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Editorial

Venous and arterial thrombosis: a continuous spectrum of the same disease?

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This editorial refers to 'A prospective study on cardiovascular events after acute pulmonary embolism'† by C. Becattini *et al.*, on page 77

Over 150 years ago, Virchow[1] first postulated that a triad of conditions predispose to thrombus formation, these three factors being abnormalities in the vessel wall, blood flow, and the coagulability of blood. The first two components of Rudolf Virchow's triad were based on his meticulous necropsy observations; the third reflects Virchow's remarkable insight that is only today, 150 years later, being substantiated at a molecular level. While Virchow was referring to venous thrombosis, the same processes have been applied to arterial thrombosis. A contemporary viewpoint of Virchow's triad should consider: inflammation, endothelial dysfunction, and atherosclerosis (i.e. abnormal vessel wall), abnormalities of haemorheology and turbulence at bifurcations and stenotic regions (i.e. abnormal blood flow), and finally, abnormalities in platelet function, coagulation, fibrinolysis, and metabolic or hormonal factors (i.e. abnormal blood constituents).[1,2]

In Virchow's triad of the twenty-first century, endothelial dysfunction emerges as the most important component. The vascular endothelium influences not only the three classically interacting components of haemostasis, but also the natural sequelae of endothelial dysfunction: inflammation and tissue repair. Two principal modes of endothelial behaviour may be differentiated, which are best defined as an anti- and a pro-thrombotic state. The vascular endothelial cell surface is possibly the major site of control of these coagulant and anticoagulant interactions.[3] Under physiological conditions, endothelium mediates vascular vasodilatation, prevents platelet adhesion and activation, blocks thrombin formation, and mitigates fibrin deposition through several pathways. Adhesion and transmigration of inflammatory leukocytes are attenuated and oxygen radicals are efficiently scavenged.[3] In the elderly, even under physiological conditions, all these factors are significantly affected. Several studies have shown vessel wall alterations, a decrease in anti-thrombin fibrinogen, factors V and VIII, plasminogen activator inhibitor, thrombin, thrombin-activatable fibrinolysis inhibitor generation, and an increase in the viscosity of blood and plasma. These significant age-related changes in coagulation and fibrinolysis may also coincide with co-morbidity and immobility in the patient.[4]

Although classical primary and secondary haemostasis only compromises the sequential formation of the 'white' and 'red' thrombus (see below), there is growing awareness that haemostasis is intimately coupled to fibrinolytic processes, inflammatory reactions, and the initiation of angiogenesis and wound healing.[3] In addition, scientific development over the last 10 years indicates that the properties of the endothelium may even govern the physiological balance of haemostasis/fibrinolysis and that endothelial derangement can account for numerous pathophysiological disturbances of primary and secondary haemostasis, fibrinolysis, and tissue repair.[3]

Venous thrombosis has been traditionally associated with red blood cell and fibrin-rich 'red clot', whereas arterial thrombi superimposed on atherosclerotic lesions with active inflammation are rich in platelets, giving the appearance of 'white clot'. Nevertheless, experimental and morphological studies suggest that inflammation and platelet activation also participate in venous thrombogenesis.[5] Coronary and pulmonary vascular release of interleukins-6 and -8 has been observed in some clinical situations. Such enhancements of cytokine and chemokine levels can lead to recruitment and activation of leukocytes at the vascular wall precipitating the localized formation of thrombin and fibrin. The behaviour of platelets, polymorphonuclear granulocytes, and monocytes in normal human arterial and venous blood, as documented by flow cytometry and direct microscopic

