von Willebrand factor: a marker of endothelial dysfunction in vascular disorders?

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Abstract

The vascular endothelium is involved in the production of many important substances which are involved in cardiovascular pathophysiology. One such substance which is synthesised by, and stored in, endothelial cells is von Willebrand factor (vWF). When released, vWF appears to mediate platelet aggregation and adhesion. Numerous clinical and experimental reports suggest that high vWF levels reflect damage to the endothelium or endothelial dysfunction. The close association between vWF and the processes of thrombus formation (thrombogenesis) or atherogenesis also suggests that high vWF levels may be a useful indirect indicator of atherosclerosis and/or thrombosis. The availability of a useful marker of endothelial dysfunction may have potential clinical value. The measurement of such a marker can perhaps be a non-invasive way of assisting in clinical diagnosis or as an indicator of disease progression. High vWF levels have also been shown to have prognostic value in patients with ischaemic heart disease, peripheral vascular disease and inflammatory vascular disease. However, there is limited information that increased vWF is actually causal in the progression of vascular disease and that measures aimed at reducing vWF levels will be beneficial. In addition, interpretation of raised plasma vWF levels is complicated by the fact that vWF may be an acute phase reactant. Further research is indicated to explore the predictive value of this marker in population studies and, perhaps, therapeutic approaches in (and the value of) modulating vWF levels or function.

Keywords: von Willebrand factor vWF; Thrombogenesis; Atherogenesis; Endothelium

1. Introduction

It has been recognised for over 150 years that abnormalities in blood flow, vessel wall and blood components may contribute towards thrombosis (Virchow’s triad) [1]. This simplified view is now modified by the recognition that the process of thrombus formation (thrombogenesis) requires complex interactions involving injury to the vascular endothelium, platelet adherence, aggregation and release, and clotting factor activation; this process eventually leads to thrombin generation and fibrin formation.

Under physiological conditions, the vascular endothelium produces many substances which are closely associated with haemostasis, fibrinolysis, the synthesis of growth factors, and the regulation of vessel tone and permeability. One such substance that is synthesised by, and stored in, endothelial cells is von Willebrand factor (vWF). As vWF release is increased when endothelial cells are damaged, vWF levels have been proposed as a possible indicator of endothelial dysfunction [2–4]. The presence of endothelial disturbance is pertinent as this may result in changes in the ability of the cell to participate adequately in both coagulation and fibrinolysis, thus predisposing to thrombus formation and atherosclerosis [5]. The availability of a useful index of endothelial dysfunction may therefore have potential value, as measurement of such a marker can be a non-invasive way of assisting in diagnosis, an indicator of disease progression and prognosis.

The known association between vWF, thrombogenesis and atherosclerotic vascular disease also suggests that high concentrations of vWF may be an indirect indicator of atherosclerosis and/or thrombosis. vWF is also known to have an important function in platelet aggregation and...
adhesion [2]. However, vWF is a sensitive marker and levels can be influenced by many pathological conditions, including the acute phase response [6].

2. Biochemistry and pathophysiology

vWF is a multimeric glycoprotein which is synthesised exclusively in endothelial cells and megakaryocytes. It has two functions: Firstly, this glycoprotein carries factor VIII in the circulation and is required for factor VIII stability in the plasma. By serving as the carrier for factor VIII, vWF may also coordinate formation of the fibrin (and platelet)-rich thrombus at the site of endothelial cell injury. Secondary, this glycoprotein may mediate initial platelet adhesion to the subendothelium by linking to specific platelet membrane receptors (glycoprotein Ib-IX complex) and to constituents of subendothelial connective tissue. This is pertinent as damage to the vascular endothelium, perhaps secondary to hypertension, hyperlipidaemia or smoking, results in platelet aggregation and adhesion at the site of injury, and the activation of the coagulation cascade [7,8]. Through multiple functional domains, each vWF subunit has binding sites for collagen, heparin, glycoprotein (GP) Ib, GPIIb/IIIa and factor VIII.

