The role of blood viscosity in the development and progression of coronary artery disease

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■ **BACKGROUND** Although a great deal of attention has been directed to the risk factors for atherosclerotic coronary artery disease, relatively little research has been focused on the role of the circulating blood itself.

■ **OBJECTIVES** To review the possible role of increased plasma viscosity and decreased cellular deformability in the pathogenesis of atherosclerotic coronary artery disease.

■ **SUMMARY** Increased plasma viscosity or decreased erythrocyte deformability may reduce blood flow in areas where blood flow is already low, such as at arterial branch points and bifurcations as well as in advanced coronary artery narrowing. Further, these factors may favor the development and progression of atherosclerotic coronary artery disease through direct mechanical effects on either the vascular endothelium or existing atheromatous plaques. Beyond their potential direct effects, each may represent a common link between recognized risk factors and the resulting disease process.

■ **CONCLUSIONS** Accumulating evidence suggests that increased blood viscosity is an independent risk factor for atherosclerotic heart disease and its complications.

■ INDEX TERMS: BLOOD VISCOSITY; CORONARY ARTERIOSCLEROSIS
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DURING THE PAST THREE decades, the study of atherosclerotic coronary artery disease has focused primarily on several well-recognized risk factors, including hypercholesterolemia, systemic hypertension, and smoking. Further efforts to define the pathogenesis of myocardial infarction and other acute coronary syndromes have been directed toward a series of mechanical events occurring at the level of the atherosclerotic plaque.

Poorly represented in the study of atherosclerotic coronary artery disease is the potential role of the circulating blood itself. Specifically, the influence of cellular rheology and plasma viscosity are recognized as key determinants of coronary blood flow, peripheral vascular resistance, and tissue perfusion.

The physical properties of plasma proteins and erythrocytes are felt to be particularly important in low-flow states, observed commonly in areas of blood flow separation (arterial branch points and bifurcations) as well as in advanced coronary artery narrowings. In these settings, increased plasma viscosity or decreased erythrocyte deformability may have an adverse effect on coronary blood flow. Fur-

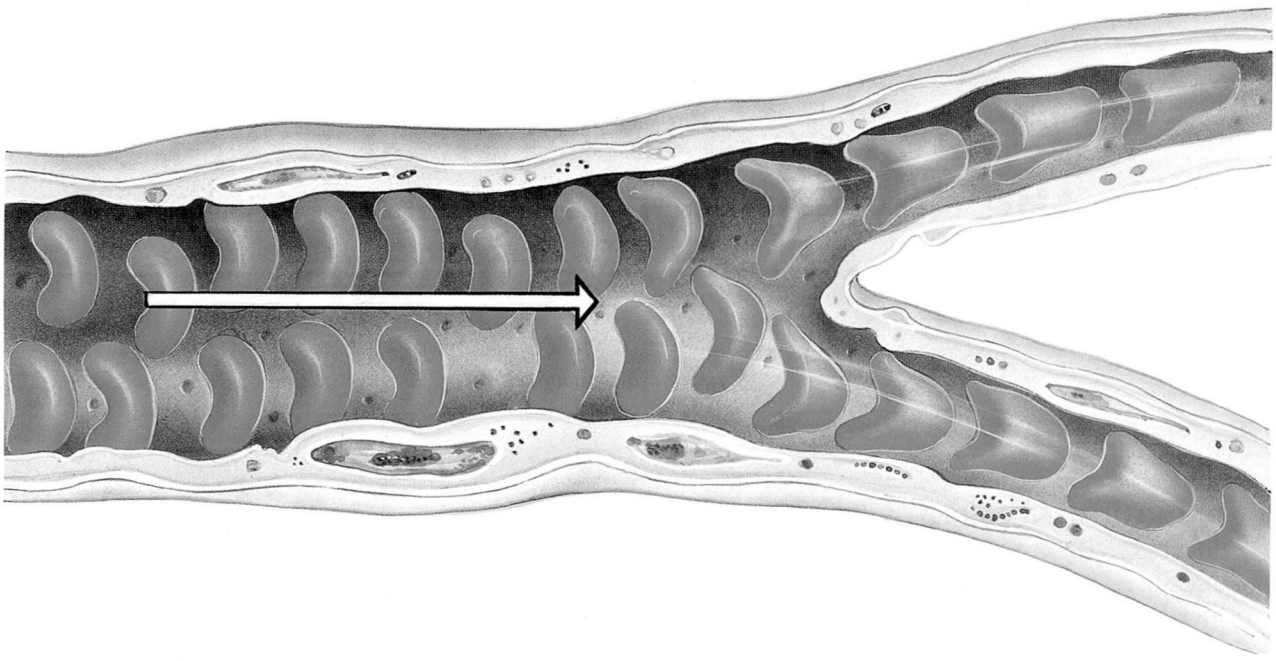

FIGURE. Blood viscosity has a tendency to increase in areas of flow separation (eg, arterial bifurcations and branch points). In these areas, erythrocytes must be capable of deforming normally, thereby reducing local viscosity, erythrocyte aggregation, platelet interactions with the vessel wall, and wall stress.

ther, they may, through direct mechanical effects on either the vascular endothelium or an existing atheromatous plaque, favor the development and progression of atherosclerotic coronary artery disease.

