Virchow's Triad Revisited: Abnormal Flow

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Key Words

Blood flow · Thrombosis · Shear stress · Endothelial cells · Platelets

Abstract

Virchow rightly recognised that blood flow plays an important role in thrombosis. The roles of blood flow in haemostasis, and in arterial, intra-cardiac, and venous thrombosis are reviewed.

In streamline (laminar) flow, shear stresses are maximal at the vessel wall, and affect endothelial cell morphology and function (e.g. secretion of NO, prostacyclin, t-PA and vWF). Platelets are also concentrated at the vessel wall (due to axial concentration of red cells) where they can be activated by high shear stresses and are well-placed to interact with vWF and sub-endothelium, resulting in platelet adhesion and the initial stages of haemostasis. On the other hand, increasing wall shear forces increase removal of thrombin and fibrin monomer, hence stasis (induced by internal or external pressure) is required to allow fibrin formation and secondary haemostasis.

Atherogenesis occurs in areas of arterial flow separation, which promotes platelet, leucocyte, LDL and fibrinogen adhesion and wall infiltration. Rheological variables (e.g. wall shear stress, viscosity, haematocrit, fibrinogen, LDL) have been correlated with the extent of ultrasonic carotid intima-media thickening.

Arterial thrombosis usually follows rupture of atherosclerotic plaques and intra-plaque haemorrhage: high intra-stenotic shear stresses may activate platelets, promoting the initial platelet-rich "white-head" of arterial thrombi, while low post-stenotic shear stresses may promote the subsequent, fibrin- and red cell-rich "red tail". Blood viscosity, platelet microemboli, and activated leucocytes may each reduce post-stenotic microcirculatory blood flow, promoting infarction. Such mechanisms may explain the associations of increased levels of blood and plasma viscosity, haematocrit, white cell count, fibrinogen and vWF with risk and outcome of myocardial, cerebral and limb infarction.

Areas of recirculating blood flow under low shear stresses predispose to intracardiac thromboembolism (e.g. atrial fibrillation, in which elevated fibrin D-dimer levels are normalised after cardioversion) and venous thromboembolism (fibrin D-dimer levels are associated with most risk factors). There is good evidence that reduction of venous stasis in the legs reduces the risk of venous thromboembolism.

There is increasing evidence that regular exercise and avoidance of immobility reduces the risk of both arterial and venous thrombosis and also has systemic antithrombotic and anti-inflammatory effects. So: "Go with the flow!"

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Introduction

Haemostasis, atherogenesis and thrombosis are processes which occur in flowing blood. Hence, the flow behaviour of blood (haemorheology) merits study. It may partly explain the localisation and morphology of arterial, intracardiac and venous thrombi within the human circulation. Furthermore, it may partly explain why increases in haematocrit, fibrinogen and other macromolecules and rigid blood cells may increase the risk of ischaemic events [1].

Flow and Haemostasis

In streamline (laminar) flow, shear stresses are maximal at the vessel wall, and affect endothelial cell morphology and function. Endothelial cells elongate and align in the direction of flow [2]. The secretion and release of endothelial defences such as nitric oxide (NO), prostacyclin (PGI₂) and tissue plasminogen activator (t-PA) are shear-dependent, hence flow regulates endothelial related vascular reactivity and confines platelet adhesion and aggregation as well as fibrin formation to sites of endothelial injury. The synthesis/release of prothrombotic and proinflammatory endothelial mediators such as tissue factor (TF), von Willebrand factor (vWF), endothelin, ICAM-1 and VCAM-1 is also shear-dependent. There is increasing evidence that some of these shear-dependent endothelial functions are under genetic control [3]. The transcriptional profile normally produces a "quiescent" endothelial phenotype [3].

Due to their displacement from central (axial) flow streamlines by the more numerous and more deformable red blood cells, leucocytes and platelets are concentrated near the vessel wall, where they are strategically placed for adhesion and activation. High shear forces at the vessel wall may activate platelets and increase their vWF-induced adhesion to exposed subendothelium. However, high wall shear forces increase removal of platelet aggregates, thrombin and fibrin monomer; hence stasis (induced by internal or external pressure) is required to allow fibrin formation and secondary haemostasis.