The synthesis of vWF is complex and multiple steps are involved. Different molecular-weight multimers of vWF exist, with the high-molecular-weight multimers found in platelets and endothelial cells, which also have a higher affinity for subendothelial cell matrix binding (especially to collagen) than do the smaller vWF multimeric species [9]. This difference suggests that since the vWF multimers produced and secreted by endothelial cells in vitro and in vivo includes ultra-large vWF forms, the structure or type of circulating vWF may eventually become more important markers of endothelial cell injury, dysfunction or stimulation than absolute levels of plasma vWF antigen; present evidence is however limited.

The secretion of vWF is via constitutive and regulated pathways (Fig. 1), and the half-life of circulating vWF is 18 hours [10]. Constitutively secreted vWF is found in the basement membrane and free in the plasma. An additional pool is present in the storage granules of platelets and endothelial cells, which can be released in response to vascular injury. In cultured endothelial cells, 95% of synthesized vWF is secreted constitutively whilst the remaining is packaged in the storage granules, termed ‘Weibel-Palade bodies’, which are analogous to the α granules seen in platelets [11]. The vWF multimers are thought to be represented by tubular structures, which are seen inside the Weibel-Palade bodies on electron microscopy; these are the large, high-molecular-weight vWF multimers that are most effective in mediating platelet binding [11,12].

Most of plasma vWF is derived from endothelial cells rather than from platelets under normal circumstances, suggesting that vWF is a good marker of endothelial dysfunction [13,14]. However, it is not clear if this also holds for every pathological situation. For example, activated platelets (and perhaps bone marrow megakaryocytes) may occasionally contribute more to the circulating pool of vWF in certain thrombotic disorders, potentially making plasma vWF a less reliable index of endothelial dysfunction under these conditions [9,11]. Platelet vWF also tends to remain bound to the platelet surface after release from α granules. In vivo, the release (rather than synthesis) of vWF from storage pools is stimulated by the administration of adrenaline, vasopressin (or its analogue, DDAVP or 1-desamino-8-D-arginine vasopressin) and nicotinic acid, resulting in an increase in plasma vWF levels. In experimental situations, vWF release from storage granules can be stimulated by thrombin, fibrin, histamine and complement proteins C5a-9 [11]. As thrombin and fibrin are found at sites of vascular injury or damage, and histamine release and complement activation occur at sites of inflammation or injury, the release of the large vWF multimers from storage granules (rather than the constitutively secreted pool) results in a rapid response to vascular injury and endothelial damage [12].

The critical role of vWF in coagulation is evident from the profound bleeding disorder that results from vWF deficiency (von Willebrand’s disease) [15]. The system for the diagnosis and classification of von Willebrand’s disease is complex, with more than 20 distinct variants described [15]. Such vWF deficiency results in defective platelet adhesion and a secondary deficiency of factor VIII, both causing abnormal haemostasis; this may lead to less thrombogenesis and atherogenesis. In experimental work, for example, pigs with von Willebrand’s disease have been shown to be protected from spontaneous and diet-induced aortic atherosclerosis and platelet thrombosis [16,17]. In man, the situation is unproven as patients with von Willebrand’s disease are often treated with vWF-rich cryoprecipitate and/or DDAVP to raise vWF levels, thus making it difficult to test this hypothesis. Some evidence is however provided by studies showing a lower-than-expected incidence of ischaemic heart disease in haemophiliac patients (who have a deficiency of factor VIII coagulant activity with normal levels of vWF) [18]. Transplantation of bone

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**Fig. 1. Synthesis and fate of vWF.** A = constitutive secretion to the plasma; B = constitutive secretion to the subendothelium; C = regulated pathway for storage in the Weibel-Palade body; D = controlled exocytosis of Weibel-Palade body.
marrow from a subject with von Willebrand’s disease into a haemostatically normal patient also did not influence vWF levels [19].

