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Virchow's Triad Revisited: Blood Constituents

Irene Chung, Gregory Y.H. Lip

Haemostasis, Thrombosis, and Vascular Biology Unit, University Department of Medicine
City Hospital, Birmingham, United Kingdom

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Virchow's triad · Thrombosis · Platelets · P-selectin · Fibrinogen · Fibrin · D-dimer · Fibrinolysis

Abstract
An update of Virchow's triad for thrombogenesis can be considered by reference to abnormalities in the endothelium/endocardium ('abnormal vessel wall'), abnormalities of haemorhelogy and turbulence at bifurcations, atheroma at vessel wall ('abnormal blood flow') and abnormalities in platelet as well as the coagulation and fibrinolytic pathways ('abnormal blood constituents'). The constituents of the blood are many and varied, but soluble coagulation factors (such as fibrinogen and tissue factor) and cells (such as platelets) are clearly important.Clearly, 'a continuum exists between health, 'statistically' increased haemostatic abnormalities in prothrombotic or hypercoagulable states and 'overtly' increased clotting in acute thrombosis. Thus, the patients with the highest levels of the markers appear to be the highest risk of disease progression, and if so, a panel of 'high risk' blood constituent indices (platelet and coagulation markers) may potentially give a composite score of risk, and may be a useful tool in predicting subjects at highest risk. Further longitudinal studies are clearly required. There is no doubt that Virchow would be impressed on how his classical triad has expanded to encompass the wide range of pathophysiological processes leading to thrombogenesis.

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Introduction

In 1856, Virchow published his now-classical triad of factors that lead to the development of thrombosis (thrombogenesis). The three components were 'abnormalities of blood vessel wall', 'abnormalities of blood constituents', and 'abnormalities of blood flow'. While Virchow originally referred to venous thrombosis, the concepts can also be applied to arterial thrombosis.

An update of Virchow's triad for thrombogenesis for the 21st century can be considered by reference to abnormalities in the endothelium/endocardium ("abnormal vessel wall"), abnormalities of haemorheology and turbulence at bifurcations, large vessels burdened by irregular atheroma, and stenotic regions (that is, Virchow's "abnormal blood flow") and finally, abnormalities in platelets as well as the coagulation and fibrinolytic pathways ("abnormal blood constituents").

The constituents of the blood are many and varied, but soluble coagulation factors (such as fibrinogen and tissue

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Professor GYH Lip, MD
Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital
Birmingham, B18 7QH., U.K

Tel: +44 121 5075080; E-mail: g.y.h.lip@bham.ac.uk

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factor) and cells (such as platelets) are clearly important.

Platelets

Platelets have long been implicated in the pathogenesis of atherosclerosis as major components of thrombosis, or as constituents of atheroma. Platelet function (or dysfunction) has been quantified by parameters such as an increased tendency to aggregate, but also by measuring the levels of platelet metabolic products in both plasma and urine, including the alpha granule constituents (beta thromboglobulin and platelet factor 4 (PF4)) and the soluble form of the adhesion molecule P-selectin (soluble P-selectin, sPsel) in the plasma1 [1-3]. Although both beta thromboglobulin and PF4 are matrix constituents of the alpha granule, PF4 is believed to compete with antithrombin III for a site on endothelial heparan glycosaminoglycans, thereby impairing the heparan-catalysed inhibition of thrombin, whilst the precise function of beta thromboglobulin is unclear[4].

These platelet molecules may differ in clinical relevance. Raised levels of varioud platelet molecules are abnormal in cancer, peripheral disease, acute myocardial infarction, diabetes, and hypertension [5-8].

The adhesion molecule P-selectin (CD62P) is of particular interest because of its role in modulating interactions between blood cells and the endothelium, and also because of the possible use of the soluble form as a plasma predictor of adverse cardiovascular events. For example, it is known that thrombin induces surface expression of P-selection on platelets [1-2]. Although present on the external cell surface of both activated endothelium and activated platelets, it now seems clear that most, if not all, of the measured plasma P-selectin is of platelet origin. P-selectin is also partially responsible for the adhesion of certain leukocytes and platelets to the endothelium (Figure 1). Increased P-selectin expression has been demonstrated on active atherosclerotic plaques, while fibrotic, inactive plaques lack P-selectin expression, and animals lacking P-selectin have a decreased tendency to form atherosclerotic plaques. Finally, increased levels of soluble P-selectin in the plasma have been demonstrated in a variety of cardiovascular disorders, including coronary artery disease, hypertension and atrial fibrillation, with some relationship to prognosis - providing evidence of platelet activation in these conditions.

