The Rheology of Blood in Vascular Disease

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Our knowledge and understanding of the mechanisms of hypertensive and ischaemic diseases are still limited, notwithstanding recent contributions, for example, in the fields of neural and endocrine control. Furthermore, the role of the vascular content itself, the blood and the factors determining its flow, has been neglected. Blood cannot be regarded as an inert fluid in blood vessels, nor can it be viewed as a Newtonian, that is a water-like, fluid. Factors contributing only to blood viscosity play a distinctive role in the flow of blood and the formation of thrombi. Furthermore, the pressure and flow functions of blood may be altered in certain segments of the microcirculation and the products of tissue damage may further modify the circulation.

The study of blood rheology can shed new light on fundamental aspects of the circulation in health and disease, particularly in terms of dynamic and flow affected blood coagulation and thrombus formation.

Instruments Used

New instruments have been developed in order to study blood viscosity and blood coagulation.

(a) Rotational Viscometers

These include the cone-in-cone viscometer (Dintenfass, 1962a,b, 1963b,
1964d), ring-in-ring viscometer (Dintenfass, 1965a,c), coaxial rhombospheroid viscometer (Dintenfass, 1968e, 1969d), and the hollow-cone viscometer (Dintenfass, 1969d). All these viscometers contain an outer rotating unit made of brass, and an inner suspended unit made of Teflon. The annulus between the cones, or between the rhombospheroids, or between the rings, requires a volume of blood less than 1 ml. Deflection of the inner (Teflon) unit is observed by following a lightspot on the semicircular plastic scale. Centring of the cones, rings, or rhombospheroids is carried out using a microscopic stage, on which the thermostated cup and a plum-bob are mounted. Guard rings were found to be of no advantage when freshly shed blood was used in the cone-in-cone geometry (Dintenfass, 1967a, 1968b). There is no blood-air interface in the rhombospheroid viscometer. Rotational viscometers were used to study the viscosity of blood, packed cells, and abnormal plasmas.

(b) Microcapillary Slit Viscometers
The parallel-plate slit viscometers (Dintenfass, 1967b,e, 1968c, 1969b) are formed of two highly polished (optical grade) glass plates, the edges of the plates being sealed. The glass plates used were of various sizes depending on the radius, or half-gap, required. Larger plates, 3 × 21 cm, were used for half-gaps of about 2 microns, and plates of 12 × 7 cm were used for half-gaps of up to 100 microns. The length of the slit capillary varied from 7 cm to 0.3 cm. Pressure drop was adjusted by moving pipettes up or down the metal framework supporting the plates. The slit capillary permitted determinations of blood viscosity under conditions simulating the microcapillary bed. Photography was carried out using a Zeiss camera and Chadwick-Helmuth Strobox flash.

(c) The Variable-frequency Thromboviscometer (VFTV)
This is an oscillatory version of the cone-in-cone viscometer, operated at high amplitude of 55 degrees (that is, the arc described is 110 degrees) and at frequencies of oscillation of 60 and 180 cycles per minute (Dintenfass, 1966a, 1967d, 1968d; Rozenberg and Dintenfass, 1966). Coagulation of blood in the VFTV results in the formation of red or white thrombi, analogous morphologically to the thrombi found in arteries (Rozenberg and Dintenfass, 1966; Dintenfass and Rozenberg, 1967a).

METHODS
Blood was obtained by venepuncture using siliconised needles and plastic disposable syringes. Both freshly shed blood and blood anticoagulated with EDTA or heparin were used.
Diseases studied included haemophilia (Dintenfass and Castaldi, 1964), coronary occlusion and peripheral arterial thrombosis (Dintenfass et al., 1966b), renal failure (Dintenfass and Stewart, 1968), hypertension (Dintenfass and Bauer, 1970), peripheral arterial disease (Dintenfass and Sharp, 1969), polycythaemia and cancer (Dintenfass and Rozenberg, 1967b), leukaemia and sickle-cell disease (Dintenfass, 1964c, 1965c). Studies on the changes in blood viscosity of thrombi during menstrual cycles were also carried out (Dintenfass et al., 1966a; Dintenfass and Yu, 1968).

