

Endothelium, venous thromboembolism and ischaemic cardiovascular events

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Summary

The association between venous thromboembolism and arterial thrombosis has emerged as consistent clinical observation in the last few years. While several experimental, epidemiological and pharmacologic studies support this association, the initial pathophysiological mechanism linking these two clinical conditions remains to be established. This review discusses the pathophysiological bases and a number of ex-

perimental and clinical observations suggesting that the common link between venous thromboembolism and arterial thrombosis is represented by a dysfunctional endothelium.

Keywords

Arterial thrombosis, atherothrombosis, venous thrombosis, endothelial cells, nitric oxide/NO

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The association between venous and arterial thrombosis

The association between venous thromboembolism (VTE) and arterial cardiovascular events has raised great interest in the last few years. The involvement of the arterial tree in patients with a previous venous thromboembolic event has been confirmed by experimental studies using carotid ultrasonography, by retrospective studies, and by prospective epidemiological investigations (1–3). In addition, preliminary retrospective observations suggesting that drugs able to prevent arterial cardiovascular events, such as statins, may also be effective in reducing the risk of VTE (4), have recently been confirmed by the first, large prospective randomised trial in this field showing that rosuvastatin prevents symptomatic VTE in apparently healthy subjects with normal low-density lipoprotein (LDL)-cholesterol and an elevated hsCRP (high-sensitivity C-reactive protein) (5). Furthermore, the increased incidence of VTE in patients with risk factors for arterial cardiovascular events points too to a common pathogenesis (6). Indeed, a number of studies, with different design and in various clinical settings, have shown an increased risk of VTE associated with most of the classic or novel risk factor for ischaemic cardiovascular disease (7–22) (► Table 1).

In the classical Virchow's triad on the abnormalities associated with thrombus formation, hypercoagulability and blood stasis have long been considered as mainly involved in the pathogenesis of venous thrombosis, while vascular damage has been considered to be involved mainly in arterial thrombosis (23). Indeed, a damage

to the arterial wall (i.e. the rupture of an atheroma) is the starting event of every atherothrombotic cardiovascular accident, but is also a crucial component of VTE complicating surgery. Besides mechanical trauma with loss of endothelium, also different forms of injury, leading to a dysfunction of the endothelium and consequently to the loss of its antithrombotic properties, may represent a trigger to thrombotic deposition. A pathogenic role of endothelial dysfunction has been definitely shown for arterial thrombosis (24), but it may also play a role in triggering VTE. Evidence for a role of an endothelial derangement in the pathogenesis of VTE is starting to accrue.

Endothelial dysfunction and thrombosis

The endothelium, a thin monolayer of cells covering the inside of both arteries and veins, has emerged as one of the pivotal regulators of hemostasis through its ability to express anticoagulant and vasodilatory molecules in health conditions and, in disease conditions, to release vasoconstrictors and to express procoagulant and cell adhesion molecules and cytokines. Under normal conditions endothelial cells exert a vasodilatory, antiplatelet and local fibrinolytic tone that prevents platelet adhesion, leukocyte attachment, as well as blood coagulation. A non-thrombogenic endothelial surface is maintained through a number of mechanisms, including the production of thrombomodulin (TM), an activator of anticoagulant protein C, the expression of heparan and dermatan

Table 1: Studies showing an increased risk of VTE in conditions associated with ischaemic cardiovascular events.

Condition	Study design	Study population	Findings	Reference
Hypertension	prospective 16 years follow-up	112,822 women Nurses' Health Study	Increased risk of PE (RR=1.9)	7
Diabetes mellitus	retrospective retrospective	Medical records of 302 patients with VTE Hospital discharge survey in 92,240,000 diabetics	Increased risk of VTE in diabetics (R=2.27)	8
			Increased risk of VTE in younger patients (RR=1.73)	9
Low HDL cholesterol	meta-analysis	5 case control and cohort studies, 895 cases and 9,841 controls	HDL lower in VTE	10
Smoking	prospective prospective	112,822 women Nurses' Health Study 57,053 men and women aged 50–64	Increased risk of PE (RR=1.9–3.3)	7
			Increased risk of VTE (HR=1.32–1.52)	11
Hypertriglyceridemia	meta-analysis	10 case control and cohort studies (1,478 cases and 30,552 controls)	Tryglycerides higher in VTE	11
Metabolic syndrome (MS)	case-control	208 VTE and 300 controls	Increased prevalence of MS in VTE (OR=1.71)	12
Elevated lipoprotein (a)	meta-analysis	6 case control studies (1,826 cases and 1,074 controls)	Increased risk of VTE (OR=1.77)	13
Family history of MI	prospective	population based, 21,330 subjects	Increased risk of VTE (HR=1.46)	14
Renal failure	prospective	community based population, 19,073 middle- and advanced-aged subjects	Increased risk of VTE (RR=2.09)	15
Microalbuminuria	Prospective, 10 years follow-up	community based, 8,592 subjects	Increased risk of VTE (HR=2.00)	16
Elevated hsCRP	prospective	population based, 10,505 subjects	Increased risk of VTE (HR=2.07)	17
Moderate hyperhomocysteinemia	prospective	264 VTE patients	Increased risk of recurrent VTE (RR=2.70)	18
Rheumatoid arthritis	large case-control	hospitalised patients	Increased risk of VTE (HR=1.99)	19
Acute infection	self-controlled case-series	20 million person-years, records from general practices	Transient increased risk of VTE (IR=2.1)	20
HIV infection	large case control	hospitalised patients	Increased risk of VTE (RR=1.43)	21
Air pollution	case control community	870 cases, 1,210 controls	Increased risk of VTE in men (OR=1.7)	22

