

Review Article

Peripheral arterial disease and Virchow's triad

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Summary

Peripheral arterial disease (PAD) is an important global healthcare problem associated with considerable morbidity and mortality. This disease is an important manifestation of atherosclerosis and the pathophysiological processes involved in its development, progression and complications are atherothrombosis and thromboembolism. Over 150 years ago, Virchow described a triad of abnormalities (abnormal blood flow, abnormal vessel wall and abnormal blood constituents) associated with

thrombus formation (thrombogenesis). An improvement in biochemical techniques has allowed quantification of various components of Virchow's triad, and as a consequence, there has been increasing interest in the measurement of such biomarkers in understanding the development and progression of PAD, as well as its symptomatic complications. This review discusses quantifiable components of Virchow's triad that have been associated with PAD and their clinical utility as risk factors for PAD.

Keywords

Arterial thrombosis, clinical studies, risk factors

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Introduction

Peripheral arterial disease (PAD), a clinical manifestation of atherosclerosis, is an important global healthcare problem. This disease encompasses a range of non-coronary arterial syndromes that are caused by the altered structure and function of arteries supplying the brain, visceral organs and the limbs (1). Most often though it is applied to disease of the latter.

PAD can be classified clinically using either the Fontaine or Rutherford classifications (Table 1) (2). Whilst the majority of patients with this disease are asymptomatic and remain reasonably stable with regards to their lower limb disease, the risk of atherothrombotic vascular complications is markedly increased in this group (3–5).

Over 150 years ago, Virchow described a triad of abnormalities (abnormal blood flow, abnormal vessel wall and abnormal blood constituents) associated with thrombus formation (thrombogenesis). Given that the underlying pathophysiological mechanisms involved in the development, progression and complications of PAD are atherogenesis and thrombogenesis, abnormalities of Virchow's triad, initially used with reference to venous thrombosis (6), has been discussed in relation to this disease (7–9). Indeed, there has been increasing interest in the components of Virchow's triad in understanding the development and progression of PAD, as well as its symptomatic complications.

Defining Virchow's triad

The original components of the triad have been updated for the 21st century – for example, *abnormal vessel wall* now relates to endothelial damage/dysfunction and structural changes within the vessel wall, whilst *abnormal blood constituents* refers to abnormalities in platelets, as well as coagulation and fibrinolytic pathways; and *abnormal flow* refers to abnormalities in haemorrhology and turbulence at bifurcations and stenotic regions (10). Improvements in biochemical techniques, notably doppler flow analysis, enzyme-linked immunosorbant assay (ELISA) and coagulation bioassays, have allowed these components of Virchow's triad to be quantified and studied in relation to their role in arterial thrombosis.

It should not be forgotten that conventional cardiovascular risk factors, including smoking, hypertension, hyperlipoproteinaemia and hyperglycaemia, also play an important role in initiating and accelerating atherogenesis (Fig. 1), also by altering components of Virchow's triad. Studies have reported that abnormalities in markers of thrombogenesis appear to be related to – and even additive to – conventional risk factors. For example, subjects with the highest tertiles of both fibrinogen and total or low-density lipoprotein (LDL) cholesterol are at greatest cardiovascular risk, compared to subjects with high cholesterol but modest fibrinogen (13). There is also mounting evidence of the prognostic value of various markers of thrombogenesis, which

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Table 1: Fontaine & Rutherford classification systems for peripheral arterial disease [2].

Fontaine		Rutherford		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate-severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischaemic rest pain	II	4	Ischaemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		IV	6	Ulceration or gangrene

suggests that they are not merely consequences of atherothrombotic diseases, but may actively contribute to the pathogenesis of vascular disease and its complications (10).