3. von Willebrand factor and platelet adhesion

The ‘binding’ or adhesion of platelets to the vessel wall, which is mediated by vWF at sites of vascular injury, appears to be one of the earliest events triggering formation of the platelet plug in thrombus formation. Circulating vWF does not bind to resting platelets in normal haemostasis. When the subendothelial matrix of the blood vessel wall is exposed, vWF binding to these matrix components promotes platelet aggregation and formation of a platelet plug [9,11]. In vitro, the shear rate is another influencing factor, and at high shear rates (similar to that seen in the microvasculature), vWF becomes essential for platelet binding [9,20].

Platelets adhere to vWF through glycoprotein IIb/IIIa receptors, which are usually available for binding only after platelet activation [20,21]. Glycoprotein IIb/IIIa is a member of the integrin family of adhesive proteins. This binding is dependent upon multimeric size with high-molecular-weight vWF having a higher affinity for the receptors than the low-molecular-weight vWF forms [22]. Modulation of this glycoprotein IIb/IIIa receptor binding by anti-glycoprotein IIb/IIIa receptor antibodies have shown clinical application in preventing restenosis after angioplasty [23], and in initial studies in patients with unstable angina and myocardial infarction [24].

However, despite the close relationship between vWF and platelets, established markers of platelet activation, such as β-thromboglobulin, do not correlate with levels of vWF [25]. In addition, aspirin, which is an inhibitor of platelet activity, does reduce β-thromboglobulin levels, but does not have any affect on vWF levels [26]. These observations support the hypothesis that plasma vWF does not arise from platelets.

4. vWF and ischaemic heart disease

There is a well-established association between vWF levels and ischaemic heart disease, suggesting a role for endothelial dysfunction in the pathogenesis of coronary artery disease. For example, increased concentrations of vWF are found in patients with previous myocardial infarction [27–30]. There is also an association between vWF with the clinical severity of angina [31]. No circadian variation in vWF levels is found, in contrast to a marked circadian variation in fibrinolytic variables [32].

Sequential changes in vWF levels following acute myocardial infarction have been well documented. In the study by Bridges et al. [33], a significant increase (by 28%) in vWF levels was demonstrated in patients who were reperfused at 90 minutes following thrombolytic therapy. Thus reperfusion in acute myocardial infarction may also result in endothelial dysfunction (thus releasing vWF), as suggested by Giustolisi et al. [34]. Alternatively, reperfusion may ‘wash out’ vWF which was released before reperfusion in endothelium or endocardium which is infarcted or ischaemic. The mechanism for vWF release in acute myocardial infarction may be related to the release of free radicals which occurs following acute myocardial infarction and reperfusion [35]. Following thrombolytic therapy with tissue plasminogen activator (t-PA), patients with angiographic patency demonstrate a fall in vWF at 24 hours post-thrombolysis, when compared to patients with an occluded artery [36,37]. In a study of patients undergoing percutaneous transluminal coronary angioplasty, there was a rise in vWF indicating endothelial injury 1 hour after inflation, which was associated with increased free radical activity [38]. Thus, one mechanism of endothelial disturbance which occurs with reperfusion with thrombolytic therapy or during angioplasty is likely to involve free radical generation.

vWF appears to be an index of increased risk for reinfarction and mortality in patients with angina and in survivors post-myocardial-infarction. In a prospective follow-up study of 123 survivors of myocardial infarction, high vWF levels were independent risk factors for both reinfarction and mortality [39]. This is consistent with results from an earlier study where patients who died within a year following myocardial infarction had significantly higher concentrations of vWF [28]. In the Progetto Lombardo Atero-Trombosi (PLAT) study, vWF levels were a significant predictor for atherothrombotic events in patients with angina pectoris [40]. Similarly, the large European Concerted Action Against Thrombosis (ECAT) study, a prospective multicentre study of 3043 patients with angina pectoris, showed that levels of vWF, fibrinogen and tissue plasminogen activator were independent predictors of subsequent acute coronary syndromes after 2 years follow-up [41]. In a 16-year follow-up study of 1393 men, Meade et al. [42] reported that increased vWF levels were a significant risk factor for fatal ischaemic heart disease events. In addition, one early longitudinal population study also reported a trend for ischaemic heart disease events to increase with elevated concentrations of factor VIII and vWF levels [43]. By contrast, only one report showed no difference in vWF levels between survivors post-myocardial-infarction compared to controls, but these patients were generally younger than the studies previously discussed [44]. In patients with ischaemic heart disease, vWF measured immediately after angioplasty is also predictive of restenosis [45]. Thus, the evidence that raised vWF levels have prognostic implications in patients with ischaemic heart disease appears persuasive.