Both platelet P-selectin and soluble P-selectin are increased in atherosclerotic disease, hypertension, diabetes mellitus and heart failure, yet there are limited follow-up data, and the prognostic values of P-selectin and other platelet markers are far from clear. For example, beta thromboglobulin does not predict the progression of coronary artery disease or cardiac event rate [9], although increased levels of beta thromboglobulin have been associated with a risk of post angioplasty restenosis [10]. Recent work indicates that beta thromboglobulin, but not PF4, predicts left atrial thrombosis among patients with atrial fibrillation, a

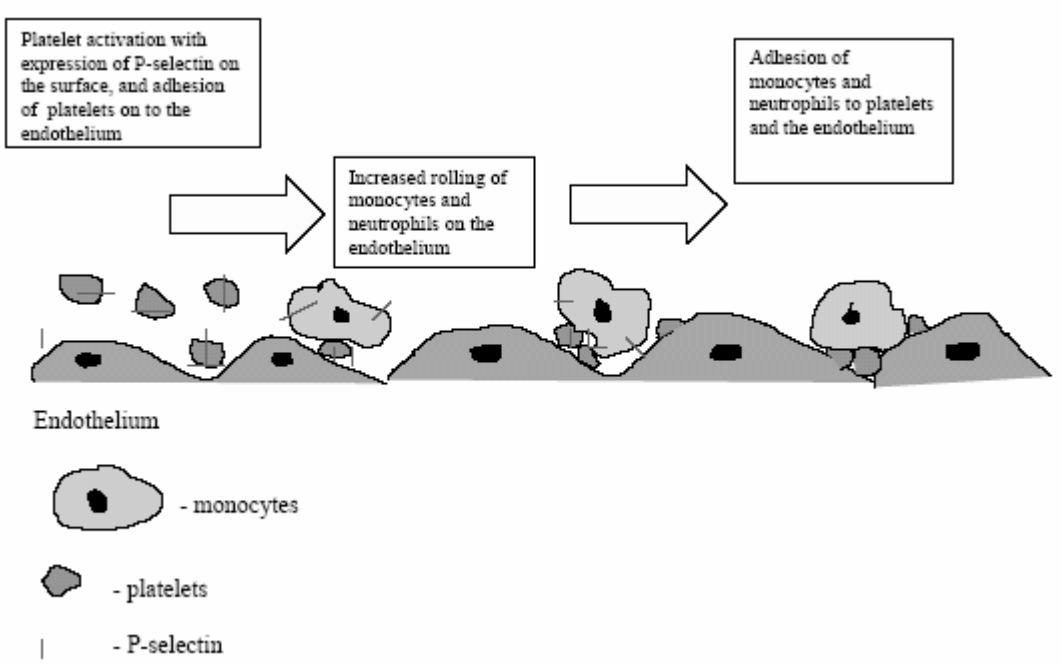

Fig. 1. Role of adhesion molecule P-selectin in modulating interactions between blood cells and the endothelium.