“Abnormal blood vessel wall”

Endothelial dysfunction is the earliest pathological process in atherogenesis (11) (Fig. 1). Atheroma, typically occurring at branches, bifurcations and curvatures, disrupts normal laminar blood flow, leading to turbulence and altered wall shear stress (WSS). The latter causes platelet activation and aggregation,

which enhances thrombus formation at these sites. Rupture of an atherosclerotic plaque, leads to exposure of its thrombogenic lipid core, which precipitates thrombus formation, causing vessel occlusion with resulting ischaemia (14).

With endothelial damage/dysfunction, there is a reduction in the bioavailability of vasodilators, such as nitric oxide (NO), leading to decreased endothelium-dependent vasodilatation and disruption of normal vascular homeostasis. This is characterised by a state of endothelial activation, which predisposes the endothelial micro-environment to a pro-inflammatory, hyper-

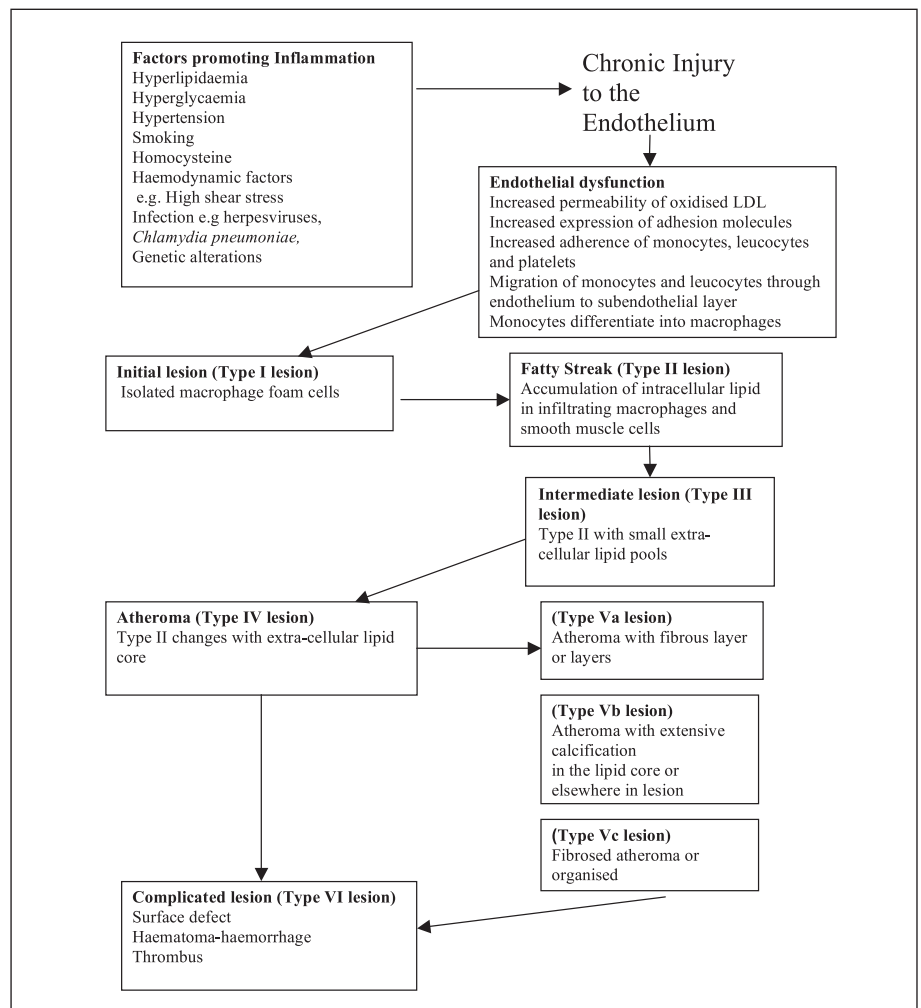


Figure 1: Stages of atherogenesis based on Ross et al. 1999 [11] and American Heart Association classification of atherosclerotic lesions [12].

coagulable or pro-thrombotic state, which promotes all stages of atherogenesis. Many of the traditional risk factors for atherosclerosis are associated with the over-production of reactive oxygen species (ROS) or increased oxidative stress (15). By reacting with NO, ROS may decrease the bioavailability of NO, thus impairing flow-mediated vasodilatation (FMD). Whilst PAD has previously been associated with a reduction in FMD (16) protocols for assessing FMD still vary among different laboratories and can be operator dependent (17, 18). This decreases the feasibility of this measurement technique as a screening tool for endothelial dysfunction in large-scale multinational epidemiological studies (19).