The blood flow within the cardiovascular system is influenced by interrelated yet unique factors that include blood viscosity, erythrocyte deformability, erythrocyte concentration (hematocrit), vessel diameter, pressure gradient, and local shear rates.[1] This article will examine the role of blood viscosity and erythrocyte deformability.

BLOOD VISCOSITY

Viscosity is a fluid's intrinsic resistance to flow within vessels. In streamline (laminar) flow along a vessel, adjacent fluid layers move relative to each other (shear) as a consequence of the viscous drag exerted by the wall. The *shear stress* is the force per unit area causing shearing (flow) and is related directly to both flow velocity and vessel diameter. Therefore, shear stress is increased in narrow areas of rapid flow (eg, arterial narrowings). The *shear rate* is the velocity gradient between adjacent fluid layers. The viscosity of a fluid is defined as the ratio of shear stress to shear rate. In laminar flow, the velocity profile is parabolic, with maximal velocity at the center of flow and maximal shear stress at the vessel wall.[2]

The importance of viscosity as a determinant of blood flow is reflected clearly in the Hagenbach-Poiseuille equation: $V = P\pi R^4/8\eta L$, where V represents volume flow rate; P, pressure gradient; R, vessel radius; L, vessel length; and η, viscosity. Therefore, resistance to blood flow comprises a vascular component and a rheologic component.

Blood viscosity is not a constant, but varies along the course of the vessel according to vascular geometry, flow separation, and local composition of the blood. Viscosity increases due to flow separation in areas such as arterial bends, bifurcations, and poststenotic regions (*Figure*). At flow velocities near zero, whole blood has a viscosity from 100 to 10 000 times that of water. In contrast, at high flow velocities, blood viscosity is only two to 10 times that of water. Although viscosity decreases steadily with decreasing vessel caliber (Fahraeus-Lindqvist phe-

nomenon), once a critical radius is reached a sudden increase in blood viscosity may occur (inversion phenomenon).[1]

Microscopically, circulating blood consists of red blood cells (erythrocytes), white blood cells (lymphocytes and polymorphonuclear leukocytes), platelets, and organic and inorganic compounds. Although each component contributes to blood viscosity, erythrocytes determine the mechanical properties of blood because (1) they occupy approximately 45% of the total blood volume, (2) their concentration exceeds that of white blood cells, and (3) they are larger than platelets. Fibrinogen and lipoproteins, both large proteins, are also major determinants of plasma viscosity.

ERYTHROCYTE DEFORMABILITY

Erythrocyte deformability has a profound effect on the mechanical properties of blood flow. The ability of an erythrocyte to change shape is dependent on two unique features: its discoid shape (which has a high ratio of surface area to volume) and its intrinsic membrane flexibility. By weight, the erythrocyte's surface membrane is 50% protein (primarily B-spectrin heterodimers and actin), 40% lipid (primarily cholesterol and phospholipids), and 10% carbohydrate. The diameter of a typical erythrocyte is 8.4 μm. As a typical human capillary is 3.0 to 4.0 μm in diameter, the erythrocyte must be capable of changing shape without changing either its oxygen-carrying capabilities or the laminar flow potential of moving blood. Interestingly, when an erythrocyte deforms, its volume and surface area do not change.

Erythrocyte deformability also is of vital importance in areas of flow separation and arterial narrowing. In these areas, impaired deformability results in an increase in both local shear stress and blood viscosity. These abnormalities may, in turn, produce either traumatic endothelial injury (impaired normal vasoreactivity and thromboresistance) or plaque disruption (*Figure*). However, these hypotheses are still unproven.

The BAKSS (Becker, Arosemena, Kealey, Steele, Savilonis) erythrocyte viscometer, developed at the University of Massachusetts Thrombosis Research Center in cooperation with Worcester Polytechnic Institute, is a sensitive device capable of exploring these potential associations in greater detail.