**Blood viscosity**

Blood, unlike water, is a very complex fluid. At near-zero flow velocities the viscosity of whole blood may be 100 to 10,000 times higher than that of water. However, at high flow velocities it may be only twice or four times that of water. Perhaps the most remarkable aspect of normal blood is that it remains fluid even at haematocrits of nearly 100 per cent. Indeed, at this haematocrit the viscosity of packed red cells can be as low as 20 centipoises in larger vessels, and even less in smaller vessels. In contrast, suspensions of rigid particles (sand, beads, etc.) achieve the consistency of brick or concrete at concentrations of about 65 per cent.

The fluidity of blood is largely due to extremely low internal viscosity of the red cell, which can be considered as a fluid drop of variable viscosity, the latter decreasing as increasing flow velocity increases (Dintenfass, 1962c, 1964e, 1965c, 1968c,d,e, 1969b, 1970a,b).

Viscosity of whole blood is determined by its haematocrit, internal viscosity of the red cell, degree of red cell aggregation, plasma viscosity, and flow velocity or, more exactly, the shear rate. The internal viscosity of the red cell, or other blood cells, is more significant at haematocrits above 70 per cent.

Internal viscosity of the red cell is greatly increased at low pH (Dintenfass and Burnard, 1966), in the presence of abnormal haemoglobin (Dintenfass, 1964c), and in hypo- or hypertonic plasma (Dintenfass, 1965c, 1968d,e, 1969b). In sickle-cell anaemia, the state of oxygenation or reduction of haemoglobin has a multifold effect on the viscosity of blood.

The degree of aggregation of the red cells as well as the size of the aggregates depends on the conditions of flow. Progressive disaggregation takes place when shear rate increases. When flow is constant, the size of the red cell aggregates depends on the intrinsic properties of blood: on the concentration of fibrinogen and other proteins, and on the individual surface characteristics of the red cells. In general, the degree of aggregation of red cells is elevated in patients with myocardial infarction, peripheral vascular disease, and renal failure.
Under conditions of homogeneous flow (as in the viscometer), the disaggregation of red cells in normal blood will take place at a shear rate of about 5 to 10 sec\(^{-1}\); in many patients the required shear rate is nearer 60 sec\(^{-1}\) (Dintenfass, 1962a,b, 1963a, 1964b). Under conditions of non-homogeneous flow (as in blood vessels) the respective values for normal subjects and patients would be 100 to 200 sec\(^{-1}\), and about 500 sec\(^{-1}\).

The existence of the 'inversion phenomenon', a well-defined critical radius corresponding to the minimal resistance to flow in capillaries of radii 2 to 100 microns, and even up to 500 microns, has been shown experimentally in in vitro systems (Dintenfass, 1967b,e, 1968d, 1970c). In vessels of radii larger than the critical radius, the viscosity of blood follows the Fahraeus–Lindqvist phenomenon; that is, the apparent viscosity of blood decreases as the capillary bore decreases. Below the critical radius the inversion phenomenon appears: there is a sudden and dramatic increase in resistance to flow and a sudden inversion of the ‘capillary bore–viscosity’ function takes place.

The critical radius of the inversion phenomenon depends, in a very sensitive manner, on the internal viscosity of the blood cells, and aggregates of these cells. This is of little importance when blood flows through large vessels but small changes of internal viscosity are of consequence when blood flows through small vessels. In the absence of platelet aggregates, the critical radius of the inversion phenomenon is only slightly affected by haematocrit, but greatly affected by blood pH (Fig. 1). However, in the presence of platelet aggregates, the size of that aggregate becomes the dominant factor. Crenation of red cells, abnormality of the membrane, the type of haemoglobin, and the size of the cell all play a role and lead to a spectrum of critical radii depending on the rheology of blood cells.