The *abnormal blood vessel wall* in PAD can also be demonstrated by abnormalities of levels of specific plasma markers of endothelial damage/dysfunction as well as by abnormalities in vessel structure, for example, intima-medial thickness and arterial stiffness, as described below. Examples of studies are summarised in the Supplementary Table 1 (available online at www.thrombosis-online.com).

Circulating markers of endothelial damage/dysfunction associated with PAD

(i) Von Willebrand factor (vWF)

Von Willebrand factor (vWF) is produced in the Weibel-Palade bodies of endothelial cells, α -granules of platelets and in sub-endothelial connective tissue. vWF is considered as a well-validated plasma marker for the measurement of endothelial damage (20) in atherosclerosis and its levels may be regulated by several factors, including blood flow, platelet number, thrombin, angiogenic markers and pro-inflammatory cytokines (21). vWF is also associated with the major established cardiovascular risk factors, and modification of these risk factors has been shown to reduce vWF levels (22–24). vWF is also a carrier for the coagulation factor VIII, and vWF promotes thrombus formation by mediating the adhesion of platelets to the subendothelium and to each other during haemostasis (25).

In the context of PAD, vWF appears to be related to the degree of endothelial damage in diseased lower extremity arteries (26). In PAD, vWF concentrations have been correlated with transcutaneous oxygen pressure, a marker of the severity of limb ischaemia (27). vWF has also been associated with both progression and severity of disease (27–30) and its elevated levels in patients with critical limb ischaemia have partially resolve with resolution of ischaemia (31), implying some improvement in endothelial function in these patients.

(ii) Soluble thrombomodulin (sTM)

Thrombomodulin (TM) is an anticoagulant protein that is specifically expressed on the surface of endothelial cells (32) and is released by these cells in a soluble form (sTM) following endothelial injury. sTM has been shown to be a specific marker of endothelial cell damage (33, 34). Bound TM normally enhances the thrombin-dependent activation of anticoagulant protein C as well as inhibits the pro-coagulant effects of thrombin (35). The loss of this anticoagulant from the endothelial surface results in a change towards a pro-coagulant state (36).

Correlations between TM and Fontaine stage of PAD have been previously reported (27, 36) illustrating the progressive re-

lease of TM following increasing endothelial injury that occurs as PAD progresses. sTM also rises after exercise in PAD patients and correlates with transcutaneous oxygen pressure (37). The prognostic value of sTM was initially suggested by sTM being only endothelial marker associated with a significant relative risk for re-stenosis after percutaneous transluminal angioplasty (PTA) in symptomatic PAD patients (38). However, sTM has not been conclusively associated with PAD in all studies. The most notable is the Atherosclerosis Risk in Communities (ARIC) study, which found no association between sTM and PAD in asymptomatic patients (39). These conclusions are also supported by other studies (26, 40, 41).

(iii) Circulating endothelial cells (CECs)

Circulating endothelial cells in the blood are thought to be the product of a disease process irreversibly damaging the endothelium, causing endothelial cells to slough off (42). This may leave a denuded sub-endothelium exposed to pro-coagulant factors in the blood and thus, potentiate thrombosis (43). In healthy volunteers, CEC numbers have been correlated with thrombomodulin levels (44). In disease states, CECs have been correlated with vWF levels and inversely correlated with flow mediated vasodilatation (FMD) suggesting they reflect endothelial cell dysfunction and damage (45). CECs have also been correlated with tissue factor in pathological disease states linking endothelial damage to ongoing thrombogenesis (45). Elevated CECs may also result in reduced NO release, further amplification of platelet thrombosis and potentiation of atherogenesis (46, 47).