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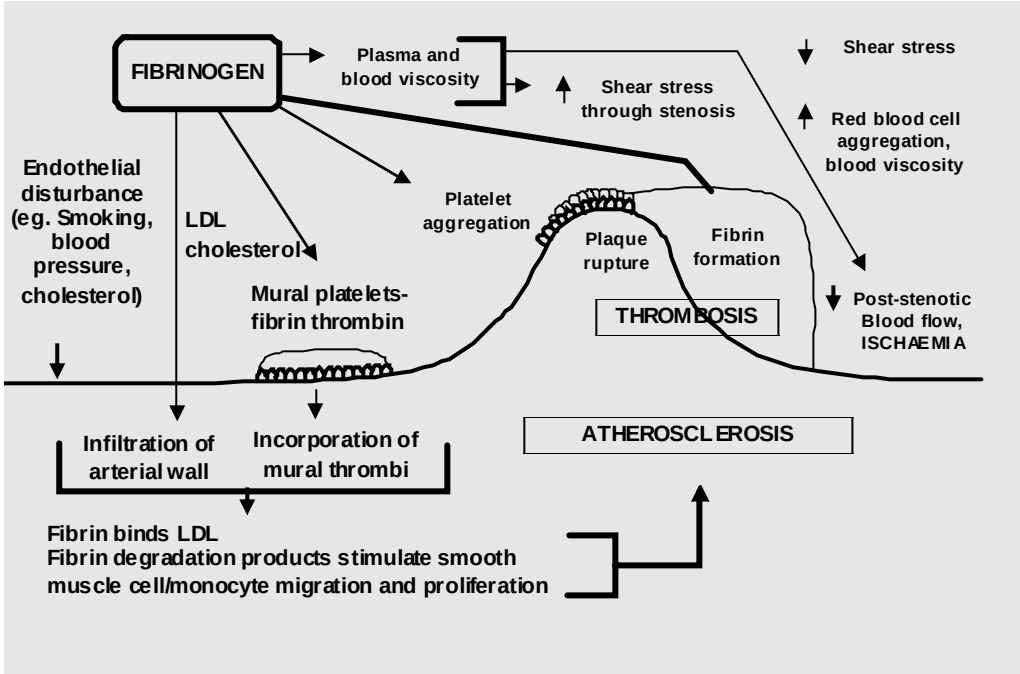

Fig. 2. Potential mechanisms by which increasing plasma fibrinogen levels may promote arterial disease and ischaemic events

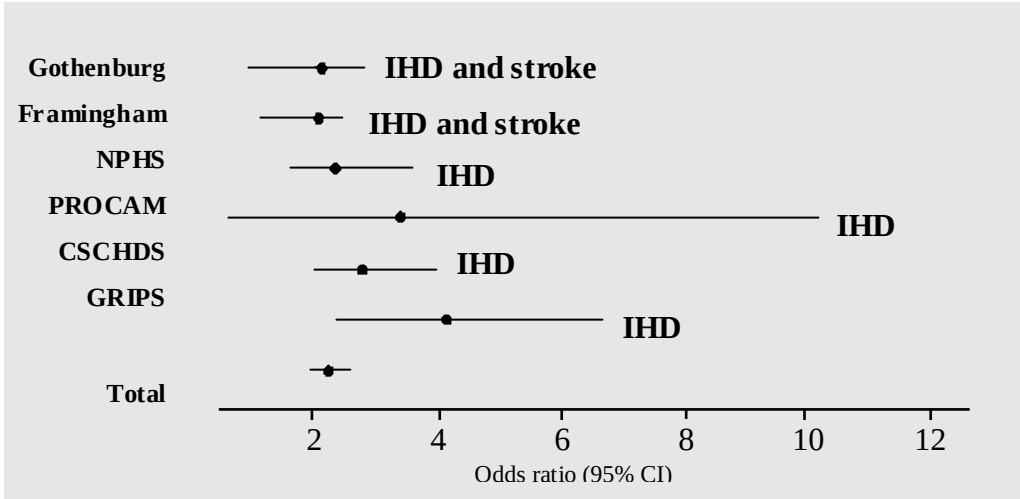

Fig. 3. Meta-analysis of six prospective studies of plasma fibrinogen levels in the primary prediction of cardiovascular events.

common cardiac arrhythmia which is associated with stroke and thromboembolism [11]. Nonetheless, in patients with atrial fibrillation, soluble P-selectin levels were not predictive of subsequent mortality or stroke [12]. In this population, however, soluble P-selectin could be related to atherosclerotic risk factors [13].

Coagulation and Fibrinolytic Factors

Thrombogenesis is finely balanced between coagulation and fibrinolytic pathways. The fibrinolytic system is primarily influenced by the interaction between plasminogen activators (such as tissue plasminogen activator) and inhibitors that modulate this activity (eg. plasminogen activator inhibitor, PAI-1).

Fibrinogen

Plasma fibrinogen is a coagulation factor, which is one of the main determinants of plasma viscosity and blood

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flow. It affects platelet aggregation and blood viscosity, interacts with plasminogen binding and in combination with thrombi mediates the final steps in clot formation. As Figure 2 illustrates, the relation among hyperfibrinogenemia, atherosclerosis and thrombosis is highly complex and complicated. As the process of thrombogenesis is very intimately related to atheroma formation (atherogenesis), thus specific thrombogenic factors such as fibrinogen (with important effects on blood rheology) may play key roles in the process of atherosclerotic lesion formation with subsequent effects on cardiovascular diseases.