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visualization, demonstrates the occurrence of platelet–leukocyte microaggregates in whole blood.[3] Analysis of venous thrombi reveals tangled pale strands of aggregated platelets and fibrin within the mass of red blood cells. Induced venous thrombus in the presence of radiolabelled platelets shows early platelet accumulation at the 'head' of the thrombus. Then, the acquisition of platelets by the thrombi slows and the clots become 'red', being predominantly composed of fibrin and erythrocytes. Clinical studies in the setting of pulmonary embolism (PE) show increased urinary excretion of thromboxane A_2, a marker of platelet activation.[6] In 87 891 patients with deep venous thrombosis (DVT) and PE included in the Antiplatelet Trialists' Collaboration, Antithrombotic Trialists' Collaboration, and Pulmonary Embolism Prevention Trial, anti-platelet therapy (mainly aspirin in the standard and low dose) showed a reduction in rates of DVT (anti-platelet agent 25 vs. control 34%), risk of clinically fatal or non-fatal PE (control 0.61 vs. 0.46% treatment arm), and rate of fatal PE 58%, all PE 43%, and DVT 29%, respectively.[5]

In the preliminary data collected from selected individuals aged 65 years or older, statins were associated with a 22% relative risk reduction of DVT. The biological explanation of how statins may attenuate the risk of DVT includes the suppression of the pro-thrombotic and endothelial-altering properties of circulating lipids, a reduction in anti-inflammatory activity, and an anti-thrombotic effect. Collaborative research among those individuals with lipid-related disorders and arterial and venous thrombotic disease could help to clarify whether it is their lipid-reducing or anti-thrombotic properties or anti-inflammatory activity, that best explain the beneficial role of statins in the treatment of atherosclerosis and their potential to do the same for venous thromboembolism (VTE).[6]

Recently, an association between arterial and venous endothelial dysfunction with atherothrombosis and thrombosis was identified. Patients with spontaneous DVT, without symptomatic atherosclerosis, were under ultrasonography of the carotid arteries. At least one carotid plaque was detected in spontaneous DVT (47%, CI 95%, 39–50), secondary DVT (27%, CI 95%, 20–34), and control subjects (32%, CI 95%, 25–39). A multivariate analysis that accounted for risk factors for atherosclerosis confirms these findings. Although the results cannot establish a causative role, they suggest a link between arterial and venous thrombotic disorders.[7]

In this issue of the *European Heart Journal*, Becattini *et al.*,[8] present the first prospective evidence that evaluates the incidence of cardiovascular events, cardiovascular death, and death due to any cause after an episode of acute VTE. The results extend our knowledge of the outcome in patients with idiopathic PE and highlight its participation as an independent predictor of cardiovascular risk. An important result of this study was the high incidence of venous and arterial thrombosis in the 3 years after the index episode. This finding establishes the necessity to consider an effective and safe long-term secondary prevention to avoid arterial and/or venous thrombosis together with early cancer detection. After acute PE, the high incidence of cardiovascular events observed in elderly and diabetic patients suggests a systemic endothelial dysfunction state secondary to different pathways. In this study, a control group was not considered. However, as was pointed out by the authors, the results prove a higher incidence than that observed in untreated patients with similar age and risk factors for arterial thrombosis.

In the study by Becattini *et al.*,[8] cardiovascular adverse events were more common and the major cause of mortality in the setting of idiopathic PE. These data provide new evidence to consider a link between venous and arterial thrombosis. Although considerable progress has been made in the diagnosis, stratification, and treatment of these thrombotic disorders, many questions remain concerning their pathogenesis and several points of coincidence have been identified. In patients with VTE and unstable coronary disease no risk factors are recognized in at least 30%. In addition, inherited or acquired anti-thrombin III, protein C and S deficiency, old age, arterial occlusive disease, hyperlipidaemia, hypertension, cigarette smoking, obesity, diabetes, stroke, hyperhomocysteinaemia, factor V Leyden, and lupus anticoagulant are potential risk factors for both atherothrombosis and venous thrombosis.[7,9,10]

Current and future trials designed to explore the link between endothelial dysfunction, venous and arterial thrombosis, the clinical possibility of simultaneous thrombosis (thrombotic crisis) in the acute phase or at follow-up, and the possibility of considering venous and arterial thrombosis as a continuous spectrum, are required. Considering the lack of existing knowledge in the field, we have a long way ahead.

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