CEC levels have been reported to be higher in PAD patients with ischaemic rest pain compared to patients with stable claudication, reflecting the irreversible endothelial damage in the more severe manifestations of PAD (48). The prognostic implications of CECs in PAD have yet to be established.

(iv) Tissue factor (TF)

Tissue factor (TF) is a cell-surface receptor for coagulation factor VIIa which is expressed on subendothelial tissue, platelets and leucocytes, and is a major initiator of thrombogenesis as part of the extrinsic pathway. TF expression is regulated by various cytokines, including tumour necrosis factor (TNF)- α and interleukin (IL)-6. Exposure of the subendothelium, either by endothelial injury or by rupture of an atherosclerotic plaque, allows TF to complex with circulating factor VIIa, which via the activation of factor X leads to the formation of thrombin and ultimately, formation of a fibrin clot. TF is elevated in prevalent PAD (49, 50) and associated with disease severity (48). TF is yet to be established conclusively as a marker of endothelial damage/dysfunction and further research is required into its prognostic value in patients with PAD.

(v) Cellular adhesion molecules (CAMs)

Cellular adhesion molecules (intracellular adhesion molecule-1 [ICAM-1] and vascular adhesion molecule-1 [VCAM-1]) are endothelial ligands for integrins expressed on leucocytes and platelets (51). These molecules facilitate platelet and leucocyte adhesion to the endothelium. Their over-expression causes increased endothelial adhesion of leucocytes and their accumulation in subendothelial regions of atheroma (52). Although con-

sidered a measurement of endothelial damage/dysfunction, CAMs are not specific to the endothelium and are expressed on a variety of other cell types. CAM expression is also up-regulated by atherogenic stimuli and their soluble levels increase in response to inflammatory cytokines and oxidised LDL (51).

The prognostic value of sICAM-1 and sVCAM-1 in PAD has not been established and there is a suggestion that their association with PAD may be race related (53). Nonetheless, elevated sVCAM-1 and sICAM-1 have both been correlated with ankle brachial pressure index, an index of PAD severity (54). In the Edinburgh Artery Study, sICAM-1 (but not sVCAM-1) was an independent predictor for the development of PAD (55, 56) and symptomatic PAD (56). There was also a significant trend between higher sICAM-1 levels and the progression of PAD over 17 years, from no disease at baseline, to moderate severity (intermittent claudication) and severe disease (i.e. critical limb ischaemia [CLI] or surgical intervention) (56). Other studies have reported raised sVCAM-1 but not sICAM-1, that correlated with the extent of peripheral atherosclerosis (41) and a higher cardiovascular event rate in symptomatic PAD subjects (57). In one study on Fontaine II-IV PAD patients, higher sVCAM-1 but not sICAM-1 levels were also seen at two weeks post percutaneous transluminal angioplasty (PTA) (58) and correlated with re-stenosis following PTA (38).

(vi) Abnormal structural indices

Various structural indices can be easily quantified in individuals using ultrasound imaging techniques, whereby abnormal measures such as carotid intima medial thickness (IMT) and arterial stiffness reflect blood vessel abnormalities.

– Intima medial thickness (IMT):

IMT measurement by ultrasonic evaluation is a well-recognised index of pre-clinical atherosclerosis (59) and a predictor of future cardiovascular events (60). IMT can be measured at a single site or several sites in the common carotid, carotid bifurcation and internal carotid arteries, but it is unclear whether generalised IMT or focal plaque formation is of more importance in determining cardiovascular risk.