The effect of rigid particles in the circulation does not have to be obvious since the presence of a larger number of rigid particles, cells, in a small segment of the circulation may lead to local increased resistance to flow because the viscosity of the fluid within such a segment can increase with shear rate or with pressure.

These mechanisms of increased resistance to flow in the microcirculation may be responsible, in some instances, for apparent vasoconstriction.

**Blood Coagulation and Thrombus Formation**

Practically every aspect of blood coagulation is affected by the flow velocity of blood and the shear rate existing during the clotting process. Clotting times, thrombus formation times, the rates of clot or thrombus formation, and the viscosity of thrombi, all decrease when the ‘casting’ shear rate (or flow...
velocity) is increased. The morphology of the clot changes in parallel with other properties, showing characteristics of the glass clot at zero or near zero shear rate, and characteristics of the white thrombus at shear rates of about 60 sec$^{-1}$ (Rozenberg and Dientenfass, 1964, 1965, 1966; Dientenfass and Rozenberg, 1965, 1967a).

Red clots are formed at low flow velocities exhibiting gel-like and highly viscous properties. The red and white thrombi formed at intermediate flow velocities are viscous and thixotropic. Coagula formed at high flow velocities (shear rates above 400 sec$^{-1}$) remain fluid, their viscosity not
necessarily higher than that of uncoagulated blood. These are ‘suspension coagula’ or ‘liquid thrombi’ in which platelet aggregates and globular particles of fibrin form suspensions mixed with the suspension of red cells (Dintenfass, 1966a, 1967d, 1968d).

The great variation in the viscosity and morphology of coagula formed at increasingly rapid blood flow are due to:

1. a progressive orientation of the fibrin network, a progressive fracture of this network and finally, at very high flow velocities, to the polymerisation of fibrin in globular form;
2. a progressive release of the disaggregated red cells from the mesh of the fibrin network; and
3. a progressively increasing rate of platelet aggregation that could be affected by ADP released from stressed red cells.

There is a quantitative relationship (Dintenfass and Rozenberg, 1965; Dintenfass, 1968a) between the shear rate and the degree of platelet aggregation. The latter also depends on the intrinsic properties of blood in the individual donor, and can be affected by disease (Rozenberg and Dintenfass, 1965). A progressive process of platelet aggregation at increasing shear rates suggests an irreversible phenomenon; i.e., that the surface properties undergo a profound change due, possibly, to mechano-chemical transformation.

The practical importance of the rheology of thrombus formation can be illustrated by the studies of patients suffering from renal failure, hypertension, and peripheral vascular disease (Dintenfass and Stewart, 1968; Dintenfass and Sharp, 1969; Dintenfass and Bauer, 1970).

The rates of thrombus formation, viscosity, and dissolution in the patients were increased in comparison to normal \((p=0.001\) and \(p=0.005\)). These results, indicating hypercoagulability, were true for the lower and the higher frequencies of oscillations, corresponding to the lower and higher range of arterial shear rates.

The increase of thrombus viscosity is not apparently related to the fibrino-
gen content, at least not in a proportional fashion. The abnormality of thrombus viscosity in uraemia may be caused by a platelet abnormality but it could not be correlated with the severity of the measurable biochemical derangement or with a qualitative platelet defect. It is not yet possible to correlate the rheological abnormalities in patients with hypertension or peripheral vascular disease with such obvious defects as increased blood pressure, blood lipid or urea level. Patients with grosser changes did show more marked rheological abnormalities.
The fact that blood viscosity was increased in a number of diseases, including infarction, polycythaemia, leukaemia, cancer, macroglobulinaemia, and sickle-cell diseases, led to the concept of the ‘blood high viscosity’ syndrome (Dintenfass, 1966b, 1967c, 1968d, 1969a) and to suggestions that such elevated blood viscosity may play an important role both in the diagnosis and aetiology of these diseases (Dintenfass, 1963c, 1964a,f, 1965b, 1969c, 1970b,c; Dintenfass and Read, 1968).