VISCOSITY AND CARDIOVASCULAR RISK FACTORS

Noticeably absent from the study of atherosclerotic coronary artery disease has been the role of circulating blood itself: specifically, the influence of plasma viscosity and cellular rheology. Beyond their potential direct effects, each, particularly plasma viscosity, may represent a common link between recognized risk factors and the resulting disease process.

Smoking

In the Multinational Monitoring of Trends and Determinants in Cardiac Disease (MONICA) project, a random sample of a population consisting of 4022 persons 25 to 64 years of age, plasma viscosity was found to be increased in men who smoke.[3] Further, the observed increase correlated directly with the degree and duration of tobacco abuse. A separate study by Rothwell et al[4] showed that several favorable hemorheologic changes take place shortly after smoking cessation. A substantial and persistent decrease in blood viscosity for both men and women occurs within 2 days, due in part to a decrease in packed cell volume as well as decreases in total plasma protein and fibrinogen concentrations.

Thus, while not extensive, the available data suggest that alterations in hemorheologic variables may be markers for increased cardiovascular risk in smokers, and that smoking cessation can reduce the risk of cardiac events. Whether this important observation is the result of hemorheologic changes requires further investigation.

Hypertension

Since blood viscosity contributes to the total peripheral resistance, it may hypothetically contribute to the development of both hypertension and its main cardiac complication, myocardial hypertrophy. In the MONICA project,[5,6] plasma viscosity demonstrated a strong association with hypertension. Other studies have observed similar findings[7] and also have suggested that the direct correlation between blood pressure and blood viscosity is, at least in part, due to the rheologic effects of an elevated fibrinogen concentration.[8]

The relationship between the vascular, neurohumoral, and viscous components of total peripheral resistance are complex and additive. Therefore, relatively small changes in blood viscosity may lead

to a clinically important increase in peripheral resistance in patients with hypertension. Although the existing data do not provide the definitive answers to the question of whether the observed increase in viscosity is the cause or the effect of hypertension, they nevertheless suggest that hemorheologic factors play an important part in determining prognosis.

Lipids

Plasma total cholesterol concentration is a well-established primary risk factor for atherosclerotic coronary heart disease. There is increasing evidence, however, that the low-density lipoprotein (LDL) cholesterol concentration may predict coronary events more accurately than the total cholesterol concentration. Surprisingly, the association between plasma lipoproteins and blood viscosity has not been examined in an epidemiological study until just recently. In the World Health Association-MONICA project, plasma viscosity was shown to have a direct linear association with total cholesterol and apolipoprotein B, and a small inverse association with both high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I concentrations.[9]

Lipids are known to play a key role in determining the fluidity of biologic membranes. Since erythrocytes lack the ability to synthesize lipids de novo, the state of their membrane fluidity depends on the existing serum lipid composition and concentration to which they are exposed. Administration of cholesterol-enriched diets in animals causes striking changes in the lipid composition of the erythrocyte membrane, which, in turn, cause profound changes in membrane fluidity.[10] The phospholipid content of the erythrocyte membrane is known to decrease with advancing age. In addition, the cholesterol ester content increases with age, leading to an increased membrane cholesterol-to-phospholipid ratio. Accordingly, membrane fluidity decreases, as does sodium-potassium adenosinetriphosphatase (Na^+, K^+-ATPase) activity.[11,12]

Sex

Women have been shown to have a lower blood viscosity than men in several large epidemiologic studies, including the Scottish Health Study and the MONICA project.[13] Interestingly, this difference decreases steadily with advancing age, especially after menopause.[13]

Atherogenesis

Studies in animals[14–16] and humans[17,18] strongly suggest that elevated plasma cholesterol concentrations, particularly the LDL fraction, promote atherosclerosis. Plasma is believed to be the source of most of the cholesterol ester present in atherosclerotic lesions.[19–21] LDL enters the atherosclerotic arterial wall at increased rates, and intact LDL has been identified in the atherosclerotic lesions of several species, including humans.

Although increased LDL influx and degradation contribute to the growth of established lesions, it is conceivable that other factors initiate the process and that changes in arterial LDL transport and metabolism occur later.

Coronary atherosclerosis in humans is strikingly focal, occurring at bends, bifurcations, and branch points. As mentioned previously, it is important that blood viscosity decrease and erythrocyte deformability increase to maintain normal blood flow. If these physiologic adjustments are not made or are prevented, coronary blood flow will be affected adversely. It also is conceivable that atherosclerosis (and thrombosis) may be stimulated by the combined effects of turbulent flow, increased shear stress, and altered viscosity.