The precise mechanism by which vWF increases cardiovascular risk in patients with angina or post-myocardial-infarction is unknown. Firstly, increased endothelial damage
in coronary artery disease may result in both increased thrombin generation and higher levels of vWF. Alternatively, as vWF has a role both in adhesion and aggregation of platelets and in coagulation, the increased levels of vWF may increase the risk of thrombogenesis in patients with pre-existing vascular wall disease, thus leading to further reinfarctions. Furthermore, vWF may simply be a marker of more severe disease, and be without direct pathophysiological significance. However (as discussed above), the relationship between vWF and coronary ischaemia may possibly in part reflect platelet activation with platelet-derived vWF, rather than purely endothelial dysfunction, since many coronary ischaemic syndromes are also associated with elevated levels of other platelet activation markers.

5. vWF and peripheral vascular disease

Levels of vWF are significantly higher in patients with peripheral vascular disease. In the Edinburgh Artery Study, for example, levels of vWF were significantly increased in 121 study cases compared with matched controls [46]. Increased levels of vWF also predicted poor outcome of infrainguinal bypass grafting [47]. In addition, Woodburn et al. [48] found that although surgical resolution of critical limb ischaemia in individual patients reduced levels of vWF, the reduction was not to levels in normal controls. This therefore suggests that endothelial cell damage in atherosclerosis is not confined to the symptomatic lesion but is widespread [48]. However, in a further study of 219 patients undergoing angiography, although vWF was again highly raised in patients relative to controls, such levels failed to correlate with a score of the severity of the peripheral vascular disease as compiled from angiogram results [49]. This provides additional support for the notion that raised vWF marks widespread endothelial cell damage.

High vWF levels have important prognostic implications in patients with peripheral vascular disease. In a 1-year follow-up of 617 patients with claudication, increased vWF carried with it a relative risk factor for a coronary event of 1.3 [50]. However, this risk was exceeded by the relative risk conferred by cross linked fibrin degradation products (2.6) and plasma viscosity (1.8) [50].

The increased levels of vWF in claudlicants may be due to the cytotoxic products of activated neutrophils [51]. High vWF levels may be associated with a consumption of the antioxidant glutathione peroxidase, thus implying a possible role of cytotoxic reactive oxygen species produced by activated neutrophils [52]. There is also an inverse relationship between vWF and glutathione peroxidase in patients with concomitant vascular disease and/or hypercholesterolaemia [52]. Alternatively, increased vWF may result from elastase production from activated neutrophils, and/or concomitant hypoxia [53].

6. vWF and conditions associated with thromboembolism

6.1. Atrial fibrillation

Atrial fibrillation is a common cardiac arrhythmia which is associated with an increased risk of stroke and thromboembolism. Recent studies point towards a hypercoagulable state in this condition [54]. In a cross-sectional study of 85 patients with atrial fibrillation, plasma levels of vWF are significantly elevated and were not altered by the concomitant use of aspirin or anticoagulation with warfarin [55]. Levels of vWF were independent of the underlying cause of atrial fibrillation and the presence of structural heart disease [55]. Similar findings were reported by Yamamoto et al. [56], who found raised peripheral blood levels of vWF in patients with mitral stenosis (most of whom were in atrial fibrillation), with similar vWF levels in the right and left atria. Although the precise mechanism for the increased vWF levels in atrial fibrillation is uncertain, abnormalities in cardiac blood flow (e.g., slow or sluggish flow within the atria) may be partly responsible, resulting in flow abnormalities and adding to endothelial disturbance in the pulmonary vasculature.