Flow, Atherogenesis and Chronic Ischaemia

Atherogenesis occurs preferentially at arterial bifurcations and bends, at which sites flow separation results in areas of low-flow, low-shear recirculation of blood cells and proteins, in contact with the vessel wall. Such flow conditions may favour adhesion of platelets and monocytes, as well as infiltration of plasma components such as low density lipoprotein (LDL) cholesterol and fibrinogen.

Rheological variables such as wall shear stress, and blood viscosity and its determinants (haematocrit, fibrinogen, LDL) have been correlated with the extent of ultrasonic carotid artery intima-media thickening (IMT) [4]. This may partly account for the predictive value of blood viscosity for stroke in the same study [5]. Blood viscosity has also been associated with the extent of coronary [6] and peripheral [7] atherosclerosis.

Blood viscosity may promote not only atherogenesis, but also intermittent exercise-induced ischaemia (stable angina, intermittent claudication) distal to atherosclerotic stenoses. In the Edinburgh Artery Study, the prevalence of claudication in a random sample of the older population was a function not only of the extent of stenoses in the arteries to the leg (ankle brachial pressure index, ABPI), but also of plasma viscosity [7]. Reduction in fibrinogen, lipoproteins and viscosity by bezafibrate doubled the walking ability of claudicants in the MRC LEADER randomised controlled trial [8; and personal unpublished observations on blood rheology]. Another recent randomised trial of a statin also observed increased walking ability of claudicants [9], possibly due to reduced blood viscosity [10]. Finally, regular exercise (walking) may increase the walking ability of claudicants partly through reductions in fibrinogen and viscosity [11-13].

Flow, Arterial Thrombosis and Acute Ischemia

Arterial thrombosis usually follows rupture of atherosclerotic plaques, and is the commonest pathophysiological process in acute coronary syndromes, ischaemic stroke and critical leg ischaemia. High intra-stenotic shear stresses may be one factor promoting arterial plaque rupture, and through high-shear activation of blood platelets they may also promote the initial platelet-rich "white head" of arterial thrombi. Distal to the atherothrombotic stenosis, low-shear stresses may promote the subsequent, fibrin- and red-cell-rich "red tail". Low post-stenotic perfusion pressure may also promote the ability of blood viscosity (which increases under low shear conditions, due to red cell aggregation), platelet microemboli, and activated leucocytes to reduce microcirculatory blood flow, promoting infarction. These rheological mechanisms may explain the associations of blood and plasma viscosity, haematocrit, erythrocyte sedimentation rate (ESR; which reflects red cell aggregation), white cell count, fibrinogen and von Willebrand factor (which mediates platelets aggregation under high-shear conditions) with the risk and the outcome of myocardial, cerebral and limb infarction [1,14-17].

Flow and Intracardiac Thromboembolism

Rheological factors may be important in pathogenesis of atrial thrombosis, which occurs in low-shear areas in dilated fibrillating atria. Such areas are visualised by "spontaneous echo contrast" at echocardiography, which is associated with increased risk of thromboembolic stroke as well as increased circulating markers of haemostatic activation [18]. Valvular thrombosis is favoured by high shear stresses through the valve, followed by areas of flow separation; while left ventricular mural thrombus occurs after myocardial infarction on damaged endothelium in areas of reduced contractility with flow separation [19].

Flow and Venous Thromboembolism

Deep vein thrombosis (DVT) of the leg usually originates in venous valve pockets, within which flow separation results in recirculation and interaction of systemically-acti-

vated platelets, leucocytes and coagulant enzymes [20]. Rheological therapies including compression devices, haemodilution with dextran, and defibrinogenation with anicrod have each been shown to reduce the risk of DVT in randomised controlled trials [1,14,20].

Exercise, Rheology and Thrombotic Risk

There is increasing evidence that regular exercise reduces the risk of arterial and venous thrombotic events. One mechanism may be that regular exercise reduces circulating levels of viscosity and haemostatic and inflammatory variables [13]. Encouraging regular exercise, and minimising immobility, may therefore reduce the risk of cardiovascular thrombotic events through systemic effects which maintain blood flow. The health message is therefore: "Go with the flow!"

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