Blood viscosity has been shown to correlate with the extent of atherosclerotic coronary disease as assessed angiographically.[22] Although the question of cause vs effect may be raised, the Fahraeus-Lindqvist phenomenon states that viscosity *decreases* with decreasing vessel caliber. It is unlikely that a critical vessel radius is reached where a sudden increase in viscosity would be anticipated (inversion phenomenon). At least in theory, increased local viscosity and decreased erythrocyte deformability may promote atherosclerosis by increasing the interaction of adhesive cells (platelets, leukocytes) and infiltrating proteins (fibrinogen, lipoproteins) with the arterial endothelium.

In the Caerphilly and Speedwell studies,[23] plasma viscosity was a strong predictor of ischemic heart disease. Other rheologic abnormalities have been observed in patients with coronary artery disease, including increased whole-blood viscosity and erythrocyte aggregation.[24–26]

Thrombogenesis

Data from the Northwick Park study,[27] Gothenberg study,[28] and the Framingham cohort[29] demonstrate a strong association between total cholesterol

concentration and fibrinogen concentration, a recognized determinant of plasma viscosity. Further, according to the results from these large epidemiologic studies, increased plasma fibrinogen concentrations may represent an independent risk factor for atherosclerotic coronary disease. Recently published data from the Caerphilly and Speedwell Collaborative Heart Disease studies also suggest that increased plasma viscosity carries an independent risk for cardiac events.[30]

The deposition of a thrombus in an area of plaque rupture is an accepted mechanism underlying the development of acute coronary syndromes (ie, unstable angina, myocardial infarction). Increased blood viscosity in these settings would be expected to have a prothrombotic effect. Surprisingly, despite the findings of animal studies and clinical investigations in humans,[31-35] population studies to date have not examined the potential association between blood or plasma viscosity and markers of heightened platelet or thrombin activity. Further, the adverse effects of increased viscosity on endothelial function (vasoactivity or thromboresistance) have not been investigated.

SUMMARY

Accumulating evidence suggests that increased blood viscosity is an independent risk factor for atherosclerotic heart disease and its complications. Given the established importance of hypercholesterolemia in the development and progression of coronary disease and the association between plasma lipoproteins and viscosity, several important questions are now being asked. Is blood viscosity the vehicle for vascular injury in the initiation of atherosclerosis? Is erythrocyte deformability a key element in preventing endothelial damage in critical areas of flow separation? Is it possible to prevent the development or hasten the regression of atherosclerotic heart disease by decreasing blood viscosity or increasing erythrocyte deformability? Answers to these questions may provide important insights into our understanding of this common disease.