In the study by Lip et al. [55], there was also a positive correlation between plasma vWF and fibrin D-dimer, an index of fibrin turnover and thrombogenesis. The latter observation is in keeping with the association between blood vessel wall (thus, endothelial) abnormalities and thrombus formation (as part of Virchow’s triad).

6.2. Left ventricular dysfunction

Patients with heart failure are at risk of thromboembolism [57]. In a study of patients with ischaemic heart disease and cardiac dysfunction, Lip et al. [29] found that those with left ventricular aneurysms (as defined by radionuclide ventriculography) had the highest levels of plasma vWF, and other prothrombotic markers such as fibrinogen and fibrin D-dimer. This finding may be explained by two possible mechanisms. Firstly, patients with the highest vWF levels were at highest cardiovascular risk, resulting in the largest myocardial infarctions, or recurrent infarctions [39], thus resulting in the most cardiac ‘damage’ and subsequent aneurysm formation. Alternatively, these patients have the greatest endothelial dysfunction (as reflected by the high vWF levels), thus leading to greater intravascular thrombogenesis, consistent with the highest plasma D-dimer levels being found in these patients [29].

Clinical and epidemiological studies on the risk of thromboembolism in patients with cardiac impairment do not however differentiate between the contribution of systolic and diastolic dysfunction to heart failure. This is pertinent as up to 30–40% of patients with congestive heart failure have normal systolic function [58]. Endothel-
lial dysfunction may thus be related to abnormalities of diastolic function seen in ischaemic heart disease. In a Doppler echocardiographic study of 106 patients with ischaemic heart disease, we found no significant differences in vWF levels between patients with and without diastolic dysfunction; this was despite correcting for the interaction with systolic dysfunction when it was present in individual patients [59]. However, patients with the greatest systolic abnormalities (with aneurysm formation) had the highest vWF levels [59].

6.3. Cerebrovascular disease

Increased vWF levels are well-recognised to be associated with ischaemic cerebrovascular events [60–62]. Patients with thrombotic strokes have also been reported to have higher vWF levels compared to those with haemorrhagic strokes [63]. The possible mechanisms for the association between vWF and cerebrovascular events include endothelial dysfunction associated with cerebral thrombosis (or other risk factors, such as hypertension) or ischaemia-related release of vWF from infarcted tissue; the precise mechanism for this association, however, remains unknown. In a pilot study of 64 patients with acute stroke (ictus < 12 hours), we have recently demonstrated significant endothelial dysfunction (with high vWF levels), which were associated with haemorrhological abnormalities (fibrinogen levels and plasma viscosity) and platelet dysfunction (with raised soluble adhesion molecule P-selectin levels) [64]. These abnormalities may act synergistically to contribute to the pathogenesis of acute stroke and its complications.

6.4. Venous thrombosis

Raised vWF levels have been associated with increased thromboembolic events, for example, in patients with deep venous thrombosis [62]. The prospective value of vWF in venous thromboembolism was shown in a study of patients after major abdominal surgery where high preoperative concentrations of vWF were associated with an increased risk of postoperative deep venous thrombosis [65]. However, Koster et al. [66] found raised vWF in patients who had suffered a deep vein thrombosis, but this effect was almost totally explained by a close relationship with blood groups and factor VIII. Consequently, there may be no evidence of excessive endothelial cell damage in this disease.

7. vWF and pulmonary vascular disease

The pulmonary vasculature has significant influences on plasma vWF levels. For example, elevated plasma vWF has also been demonstrated in patients with elevated pulmonary vascular resistance and decreased cardiac output, irrespective of the presence of mitral stenosis [67]. In primary pulmonary hypertension, histological evidence of injury to pulmonary endothelial cells is associated with elevations of plasma vWF, thus contributing to the risk of thrombosis and a haemodynamically-induced increase in the endothelial release of vWF [68].