Increased blood viscosity can be due to elevation of different parameters in different diseases. Thus, in polycythaemia, the increased viscosity is due to the high concentration of red cells, but in leukaemia it may be the increased concentration of leucocytes, which are much more rigid than the red cells, or to the presence in plasma of nucleic acid, released by disintegrating white cells. In myocardial infarction the most pronounced increase is in the aggregation of the red cells; in sickle-cell diseases the viscosity elevation is due to increased rigidity of the red cells, and so on. The important point is that in most of these diseases there is an elevation of the viscosity of whole blood, more or less pronounced at higher or lower shear rates, that can be ascribed to a subphase specific to a particular disease or group of diseases.

Increased blood viscosity results in a slower blood flow and decreased oxygen transport, both of which may lead to increased aggregation and increased rigidity of the red cells, increased plasma skimming, and increased permeability of the vessel wall. The last two factors may enhance localised haemoconcentration.

Increased rigidity of red cells, whether due to genetically determined defects, increased hydrogen ion concentration, hyper- or hypotonicity, or antigen-antibody reactions, and increased aggregation of the red cells perhaps due to immunological reactions, toxins or abnormal proteins, will impair tissue perfusion and slow blood flow; the subsequent hypoxia and acidosis result in a further increase of blood viscosity.

Platelet aggregates and liquid thrombi play a crucial role in the rheology of blood flow. Circulating catecholamines and adenine nucleotides can lead to platelet aggregation as a primary phenomenon and, possibly, to initiation of blood coagulation.

The presence of thrombi decreases the viscosity of whole blood, and even the initial stages of coagulation lead to increased aggregation of the red cells. The higher the viscosity of a thrombus, the more of an obstacle it is to blood flow. The higher the rate of dissolution of thrombi, accompanied by showers of micro-emboli, the greater the damage to be expected in the related areas.
of the microcirculation. The greater the irregularity of the vessel wall and the narrower the lumen, and hence the higher the shear rate, the greater will be the ease of formation of platelet aggregates and liquid thrombi. Such a stenotic region can act as a sort of 'machine gun' forming and shooting off platelet aggregates into the microcirculation.

A small change in two or more of the subphases of blood may result in a greatly magnified synergistic increase in blood viscosity and an increase in the critical radius of the inversion phenomenon (Figs 1 and 2). A localised increase in blood viscosity and a simultaneous increase in the critical capillary radius may provide a mechanism for transient or intermittent interruptions of blood flow.

The vicious circle initiated by increased blood viscosity in a localised area of the microcirculation can spread to affect other areas, leading to ischaemia, infarction or thrombosis.

Jorgensen et al. (1967) and Mustard et al. (1968) noted that the presence of platelet aggregates led to slower blood flow and red cell sludging, and these both result in renal infarction. The hypothesis of Moore and Mersereau (1965) that renal ischaemia is of embolic origin is well known.

It is likely that excessive constriction of the small vessels can be mimicked by an increase in the viscosity of whole blood or in one or more of its subphases.

It is possible that rheological changes in the blood contribute to the processes leading to myocardial infarction, arterial thrombosis, and peripheral vascular disease.

CONCLUSION

A study of the viscosity of blood and of thrombi in patients with hypertension, renal failure, myocardial infarction, peripheral vascular disease, polycythaemia, sickle-cell disease, and other diseases, showed an increase in rheological parameters. In all these cases one would expect impaired tissue perfusion. Similarity in the general pattern of change, especially in patients with vascular diseases, suggests that the characteristic increase in viscosity results from a common mechanism. Details of this pathway, such as the dominance of any one subphase, may establish a more exact relationship between particular diseases and the subphases responsible for increase of blood viscosity.

The increased blood viscosity may or may not play an aetiological role in any of these diseases but it does exaggerate the lesion, creating a vicious circle of physiological abnormality.

Paraphrasing Carter (1969), one could speculate that individuals are at risk of developing vascular and ischaemic diseases when polygenic and multi-
factorially determined rheological thresholds are passed. These thresholds may vary among individuals in regard to aggregation of red cells or platelets, or to sensitivity of blood vessel response to a decreased blood flow.

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