REFERENCES

1. **Dintenfass L.** Blood rheology in pathogenesis of the coronary heart diseases. Am Heart J 1969; **77**:139–147.
2. **Goldsmith HL, Turitto VT.** Rheological aspects of thrombosis and hemostasis: basic principals and applications. ICTH Report; Subcommittee on Rheology of the International Committee on Thrombosis and Hemostasis. Thromb Haemost 1986; **55**:415–435.
3. **Ernst E, Koenig W, Matrai A, Filipiak B, Stieber J.** Blood rheology in healthy cigarette smokers: results from the MONICA Project, Augsburg. Atherosclerosis 1988; **8**:385–388.
4. **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; **79**:500–503.
5. **Koenig W, Sund M, Ernst E, Keil U, Rosenthal J, Hombach V.** Association between plasma viscosity and blood pressure. Am J Hypertens 1991; **4**:529–536.
6. **Koenig W, Sund M, Ernst E, Matrai A, Kiel U, Rosenthal J.** Is increased plasma viscosity a risk factor for high blood pressure? Angiology 1989; **40**:153–163.
7. **Cloix J-F, Devynck M-A, Brentano J-LF, Meyer P.** Plasma protein changes in primary hypertension in humans and rats. Hypertension 1983; **5**:128–134.
8. **Letcher RL, Chien S, Pickering TG, Sealey JE, Laragh JH.** Direct relationship between blood pressure and blood viscosity in normal and hypertensive subjects. Am J Med 1981; **70**:1195–1202.
9. **Koenig W, Sund M, Ernst E, Mraz W, Hombach V, Keil U.** Association between rheology and components of lipoproteins in human blood. Circulation 1992; **85**:2197–2204.
10. **Cooper RA, Leslie MH, Knight D, Detweiler DK.** Red cell cholesterol enrichment and spur cell anemia in dogs fed a cholesterol-enriched, atherogenic diet. J Lipid Res 1980; **21**:1082.
11. **Nelson GJ.** Lipid composition of erythrocytes in various mammalian species. Biochim Biophys Acta 1967; **144**:221.
12. **Svanborg A, Bengtsson C, Lindquist O, Roupe S, Steen B.** Plasma lipid changes in the female in aging and the menopause. Results from three population studies. Clin Chim Acta 1977; **79**:299.
13. **Lowe GDO, Smith WCS, Tunstall-Pedoe H, et al.** Cardiovascular risk and haemorheology. Results from the Scottish Heart Health Study and the MONICA Project, Glasgow. Clin Hemorheol 1988; **8**:517–524.
14. **Roach MR, Fletcher J, Cornhill JF.** The effect of the duration of cholesterol feeding on the development of sudanophilic lesions in the rabbit aorta. Atherosclerosis 1976; **25**:1–11.
15. **Watanabe Y.** Serial inbreeding of rabbits with hereditary hyperlipidemia (WHHL-rabbit). Incidence and development of atherosclerosis and xanthoma. Atherosclerosis 1980; **36**:261–268.
16. **Steinberg D.** Lipoproteins and atherosclerosis. A look back and a look ahead. Arteriosclerosis 1983; **3**:283–301.
17. **Sorlie PD, Garcia-Palmieri MR, Castillo-Staab MI, Costas R Jr, Oalmann MC, Hanlik R.** The relation of antemortem factors to atherosclerosis at autopsy. The Puerto Rico Heart Health Program. Am J Pathol 1981; **103**:345–352.
18. **Solberg LA, Strong JP.** Risk factors and atherosclerotic lesions. A review of autopsy studies. Arteriosclerosis 1983; **3**:187–198.
19. **Newman HAI, Zilversmit DB.** Quantitative aspects of cholesterol flux in rabbit atheromatous lesions. J Biol Chem 1962; **237**:2078–2084.
20. **Christensen S.** Transfer with labeled cholesterol across the aortic intimal surface of normal and cholesterol-fed cockerels. J Atheroscler Res 1964; **4**:151–160.
21. **Zilversmit DB.** Cholesterol flux in the atherosclerotic plaque. Ann NY Acad Sci 1968; **149**:710–724.
22. **Lowe GDO, Drummond MM, Lorimer AR, et al.** Relation between extent of coronary artery disease and blood viscosity. Br Med J 1980; **2**:673–674.
23. **Yarnell JWG, Sweetnam PM, Elwood PC, et al.** Haemostatic factors and ischaemic heart disease—The Caerphilly Study. Br Heart J 1985; **53**:483–487.
24. **deSimone Giovanni, Devereux RB, Cien S, Alderman MH, Atlas SA, Laragh JH.** Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. Circulation 1990; **81**:107–117.

25. **Fuchs J, Weinberger I, Rotenberg Z, et al.** Plasma viscosity in ischemic heart disease. Am Heart J 1984; **108:**435–439.
26. **Rainer C, Kawanishi DT, Chandraratna AN, et al.** Changes in blood rheology in patients with stable angina pectoris as a result of coronary artery disease. Circulation 1987; **76:**15–20.
27. **Meade TW, Brozovic M, Chakrabarti RR, et al.** Haemostatic function and ischemic heart disease: principal results of the Northwick Park Heart Study. Lancet 1986; **2:**533–537.
28. **Wilhelmsen L, Svardsudd K, Korsan-Bengtsen K, Larsson B, Welin L, Tibblin G.** Fibrinogen as a risk factor for stroke and myocardial infarction. N Engl J Med 1984; **311:**501–505.
29. **Kannel WB, Wolf PA, Castelli WP, D'Agostino RB.** Fibrinogen and risk of cardiovascular disease: The Framingham Study. JAMA 1987; **258:**1183–1186.
30. **Yarnell JWG, 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.
31. **Vita JA, Treasure CB, Ganz P, et al.** Control of shear stress in epicardial coronary arteries of humans: impairment by atherosclerosis. J Am Coll Cardiol 1989; **14:**1193–1199.
32. **McLenachen JM, Vita J, Fish RD, et al.** Early evidence of endothelial vasodilator dysfunction at coronary branch points. Circulation 1990; **82:**1169–1173.
33. **Tanner FC, Noll G, Boulanger CM, Lucher TF.** Oxidized LDL inhibit relaxation of porcine coronary arteries. Circulation 1991; **83:**2012–2022.
34. **Harlan JM.** Leukocyte-endothelial interactions. Blood 1985; **65:**513–525.
35. **Ge M, Tang G, Ryan TJ, Malik AB.** Fibrinogen degradation product fragment D induces endothelial cell detachment by activation of cell-mediated fibrinolysis. J Clin Invest 1992; **90:**2508–2516.