8. vWF and diabetes

Abnormalities of vWF have also been demonstrated in diabetics and may be involved in the pathogenesis of diabetic vasculopathy [69–71].

For example, a raised urinary albumin excretion in non-insulin-dependent diabetes is an index of early diabetic nephropathy that is also associated with increased vWF levels and a high risk of cardiovascular disease [71]. It is therefore considered that dysfunction of vascular endothelium may be one link between the microalbuminuria and atherosclerotic cardiovascular disease found in non-insulin-dependent diabetics. Similarly diabetics with neuropathy have significantly elevated vWF levels [72].

In a population-based cross-sectional study, however, vWF levels were found to be unrelated to the metabolic factors involved in the insulin resistance syndrome [73]. Despite the apparently clear paradigm that patients with the poorest glycaemic control are at greatest risk of adverse cardiovascular risk, Steiner et al. [74] were unable to correlate vWF levels with either HbA1c or fructosamine in non-insulin-dependent diabetics.

9. vWF and hypertension

With age and hypertension, the role of the protective mechanisms of the endothelium diminish, and changes in vasoactive endothelial factors (such as endothelin, prostaglandins, etc.) become more important for the maintenance of blood pressure and cardiovascular haemodynamics [75]. Plasma vWF may therefore be a marker for such endothelial dysfunction or disturbance in hypertension, in view of the increase in plasma vWF seen in vascular disease [76].

Levels of vWF are significantly increased in patients with hypertension, but are normalised in patients in whom hypertension was successfully treated with antihypertensive drugs [77]. We have recently demonstrated increased levels of plasma vWF, fibrinogen and the soluble adhesion molecule P-selectin (a possible marker of platelet activity) in patients with hypertension, which were significantly correlated with diastolic blood pressure levels, but (in contrast to previous reports [77]) levels of these markers were unrelated to whether or not antihypertensive treatment was used or good blood pressure control was achieved [78].

Varizi et al. [79] also reported high vWF levels in hypertensives, which were associated with diastolic blood pressure levels. In addition, there was a modest correlation to the left ventricular posterior wall and ventricular septum.
thickness, and to the left ventricular mass index [79]. The latter is an index of hypertensive target-organ damage, and hypertensives with left ventricular hypertrophy are well-recognised to be at high risk of cardiovascular complications. Another index of hypertensive end-organ damage, microalbuminuria (defined as the excretion of urine albumin between 20 and 200 μg/min) is also related to endothelial dysfunction, suggesting that microalbuminuria reflects systemic dysfunction of the vascular endothelium [80]. When compared to hypertensives without microalbuminuria or controls, vWF levels were significantly higher in hypertensive patients with microalbuminuria [80].

In pregnancy-induced hypertension and pre-eclampsia, mean vWF levels were significantly higher compared to healthy pregnant women, and levels were correlated to the severity of the condition [81,82]. There was also an excess of large, medium and small sized vWF multimers in the patients with pregnancy-induced hypertension, perhaps reflecting endothelial injury [82]. This may play a role in the microangiopathy observed in the disease.

Although endothelial dysfunction or damage can be present as a result of hypertension, others have considered that endothelial damage may actually promote hypertension [83]. The presence of endothelial damage may be one mechanism by which patients with hypertension are at risk of thrombogenesis and atherogenesis; this is reflected by the observation that whilst the arterial tree is exposed to increased pressure flow, paradoxically the complications of hypertension are mainly thrombotic rather than haemorrhagic.

10. vWF and inflammatory vascular disease

Elevated vWF levels have been demonstrated in patients with inflammatory vascular disease and associated disorders, including vasculitis, Sjögren’s syndrome, Felty’s syndrome, giant cell arteritis and polyarteritis nodosa [84]. For example, studies in patients with Raynaud’s phenomenon, which included patients with and without atherosclerosis or connective tissue disease, showed high levels of vWF in all patients [85]. Patients with systemic sclerosis and Raynaud’s phenomenon also have increased vWF, especially if diffuse disease was present [86].