Common carotid IMT has been significantly correlated with the conventional cardiovascular risk factors, such as smoking, diabetes mellitus and LDL cholesterol (61, 62). Only C-reactive protein (CRP) and fibrinogen seem to be unequivocally related to IMT (63). Recent studies in dyslipidaemic and diabetic patients have reported that a combination of carotid IMT and Framingham Risk Score improved the prediction of subsequent cardiovascular events, better than using the Framingham Risk Score alone (64, 65).

IMT is associated with both asymptomatic and symptomatic PAD (59, 66, 67). In PAD subjects, high common carotid IMT is significantly associated with a risk of subsequent cardiovascular events, independent of conventional risk factors (67). However, it is not evident from the published literature whether carotid IMT alone contributes to risk prediction above what is provided by traditional cardiovascular risk factors nor the effect of routine IMT measurements on patient outcomes.

– Arterial stiffness:

The elastic property of arteries varies along the arterial tree; proximal arteries being more elastic than the stiffer distal ar-

teries. Normally, the systolic pressure wave is transmitted forwards along the more elastic proximal arteries, with the stiffer distal vessels causing resistance to flow and wave reflections (68). Branches and bifurcations along the vessel also contribute to reflected pressure waves. With age, and atherosclerosis-associated accumulation of arterial calcium and elastin, there is decreased elasticity and compliance of proximal arteries (69), although arterial stiffening with age does not appear to be dependent upon the presence of atherosclerotic disease (70). Arterial stiffness may therefore be considered both an index of endothelial dysfunction and an index of abnormal blood flow.

Indices of arterial stiffness include pulse wave velocity and aortic augmentation index (AIx). Arterial stiffness has been reported to be an independent predictor of cardiovascular mortality (71, 72). Increased arterial stiffness and/or pulse wave reflections are both associated with the conventional cardiovascular risk factors such as obesity, smoking, hypertension, hypercholesterolaemia and diabetes mellitus, along with novel risk factors, including hyperhomocysteinaemia and raised CRP (68).

The elastic properties of large and small arteries are reduced in PAD patients compared to controls (73, 74). The arterial pulse wave form is also altered in these patients (75) suggesting altered vascular tone in these patients. Arterial stiffness may also be improved by aerobic exercise, possibly due to improved endothelial function or by anti-inflammatory and antithrombotic effects (76). AIx is reported as being independently associated with lower ABPI (77) along with a reduced walking distance in subjects with PAD (78). As with other novel risk factors, arterial stiffness has not yet shown any additional benefit over and above traditional risk factors in determining prognosis in patients with PAD.

“Abnormalities of blood constituents”

Many blood constituents have been implicated in PAD development, progression and prognosis along with acute thrombotic complications. Examples of studies reporting associations between these factors and PAD can be found in Supplementary Table 1 (available online at www.thrombosis-online.com).

Platelets

Important thrombogenic platelet components include α -granule constituents (vWF, fibrinogen, factor V, thrombospondin, β -thromboglobulin) and an adhesion molecule expressed on α -granule membranes, P-selectin. The latter is transferred to the plasma membrane through membrane fusion after platelet stimulation and activation and hence, has been used as an index of platelet activation (79). Cardiovascular risk factors, including smoking, dyslipidaemia, hypertension and diabetes mellitus all cause chronic endothelial cell injury, thus stimulating CAM expression and resulting in increased platelet adhesion to the endothelium (Fig. 2). Acute endothelial injury or rupture of a complicated plaque leads to exposure of the sub-endothelium and binding of platelets via sub-endothelial bound vWF thus potentiating thrombosis. Altered shear stress states also induce platelet activation, aggregation and microparticle formation (80–82), further potentiating thrombogenesis.

Adverse indicators of platelet function in PAD have been reported, including increased β -thromboglobulin (83), increased platelet aggregation (84, 85), increased fibrinogen binding (30),

increased platelet P-selectin and soluble P-selectin (86, 87), and an increase in platelet microparticles (88). Platelet and soluble P-selectin levels also independently predict disease severity in PAD (88). In another study, symptomatic subjects undergoing PTA demonstrated a correlation between soluble P-selectin and re-stenosis at follow-up (38).