Of note, fibrinogen levels have been shown to associate positively with age, obesity, smoking, diabetes and LDL-C and inversely with HDL-C, alcohol use, physical activity and exercise level [14]. Increased fibrinogen is also associated with many different forms of vascular and inflammatory disease, with prognostic implications. Many studies have demonstrated that increased fibrinogen concentrations are associated with the presence of vascular disease compared with controls [15-19], independently of risk factors, such as smoking[18] or diabetes [20]. Fibrinogen levels also related to severity of coronary artery disease at angiography [19,21], as well as ankle brachial pressure [22]. In hypertension, raised plasma fibrinogen levels have been associated with target organ damage, and altered by treatment [23,24].

There is a significant association between fibrinogen levels, and mortality and cardiovascular events [Figure 3]. Indeed, the relative risk for future events is approximately 2 fold higher for individuals in the top centile as compared to the bottom centile of fibrinogen levels. Increased fibrinogen levels predict those people who subsequently develop peripheral vascular disease [25]. In patients with intermittent claudication, plasma fibrinogen concentrations are an independent predictor of death [26,27]. In hypertension, the Leigh general practice study showed that hypertensives with fibrinogen levels >3.5 g/l had a 12-fold higher cardiovascular risk than those with fibrinogen <2.9g/l [28].

However, despite the correlations between fibrinogen and the risk of coronary disease, there is no convincing evidence to show that lowering the fibrinogen level will result in a reduction in risk. For example, niacin supplementation reduces plasma fibrinogen levels with some resolution of critical ischaemia [29-30] Whereas long-term ibuprofen or pentoxifylline were reported to increase claudication distance in patients there is no significant effect on their plasma fibrinogen concentrations [31].

Fibrin D-dimer

Raised levels of fibrin D-dimer are fibrin degradation products which are an index of intravascular thrombogenesis and fibrin turnover - levels are increased among patients with cardiovascular disease, including diabetes mellitus, peripheral vascular disease [16] and smokers [18].

High levels of fibrin degradation products may have significant prognostic implications. For example, there is a relationship between fibrin degradation products (FDPs) and the angiographic extent of peripheral vascular disease, with FDPs being an independent predictor of severity [19]. In 1993, the Edinburgh Artery Study reported an independent relationship between FDPs and cardiovascular events in patients with peripheral vascular disease [31]. However, the same investigators subsequently reported that there was no longer found an independent relationship between FDP levels and peripheral vascular disease progression [25]. In hypertensive patients who experienced a new cardiovascular event over a 4 year follow up period, there was evidence of greater higher fibrin D-dimer and endothelial damage/dysfunction compared to those who were free of complications [32].

More recently, Vene et al. [33] have suggested high levels of D-dimer are significant predictors of cardiovascular events in AF patients, irrespective of oral anticoagulant therapy usage. Also, fibrin D-dimer levels may have implications in stroke progression. Barber et al. [33] showed excess thrombin generation and fibrin turnover in patients with progressing ischemic stroke, suggesting that measurement of fibrin D-dimer levels could identify patients at high risk for stroke progression. Further research is required to determine whether such patients benefit from acute interventions aimed at modifying hemostatic function.

Fibrinolysis

The fibrinolytic system is primarily influenced by the interaction between plasminogen activators (such as tissue plasminogen activator (tPA), which promotes fibrinolysis) and inhibitors that modulate this activity (such as plasminogen activator inhibitor, PAI-1). Impaired fibrinolysis as demonstrated by the elevated levels of plasminogen activator inhibitor (PAI) activity have also been demonstrated as an independent variable associated with coronary heart disease.

In addition, impaired fibrinolysis is seen in patients with the insulin resistance syndrome and obese patients, and could explain the increased risk of atherogenesis in these patients. Indeed, high plasma concentrations of PAI-1 occurs in both normoglycemic subjects with insulin resistence and patients with type 2 diabetes [35]. Plasma concentrations of other thrombotic risk factors, such as coagulation factor VII, von Willebrand factor, and fibrinogen, are also correlated with insulin resistence and are high in patients with type 2 diabetes [35,36]. Thus, PAI-1 has a role in atherothrombotic disorders through a close link with other risk factors in people with insulin resistence.