RR, relative risk; OR, odds ratio; HR, hazard ratio; R, standardised morbidity ratio; IR, incidence ratio; PE, pulmonary embolism.

sulphate, which accelerate the thrombin-inhibitory activity of antithrombin III and of heparin cofactor II, the constitutive expression of tissue factor pathway inhibitor (TFPI), an inhibitor of tissue factor, and the local production of tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), the main effectors of physiologic fibrinolysis. Crucial to many of the antithrombotic activities of endothelium are the synthesis of prostacyclin (PGI₂) and of nitric oxide (NO).

NO is a powerful vasodilatory agent, but is also a strong antiplatelet substance, an inhibitor of leukocyte adhesion and activation and a suppressor of smooth muscle cell proliferation (25). PGI₂ is a vasodilator, an inhibitor of platelet activation and a suppressor of leukocyte adhesion and activation (25). Noxious stimuli, either physical (e.g. trauma) or functional (e.g. sepsis), provoking a disturbance to the endothelial monolayer, turn the endothelium into

a prothrombotic and proinflammatory surface favouring platelet and leukocyte deposition, local blood clotting activation and smooth muscle cell proliferation. In particular, upon activation, endothelial cells respond with an increased surface expression of cell adhesion molecules (such as P- or E-selectin, ICAM-1 or VCAM-1) that promote the adhesion and activation of leukocytes, an event that initiates and amplifies inflammation and contributes to thrombosis. Activated leukocytes, in particular monocytes, express tissue factor (TF), a strong trigger of blood clotting (► Fig. 1).

Endothelial dysfunction has been conclusively shown to be an early event in the progression of atherothrombosis and to have a predictive value for future ischaemic cardiovascular events (24, 26).

In the context of arterial ischaemic cardiovascular disease, endothelial dysfunction, and in particular a reduction of the biosyn-