Fibrinogen

Fibrinogen is an important component of the coagulation system, as a pre-cursor of fibrin, and a major determinant of plasma viscosity. Fibrinogen plays an important role in platelet aggregation and mediates the adhesion of platelets to the endothelium via binding with ICAM-1 on its surface (89). Fibrinogen also plays a major role in inflammation by facilitating a chemotactic response via increased leucocyte adherence to the endothelium (89). High fibrinogen levels have been associated with smoking, diabetes, LDL cholesterol and obesity, and levels are inversely correlated with high-density lipoprotein (HDL) cholesterol, alcohol use and physical activity (89).

Fibrinogen has long been recognised as having prognostic implications for cardiovascular mortality. A recent meta-analysis reported moderately strong associations between fibrinogen levels and the risk of coronary heart disease, stroke and other vascular (and non-vascular) mortality (90). The mechanism(s) for this relationship are unknown but hyperfibrinogenaemia increases platelet aggregation, as well as providing a ready source of fibrin. Increased fibrinogen levels favour a higher rate of fibrin formation, thus leading to a tighter gel structure that most likely is more thrombogenic than structures formed in lower fibrinogen levels (91).

Hyperfibrinogenaemia has been associated with prevalent PAD, disease severity and with increased mortality risk in this disease (86, 92–95). Raised pre-interventional levels of fibrinogen are related to a greater risk of re-stenosis following PTA (96, 97), with patency rates being significantly associated with fibrinogen levels, independent of other factors (98). Importantly, the 17-year follow-up to the Edinburgh Artery Study reported strong and independent associations between fibrinogen and incident PAD (56). Another recent study reported fibrinogen to be an independent predictor of all-cause mortality risk in PAD (99). However, fibrinogen may not improve the predictive ability over and above traditional cardiovascular risk factors and ABPI for PAD (56, 99). Also, despite the correlations between fibrinogen and cardiovascular risk, there is no convincing evidence to show that lowering plasma fibrinogen levels will result in a significant reduction in risk.

Fibrin D-dimer

Fibrin D-dimer is a measurable breakdown product of cross-linked fibrin, and marks ongoing intravascular thrombogenesis and abnormal fibrin turnover. It is a specific marker of fibrinolysis but also reflects the severity of a hypercoagulable state (100). D-dimer has been reported to induce the synthesis and release of inflammatory cytokines (101) and has a significant association with cardiovascular diseases and risk factors (102, 103). With reference to PAD, high D-dimer levels have been associated with disease severity (28, 56) and functional impairment (101) but not significantly associated with the development of (56) or progres-

sion of disease (104, 105). In claudicants, however, raised D-dimer levels do predict fatal and non-fatal coronary events (106). Further research is required to determine whether lowering D-dimer levels has any effect on cardiovascular outcomes.

Fibrinolysis

The fibrinolytic system consists of the circulating pro-enzyme plasminogen, which on activation to produce plasmin by tissue plasminogen activator (tPA) and urokinase, promotes fibrinolysis (107). tPA a serine protease, normally found on the endothelial cell surface, and is secreted following vascular injury. Fibrinolysis is inhibited by the pro-coagulant factor plasminogen activator inhibitor (PAI)-1, a serine protease inhibitor (108) and hence, this is a marker of impaired fibrinolysis and atherothrombosis. PAI-1 is synthesised by a number of different cells, but it is endothelial derived PAI-1 that is primarily responsible for its levels measured in the plasma (109, 110).

Endothelial dysfunction results in activation of endothelial cells, generating an imbalance between tPA and PAI-1, which creates a pro-coagulant surface. Although these factors are found at the endothelial surface, they are usually measured as markers of fibrinolysis and not as indices of endothelial dysfunction per se (111).