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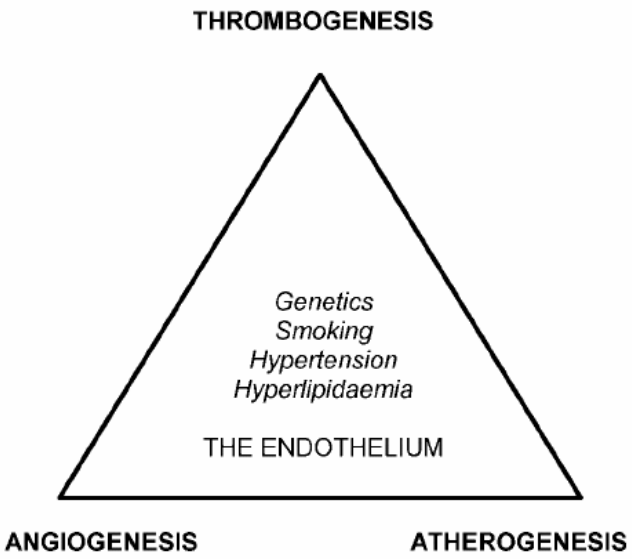

Fig. 4. Thrombogenesis, atherogenesis and angiogenesis in vascular disease: the Birmingham 'Vascular Triad'

Activated PAI-1 is synthesized in platelets as well as endothelial cells. High plasma PAI-1 levels are associated with various thrombotic disorders [37-40] and are an independent risk factor for reinfarction in patients who have had a first myocardial infarction before the age of 45 years [41,42]. There is also evidence that high plasma PAI-1 concentrations are associated with the progression of coronary syndromes, the development of myocardial infarction and angiographic coronary artery disease [43,44]. Decreased tissue plasminogen activator (tPA) have been associated with higher levels of PAI-1 [45,46] although there are limited data on the relationship of tPA levels to outcomes.

Other Factors

Homocysteine is an amino acid derived from dietary methionine. Although not a coagulation factor per se, homocysteine represents a blood constituent with implications for thrombogenesis, and indeed, patients with homocysteinuria are known to have a much higher incidence of atherosclerotic vascular disease and premature atherothrombosis47. Also, cross sectional and retrospective data show a positive relationship between mild to moderate hyperhomocysteinemia and atherosclerosis; with plasma levels above 15 mol/l having a relative risk of one and a half to two times higher than those with lower levels. However, prospective studies have been less convincing, and prospective trial data showing that reducing homocysteine levels reduces the risk of coronary disease are awaited.

A wide range of other blood constituents (such as leucocytes, inflammatory cytokines, growth factors, matrix metalloproteinases (and their inhibitors), etc) are all likely have roles in contributing to, or promoting, thrombogenesis. Nonetheless, a detailed treatise on all these factors is far beyond the scope of this broad overview. However, it is worth mentioning that thrombogenesis is intimately linked to atherogenesis, and both are associated with angiogenesis. Indeed, it is increasingly recognised that the process of angiogenesis is very evident in atherosclerotic vascular disease [48]. For example, the vasa vasorum in the adventitia and media are at a higher density in atherosclerotic tissue, and greater neovascularisation leads to collateral growth bypassing arterial obstruction and/or stenoses. Certainly, increasing data point towards a close relationship between thrombogenesis, atherogenesis and angiogenesis, which has recently be proposed as a new 'vascular triad' (the Birmingham vascular triad), with the endothelium central to the processes [49] (Figure 4).

Conclusion

Blood constituents may provide information useful in identifying those at risk of accelerated disease progression, in monitoring this progression, or in clinical staging. It appears that "…..a continuum exists between health, 'statistically' increased haemostatic abnormalities as a prothrombotic or hypercoagulable state, and 'overtly' increased clotting in acute thrombosis. Thus, the patients with the highest levels of the markers appear to be the highest risk of disease progression, and if so, a panel of 'high risk' blood constituent indices (platelet and coagulation markers) may potentially give a composite score of risk, and may be a useful tool in predicting subjects at highest risk. Further longitudinal studies are clearly required. There is no doubt that Virchow would be impressed on how his classical triad has expanded to encompass the wide range of pathophysiological processes leading to thrombogenesis.

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