Two serial studies in patients with inflammatory vascular disease are of note: Wallberg-Jonsson et al. [87] measured vWF and two non-specific endothelial markers—tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI)—in 74 patients with rheumatoid arthritis. Two years later, increased vWF, but not tPA or PAI, remained as a multivariate predictor of the patients who suffered a thromboembolic event. We have also shown that increased vWF predicts death in patients with systemic sclerosis [88].

With improvements in immunosuppressive therapy, fewer patients with systemic lupus erythematosus (SLE) are dying of the autoimmune disorder, but, instead, vascular complications have become more common. vWF may have a role in the pathogenesis of cardiovascular disorders in these patients, as levels are also significantly increased in such patients [89,90]. For example, immunoglobulins (especially IgG) from patients with SLE can stimulate vWF release and this may be implicated in the thrombotic events observed in these conditions [91]. In addition, endothelial cell dysfunction has been related to the presence of anti-endothelial-cell antibodies [92] and anti-phospholipid antibodies (which cross-react with the endothelium) [93]. These antibodies may result in endothelial cell damage by various mechanisms such as complement activation (perhaps by immune complex formation) [94], antibody-dependent cell cytotoxicity [95] or by the inhibition of prostacyclin production [96,97]. The diversity of possible mechanisms is mirrored by the wide spectrum of autoantibodies found in SLE. A study by Lindsey et al. [91] demonstrated that immunoglobulin G from patients with SLE or antiphospholipid syndrome was capable of stimulating vWF release and this ability may be implicated in thrombogenesis. However, there was no correlation between either anti-endothelial or anti-cardiolipin antibodies and vWF release [91].

11. vWF and homocysteinuria

Homocysteinuria is an inborn error of metabolism associated with thrombotic and vascular complications, where excess homocysteine is toxic to the endothelium [98]. This is demonstrated in in-vitro studies where homocysteine inhibits vWF processing and secretion by preventing intracellular transport [99]. Homocysteine and cysteine also promote the detachment of endothelial cells in vitro [100], and the former is cytotoxic to endothelial cells in vitro and will enhance the release of vWF [101]. In addition, hyperhomocysteinaemia is a risk factor for intermittent claudication [102], and (as discussed above) high vWF levels are found in such patients, with important prognostic implications.

12. Possible measures to alter vWF levels

It follows from the above that if high levels of vWF are to be avoided, then steps should be taken to do so. There are two approaches: (i) to treat the risk factors for atherosclerosis, and (ii) to develop new agents to inhibit the activity of vWF [103]. As yet, there are no definitive methods of therapeutically altering plasma vWF levels. There is also no evidence that measures to reduce circulating vWF will have beneficial effects in modifying cardiovascular risk.

12.1. Treatment of the risk factors of atherosclerosis

Since vWF is increased in each of the four major risk factors for atherosclerosis (hypertension, hypercholesterol-
aemia, smoking and diabetes), then modifying these factors may perhaps reduce vWF [104]. For example, lower levels of vWF may be obtained in diabetics who are able to control their ketoacidosis [70]. Clinical population studies have also indicated that patients whose hypertension has been successfully treated have lower vWF than those similar patients whose hypertension has yet to be brought under control [77]. Similarly, patients with coronary artery disease who had been on a strict diet for 3 years to reduce their cholesterol had lower levels of vWF than a similar cohort who were not intensively dieted [105]. In this study, levels of vWF correlated with both total cholesterol and inversely with dietary polyunsaturated fats [105]. This supports the hypothesis that certain lipoproteins (especially oxidised low-density lipoproteins) are cytotoxic to the endothelial cells in vitro and so may be important in atherogenesis [106]. The inverse correlation between dietary polyunsaturated fats and vWF implies that the former are beneficial to the endothelium, which is consistent with previous observations [107] and epidemiological studies relating adipose tissue fatty acid analysis to coronary heart disease [108]. There is also preliminary evidence that conventional lipid-lowering therapy will reduce vWF in patients who are hypercholesterolaemic with or without symptomatic vascular disease [109]. The control of other risk factors, including obesity, and abstention from smoking and control of hypertension [14,110] may reduce vWF levels.