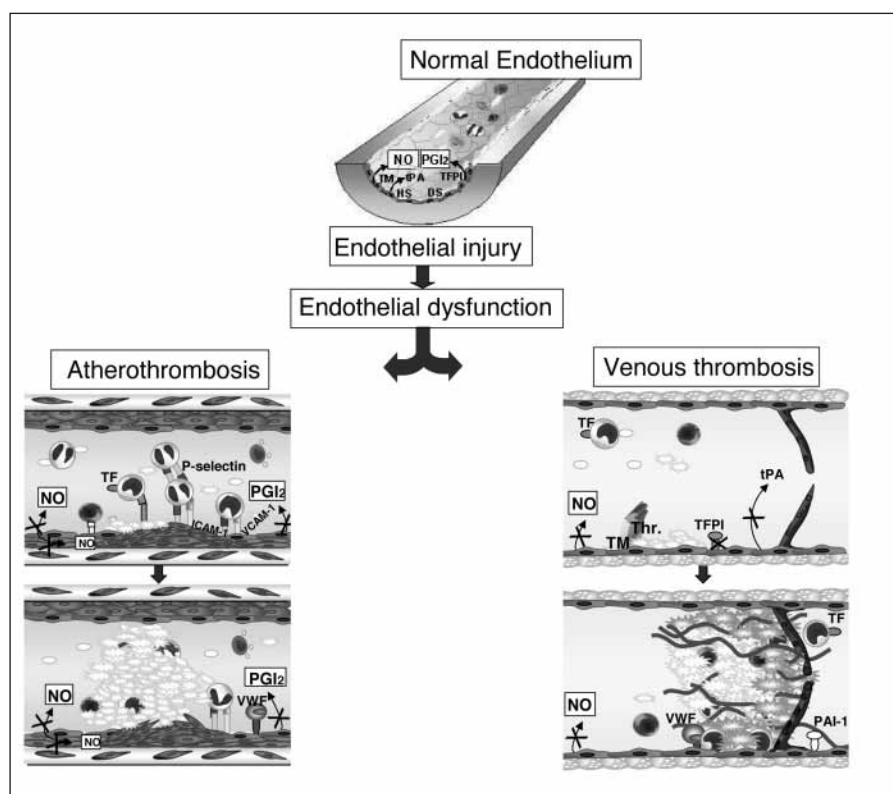


Figure 1: Schematic representation of the role that endothelial dysfunction may have in the development and complications of arterial atherothrombosis (left) and of venous thrombosis (right). DS, dermatan sulphate; HS, heparan sulphate; ICAM-1, intercellular adhesion molecule-1; NO, nitric oxide; PAI-1, plasminogen activator inhibitor -1; PGI₂, prostacyclin; P-sel, P-selectin; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin; tPA, tissue plasminogen activator; VCAM-1, vascular cell adhesion molecule-1; VWF, von Willebrand factor.

Table 2: Conditions associated with arterial endothelial dysfunction in which an impaired function of venous endothelium has been shown.

Clinical condition	Method of study of venous endothelial function	References
Diabetes	Acetylcholine-induced relaxation of saphenous vein rings	30
Elevated hsCRP levels	Acetylcholine-induced relaxation of saphenous vein rings	31
Arterial hypertension	Dorsal hand vein compliance technique	36
Smoking	Dorsal hand vein compliance technique	37
Heart failure	Dorsal hand vein compliance technique	38
Renal failure	Dorsal hand vein compliance technique	39
Acute infections	Dorsal hand vein compliance technique	40
Coronary artery disease	Relaxation of saphenous vein rings by resveratrol	41
Hyperlipidemia	Relaxation of saphenous vein rings to calcium ionophores	42

thesis or of the biologic activity of NO, has been identified as a fundamental component of the pathophysiology of atherosclerosis and shown to be associated with risk factors such as diabetes, hypercholesterolaemia, hyperhomocysteinaemia, hypertension and smoking (24, 26). Endothelial dysfunction is associated with an increased oxidative stress and with inflammatory changes that play a role in the development of atherosclerosis in the early stages, while later they increase the vulnerability of fully developed plaques facilitating their rupture (26).

In the context of VTE, a dysfunctional venous endothelium may express increased amounts of von Willebrand factor (vWF), tissue factor (TF), plasminogen activator inhibitor (PAI)-1, and factor V, all of which may promote blood clotting and participate in the development of a thrombus (27). In particular, immunohistochemistry of ilio-femoral veins out autopsy of patients dying of VTE revealed the constant presence of VWF in mural thrombi, and an anti-VWF antibody reduced venous thrombosis in a rabbit VTE model (28). A dysfunctional venous endothelium also favours the interactions with circulating tissue factor-bearing microparticles, further triggering localised blood clotting activation (29).

While many studies have assessed the dysfunction of arterial endothelium in clinically established atherothrombotic disease or in relation to the presence of classical or novel cardiovascular risk factors, only a few studies have focused on the dysfunction of venous endothelium.

Venous endothelial function can be studied in humans either by invasive methods, i.e. by assessing *ex vivo* the contraction of rings of vein tissue excised at surgery (30, 31), or by a minimally invasive method which assesses the diameter of a dorsal vein of the hand in response to pharmacologic stimuli (32). The studies so far performed using these methods show that NO plays a central role in the regulation of venous endothelial function, similarly to what it does for arterial endothelial function (33, 34). Interestingly, what emerges from these studies is that conditions associated with arterial endothelial dysfunction, like hypertension, smoking, diabetes, coronary artery disease, heart failure and renal failure, are also characterised by a dysfunction of venous endothelium (30, 31, 35–42) (► Table 2).

A number of additional clinical observations point to a common pathogenic role of endothelial dysfunction in venous and arterial thrombosis. In particular, acute reactions to infectious agents are associated with an increased risk of both arterial ischaemic events and VTE and are accompanied by both arterial and venous endothelial dysfunction (40, 43, 44); increased circulating levels of some biomarkers of endothelial dysfunction, like endothelial microparticles or P-selectin, are associated with both an enhanced risk of cardiovascular events and of VTE (45–47); recent data have shown in patients with VTE an increase of circulating fibronectin, an endothelium-released plasma factor previously shown to correlate with arterial endothelial dysfunction (48, 49); several other clinical conditions characterised by an impaired arterial endothelial function, like airpollution, chronic HIV infection, a family history of myocardial infarction, the metabolic syndrome, rheumatoid arthritis and microalbuminuria, have been reported to be associated not only with an increased risk of arterial events but also of venous thrombosis (12, 14, 16, 19, 21, 22, 50–52).