Elevated plasma PAI-1 decreases fibrinolysis and enhances thrombosis, and antibodies directed against PAI-1 prevent the progression of thrombosis (108). PAI-1 has also been detected in the intima of atheroma, thus supporting its role in the pathogenesis of this condition (108). Plasma PAI-1 is influenced by a number of hormones and cytokines (112) and has been associated with hyperglycaemia, hypertriglyceridaemia and insulin resistance (107, 113), which are all components of the metabolic syndrome. Both tPA and PAI-1 have previously been associated with prevalent PAD and severity of disease and PAI-1 activity has been correlated with re-stenosis after PTA (97, 114). Although tPA was not associated with incident PAD in the Edinburgh Artery Study, elevated tPA levels have been associated with the presence of and increasing severity of PAD (56).

Lipoprotein (a)

Lipoprotein(a) (Lp(a)) is a large protein molecule that consists of two components: an LDL-like particle and an attached apolipoprotein(a) (apo(a)) (115). Due to its structural similarity to plasminogen, Lp(a) inhibits plasminogen binding to fibrin and endothelial cells by inhibiting tPA (116), and therefore fibrinolysis (and promoting thrombosis) (117, 118). Lp(a) accumulates in atheroma and may impair endothelial function and induce smooth muscle proliferation (107)]. Little research into the prognostic benefit of Lp(a) in PAD exists. Lp(a) has been reported to be an independent risk factor for PAD (119) as well as severity of disease (119, 120).

Inflammatory factors

Inflammation plays a major role in all stages of atherogenesis (11). Inflammation occurs in response to a variety of stimuli and is also associated with many traditional cardiovascular risk factors, including dyslipidaemia, hypertension, diabetes mellitus, obesity and infection (11, 121) (Fig. 2).

Of the wide range of inflammatory indices, IL-6 and CRP have probably been most investigated. IL-6 is a pro-inflammatory cytokine that induces a prothrombotic state by increasing expression of fibrinogen, TF, factor VIII and vWF (56). IL-6 also activates endothelial cells and their adhesiveness by up-regulating E-selectin, ICAM-1 and VCAM-1, thus leading to increased leucocyte-endothelial binding and increasing platelet production (56). CRP is a circulating acute phase protein synthesised by the liver, and its release is stimulated by IL-6 and other pro-inflammatory cytokines along with promoting monocyte chemotaxis and TF expression (113).

CRP has pro-atherogenic effects on all cellular components of the endothelium. It inhibits endothelial cell NO synthase resulting in reduced bioavailability of NO and decreased endothelial dependent vasodilatation. CRP increases expression of ICAM-1 and VCAM-1, whose effects are discussed above, and increases production of PAI-1, which inhibits fibrinolysis (122, 123).

IL-6 and CRP are associated with PAD development, progression and severity of disease (86, 113, 124–127). Elevated CRP levels are also associated with functional impairment (101) and increased thrombotic complications in symptomatic PAD (128). In the Edinburgh Artery Study, CRP was one of the few markers significantly associated with PAD after 17 years follow-up, even after adjusting for cardiovascular risk factors (56). As with fibrinogen, Lp(a) and haematocrit, CRP provided very little prognostic information for incident PAD to that obtained by cardiovascular risk factors and ABPI (56). IL-6 only showed weak associations and were attenuated when these risk factors were accounted for (56).

Homocysteine

Homocysteine is a highly reactive, sulphur containing amino acid formed as a by-product of methionine metabolism. Adverse effects of homocysteine include vascular endothelial injury (129), increased adhesion molecule expression (130) smooth muscle proliferation, and oxidation of LDL, which contributes to a prothrombotic vascular endothelial microenvironment (131, 132).

