen concentration is significantly associated with  $\beta$  Bcl I,  $\beta$  C448,  $\beta$  Hae III and  $\beta$  -1420. The mean fibrinogen concentration is approximately proportional to the number of less frequent alleles. The  $\beta$  Bcl I,  $\beta$  C448, and  $\beta$ -1420 polymorphisms are in strong positive linkage disequilibrium with the  $\beta$  Hae III polymorphism. Controversial data concerning fibrinogen genetic variability exists. Papageorgiou *et al* reported that there is no difference between G455A and the G58A fibrinogen genetic polymorphisms on atherosclerotic influence<sup>[16]</sup>. They also noticed for the first time that the G455A variant changes the amount of D-dimer as strongly as fV activity. On the other hand, Fowkes FG *et al*<sup>[17]</sup> described  $\beta$  -fibrinogen influence on an increased risk of atherosclerotic disease.

## RELATION BETWEEN FIBRINOGEN AND PLATELETS

Platelet - vessel wall interaction plays an influential pro-atherogenic role<sup>[18]</sup>. Fisher and Meiselman described positive relations between fibrinogen and B-thromboglobulin in patients with severe cerebrovascular incidents<sup>[19]</sup>. B-thromboglobulin is a protein that is accumulated in alpha granules of the platelet and released in large amounts upon platelet activation. Platelet activation and aggregation occur via a complex, multi-factorial process and fibrinogen is the main aggregating platelets factor. Therefore theories that an increased amount of fibrinogen plays an important role in activation and aggregation of platelets and its role in atherosclerosis are suggested<sup>[20]</sup>.

## FIBRINOGEN AND BLOOD VISCOSITY AS A SIGNIFICANT CARDIOVASCULAR RISK FACTOR

Lipid disorders are an important risk factor for coronary heart disease, but a more prominent risk factor is a fibrinogen. According to the ECAT trial (European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study), high plasma fibrinogen concentration was associated with an increased risk of the coronary events, including sudden cardiac death. The risk of coronary event

remains low in the case of high cholesterol, as long as the fibrinogen level remains low<sup>[21]</sup>. Lowe *et al*<sup>[22]</sup> reported an increased blood viscosity with evidence of coronary artery disease. Fibrinogen and the plasma viscosity positively correlate with the degree of coronary artery disease and with other known vascular risk factors (such as age, female sex, cigarette smoking, serum levels of total and low-density lipoprotein cholesterol and triglycerides, blood pressure, body mass index, and history of diabetes). There are also highly significant inverse associations between plasma fibrinogen level and serum levels of high-density lipoprotein cholesterol and albumin<sup>[23]</sup>.

In unstable angina elevated concentration of fibrinogen increases the risk of an infarct or sudden cardiac death<sup>[24-25]</sup>. In patients with myocardial infarction treated by primary coronary intervention an increased fibrinogen is a predictor of no-reperfusion phenomenon and positively correlates with the size of the myocardial infarction<sup>[26]</sup>. According Kannel *et al* fibrinogen is a predictor of cardiovascular disease only in men, by adjustment for established risk factors. In women after adjustment fibrinogen level is marginally significant related to the cardiovascular incidence<sup>[27]</sup>.

Fibrinogen is also a strong predictor of fatal or non-fatal, both new or recurrent coronary heart diseases and sudden death, for both sex in the middle-age<sup>[28]</sup>. In men who were smokers at baseline, there was no significant correlation between fibrinogen and coronary heart disease or mortality<sup>[29-31]</sup>.

Although, Yano *et al* suggested that it is positively association between fibrinogen and mortality from a broad spectrum of diseases in elderly Japanese-American men<sup>[32]</sup>.

Although Danesh *et al* regarded there are associations between usual plasma fibrinogen level and the risks of coronary heart disease, other vascular mortality (including aortic aneurysm, heart failure, and acute pulmonary heart disease), and even stroke and non vascular mortality (mainly cancer) in healthy middle-aged individuals. But after taking account of baseline values of known vascular factors the strength of these correlations were attenuated, with the exception of stroke<sup>[33-36]</sup>.

Also after adjustment for CRP and albumin levels associations between fibrinogen and vascular and non-vascular mortality risk in older men was non-significant<sup>[37]</sup>. In contrast Hong *et al* found no significant association between fibrinogen and the presence of aortic plaque measured by Cardiovascular Magnetic Resonance Imaging after adjusting for age, sex, and clinical covariates<sup>[38]</sup>. Fibrinogen concentration is also linked with the calcium score and the plaque burden<sup>[39]</sup>. High level associated with high Lp(a) levels significantly increased the risk of coronary heart disease in men without a history of prior chronic disease<sup>[40]</sup>.