Venous and arterial thrombosis: A matter of endothelium

Based on the above considerations, it is conceivable that the common initial pathogenic event linking VTE to atherothrombosis is represented by the perturbation of endothelial function.

We have indeed recently shown that patients with spontaneous VTE, carefully selected to exclude all known cardiovascular risk factors, present endothelial dysfunction. The defect is of about the same magnitude of that observed in patients with cardiovascular risk factors who subsequently experience ischaemic events (53). The impairment of arterial endothelial function seems to be specific of patients with spontaneous VTE, in fact patients with primary antiphospholipid antibody syndrome, who also are prone to VTE, do not have endothelial dysfunction (54).

The recent JUPITER trial on the effects of rosuvastatin in a large population of apparently healthy men and women with normal LDL-cholesterol but a raised hsCRP showed beneficial effects on both arterial ischaemic cardiovascular events and VTE (5, 55). Statins are able to reverse endothelial dysfunction by mechanisms in

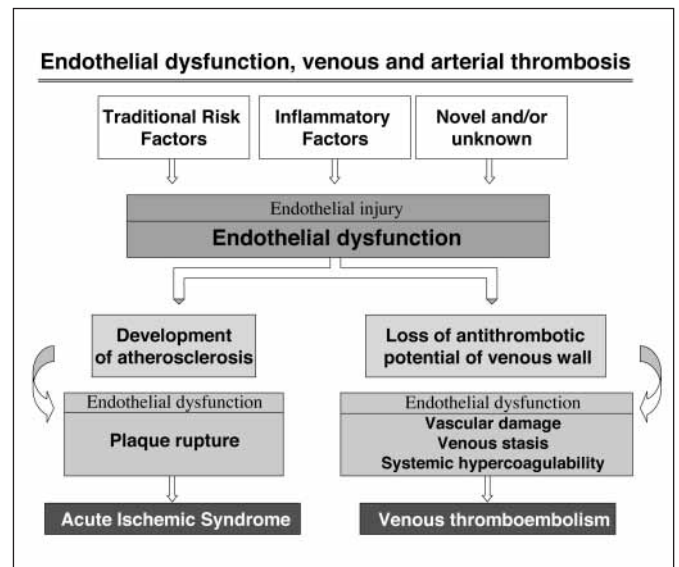


Figure 2: Common pathogenic role of endothelial dysfunction in venous and arterial thrombosis. Different forms of injury may lead to endothelial dysfunction both in arteries and veins, leading to loss of anti(athero)thrombotic properties and vascular decompensation. In turn, endothelial dysfunction is crucial in the initiation of atherosclerosis in the arterial bed, and in the loss of antithrombotic properties of the vessel wall in the venous bed. In the face of established atherosclerosis, endothelial dysfunction contributes to precipitate acute ischaemic events; in the face of dysfunctional venous endothelium, further inciting stimuli precipitate VTE.

part independent from their lipid-lowering activity (56), and this property may contribute to explain why rosuvastatin was able to prevent thrombosis in both circulatory beds.

Interestingly, in that study the rate of VTE was higher in patients with a baseline hsCRP greater than 5 mg/l (5). In a previous study, in a cohort of patients with coronary artery disease, increased hsCRP was the only independent predictor of venous endothelial dysfunction (31) and a raised hsCRP reportedly correlates with arterial endothelial dysfunction (57).

Therefore, classical risk factors for ischaemic cardiovascular events, some of the novel risk factors, and perhaps some yet unidentified pathogenic noxae, may induce a simultaneous dysfunction of the arterial and venous endothelium; in turn, endothelial dysfunction will later lead to the development of either arterial or venous thrombosis depending on concomitant inciting conditions (► Fig. 2).

Venous blood stasis, one of the conditions precipitating VTE, may produce regions of low or zero shear-stress in veins, especially at the level of venous valves (58), and shear-stress, even the low shear-stress driven by venous-type blood flow, is an essential stimulus for the production of NO by the endothelium (59, 60). Thus venous stasis, by interrupting shear-stress, may further impair one of the essential antithrombotic properties of venous endothelium, facilitating the development of thrombosis.

Future developments

The conclusive proof that venous endothelial dysfunction represents a trigger for VTE will come from studies on the predictive value of venous endothelial dysfunction for the subsequent development of new or recurrent venous thrombotic events. In addition, the prospective evaluation of the effect of drugs able to reverse arterial endothelial dysfunction on venous endothelial dysfunction is also highly warranted. Data showing that L-arginine or ascorbic acid, that reverse arterial endothelial dysfunction, also ameliorate impaired venous endothelial function are encouraging in this direction (39, 61). In case new agents ameliorating venous endothelial function emerge, it seems logic to address in future trials their role in the long-term prevention of arterial ischaemic events in addition to established therapies.

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