Homocysteine has been associated with an increased risk of PAD and lower ABPI measurements in a previous meta-analysis (133) but this finding has been disputed (134). In the Multi-Ethnic Study of Atherosclerosis, homocysteine was significantly associated with PAD, even after adjustment for traditional risk factors (125). Elevated homocysteine levels have also been associated with lower patency rates following revascularisation procedures and lower mean amputation-free survival (135). As homocysteine levels increase following an acute thrombotic event, it is difficult to know whether increased thrombosis is due to elevated homocysteine or vice versa. This may be the reason why a link between elevated homocysteine and PAD has not been conclusively confirmed.

“Abnormal blood flow”

Quantification of the flow properties of blood can be made by measuring haemorrhological indices, and by measuring wall shear stress (see Supplementary Table 1 available online at www.thrombosis-online.com).

Haemorrhological indices that have been investigated previously in PAD include blood viscosity (influenced by erythrocytes, leucocytes and platelets) and plasma viscosity and its determinants, including fibrinogen, vWF and lipoproteins (56, 90, 136). Haematocrit, blood viscosity, plasma viscosity and fibrinogen have each been reported to be significantly related to the severity of PAD; for example, blood viscosity and fibrinogen remained significantly associated with ABPI on multiple regression analysis (136). Blood viscosity and its determinants are also correlated with common carotid artery IMT, in a linear fashion (137). In the Edinburgh Artery Study, all rheological markers were significantly increased at baseline in all subjects who developed PAD over 17 years follow-up (56). Plasma viscosity is an independent risk factor for progression of atherosclerosis in claudicants (138). The effect of haemorrhological indices on PAD in the Edinburgh Artery Study was modest and was considerably reduced after adjusting for traditional risk factors (56). These indices alone are therefore unlikely to offer additional clinical value in PAD risk prediction.

Wall Shear Stress (WSS)

WSS is the force that contrasts friction applied to the blood by the vascular wall (139). Its two components are shear rate (the rate at which adjacent layers of fluid move with respect to each other) and blood viscosity (the capacity of the blood to offer resistance to flow) (140). Important determinants of WSS are geometric factors, such as bifurcations, tortuosity and aneurysms, as well as various biological and systemic factors, such as systolic blood pressure and NO (140, 141).

Both the synthesis and release of various prothrombotic and pro-inflammatory mediators and the secretion and release of endothelial defences (e.g. NO and prostacyclin) are shear-dependent (9). Specific arterial sites, such as branches, bifurcations and curvatures cause specific alterations in the flow of blood, resulting in decreased WSS and increased turbulence (11). Decreased WSS is associated with decreased NO synthase production, reduced endothelial cell repair, increased ROS, increased endothelial cell permeability to LDL, increased leucocyte adhesion (via ICAM-1 and VCAM-1), and an increase in apoptosis and smooth muscle proliferation (142–145). The impaired normal laminar shear stress that occurs at bifurcations and branches may reduce local production of endothelial-derived NO leading to less endogenous atheroprotective mechanisms at these sites (121). These sites are therefore more susceptible to atherosclerosis.

WSS is associated with traditional risk factors, but only smoking, age and triglycerides remained significantly associated with this on multivariate analysis (146). An inverse relationship exists between WSS and carotid wall thickness has been reported (147). The IMT in undiseased abdominal aorta necropsy specimens from young adults correlated significantly with mean, minimum and oscillatory WSS (148–150), suggesting a role of this marker even in the early stages of atherogenesis. Common carotid artery WSS is a local risk factor for PAD and is reduced in patients with symptomatic disease (139, 146) and aneurysms (146).

Conclusion

The pathophysiological processes involved in PAD and its symptomatic manifestations are atherogenesis and thrombogenesis. There is evidence that abnormalities in the three components of Virchow's Triad are related to the severity and prognosis of PAD.

Subjects afflicted with this common disease have a high morbidity and mortality from atherothrombotic events. This may partly be explained by the ongoing endothelial and enhanced coagulation activation that occurs in these subjects causing a hypercoagulable or pro-thrombotic state. Attention to this state may possibly provide answers to the future management of this condition.

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