## FIBRINOGEN AND OTHER BIOMARKERS OF INFLAMMATION

Fibrinogen value is strongly and positively associated with increased CRP and moderately inversely correlated with albumin. According Clarke *et al.* meta-analysis, it seems that stronger predictors for both vascular and nonvascular mortality than fibrinogen are CRP and albumin level in older men, treated equally. CRP and albumin remain significantly predictive of risk of vascular mortality even after taking known vascular risk factors such as smoking, blood pressure, blood lipids, and diabetes mellitus and other inflammatory factors.

However, The Centers for Disease Control and Prevention and the American Heart Association recommended using measurements of CRP in the prediction of coronary heart disease, the strength of

the association of CRP with ischaemic heart by adjustment for the known vascular risk factors, such as smoking, blood pressure, blood lipids, and diabetes mellitus, was less significant than thought<sup>[41]</sup>. Some studies suggested that CRP adds prognostic information to that conveyed by the Framingham risk score in women<sup>[42]</sup>.

Lind *et al* reported incidence of cardiac events and death due to cardiovascular diseases in middle-aged men predicted by plasma levels of fibrinogen is modified by other inflammation-sensitive proteins such as orosomucoid ( $\alpha$ -acid glycoprotein,  $\alpha$ 1-antitrypsin, haptoglobin and ceruloplasmin. Maybe these facts cause contentious data of predicting value of fibrinogen concentration in cardiovascular diseases<sup>[43]</sup>.

## MECHANOTRANSDUCTION

Low/oscillatory shear stress, through a variety of membrane molecules and complex not yet fully understood mechanisms, promotes the atherogenic genes expression with concomitant suppression of atheroprotective genes. This phenomenon is termed mechanotransduction. It promotes the recruitment of leukocytes and platelets into the intima and the expression of proinflammatory and prothrombotic factors as well as adhesion molecules at the plaque<sup>[44-47]</sup>. Through scanning electron microscopy at the points of complex disturbed flow endothelial cells exposed to low SS were shown to be polygonal and flat in shape, whereas those at the physiological SS become spindle-shaped, engorged and aligned along the blood flow direction. In the points of disturbed flow and flow separation, actin fibers are short, randomly oriented, and localized mainly at the endothelial cells periphery, with intercellular junctional proteins discontinued. As a consequence blood borne particle accumulation is facilitated<sup>[48]</sup>.

## GENETIC POLYMORPHISM OF NITRIC OXIDE

NO (nitric oxide) is a substance which has vasodilating properties. The relationship between eNOS (nitric oxide synthase) and haemorheological properties was documented by correlations with RBC aggregation<sup>[49]</sup>. The researchers have proved the association between polymorphisms of eNOS gene and cardiovascular artery diseases. G or T at position 894 of nucleotide lead to a glutamic acid or an aspartic acid at amino acid position 298. Moreover, a significant correlation between plasma NO concentrations and eNOS Glu298Asp polymorphism according to genotype and allele was also not found<sup>[50]</sup>. However, Cam SF *et al* documented positive correlations<sup>[51]</sup>.

## MODIFICATION OF THE FIBRINOGEN LEVEL

There is no direct treatment to lowering fibrinogen concentration. Streptokinase administration results not only in lysis of fibrin within the clot, but also in circulating fibrinogen<sup>[52]</sup>. Fibrates and some of the statins may combine lipid-lowering with a beneficial effect on fibrinogen level<sup>[53]</sup>. This effect is independent of changes in cholesterol and triglyceride concentrations<sup>[54]</sup>. Extracorporeal methods for elimination of fibrinogen by chromatography is too costly and not for routine clinical use<sup>[55]</sup>.

Estrogen arrangement of progesterone<sup>[56-57]</sup> or raloxifene<sup>[58]</sup> belonging to SERM (Selective Estrogen Receptor Modulators) reduce the amount of fibrinogen, yet these medications do not decrease but even increase coronary episodes<sup>[59-60]</sup>. Even changing lifestyle can reduce fibrinogen level.

## CONCLUSION

Summing up-multiple parameters of coronary artery disease are accompanied by the deterioration of the macro-and microrheological parameters, consisting in the increase of the blood and plasma viscosity. Contentious data may cause that not everybody believe in cardiovascular disease predicting ability of fibrinogen. But if we will find out the confounding risk factors impacting on fibrinogen and other hemorheological parameters we can use them to predicting vascular morbidity and mortality including sudden death even in young non-symptomatic people. For this reason large, well-planned and comprehensive studies are required. They should take into account differences in gender, races/ethnicities of individuals and be done by using one optimal technique for measures of atherosclerosis.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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