12.2. Development of new drugs

The central role of vWF in thrombogenesis has made it a target for research into antithrombotic therapies centred on antibodies, peptides, or other compounds that inhibit vWF function, which have been suggested as potential new anticoagulants [103]. This inhibition may be possible at a number of sites on the vWF molecule. Engineered heparins can inhibit vWF-dependent platelet aggregation and vWF-platelet binding [111]. Dardik et al. [112] have demonstrated reduced platelet binding to an extracellular matrix with a recombinant GPIb-binding peptide. Aurin tricarboxylic acid inhibits ristocetin-induced, vWF-mediated platelet aggregation [113]. All these approaches have potential as exciting new tools to minimise the procoagulant activity of vWF and may therefore be future therapeutic agents.

13. Are raised vWF levels in vascular disease a cause or effect?

Until recently, our understanding of the role of vWF in vascular disease has been based on cross-sectional studies and epidemiologic observations. Elevated plasma vWF levels are consistently associated with various cardiovascular disorders (coronary, cerebrovascular and peripheral artery disease) and the risk of vascular events. It has been suggested that these associations may be explained by a reactive or secondary rise in plasma vWF (and other haemostatic factors) either as an acute phase response or as an atherosclerosis-related ‘haematological stress syndrome’ [114]. The processes of thrombogenesis and atherogenesis have certain similarities to inflammatory disease that develop as a result of metabolic, physical and environmental injury to blood vessels; thus the elevations in plasma vWF levels may reflect the severity of vascular disorders as a secondary phenomenon rather than act as a true prognostic factor. Indeed, vWF may have some characteristics of an acute phase reactant, being increased in infections, acute inflammation and malignancy [6]. For example, significant elevations in vWF have been reported in patients with active inflammatory processes (such as giant cell arteritis, polymyalgia rheumatica and in malignancy with metastases) [115,116]. Thus, interpretation of raised vWF levels may be complicated by its behaviour as an acute phase reactant. Nevertheless, measurement of vWF levels may be more useful than that of acute phase reactants such as C-reactive protein or the ESR as vWF is probably more ‘specific’, and may imply vascular disease (unlike the CRP or ESR).

Raised plasma vWF levels are also known to precede cardiovascular events. This is indicated by the possible prognostic value of vWF, for example, in predicting acute coronary syndromes in patients with angina [41], reinfarction following myocardial infarction [39] and in patients with peripheral vascular disease [47,50], as discussed above. In addition, there is also an association between vWF with the clinical severity of angina [31]. In patients with inflammatory vascular disease, such as rheumatoid arthritis and systemic sclerosis, vWF levels have prognostic implications, with high levels predicting mortality, disease progression and cardiac events [87,88,116]. However, whilst elevated vWF levels have been shown to precede cardiovascular events, this may merely reflect the severity of the underlying disease and causation is not necessarily implied. For example, high vWF levels are found following endothelial injury by cardiovascular risk factors such as smoking, hypertension or hyperlipidaemia.

There is experimental evidence that vWF levels may be increased by glucocorticoids and cytokines such as interleukin-1 and tumour necrosis factor which are produced by monocytes and macrophages [117,118]. However, since vWF is also an acute phase protein, increased levels may simply reflect endothelial activation or stimulation, and not endothelial dysfunction [6]. Thus, occlusive disease of arteries by thrombus may cause a reactive increase in vWF. The well-established increases in plasma vWF levels in many cardiovascular disorders and atherosclerosis risk factors are however not always associated with an active acute phase response [14,76–78].

The precise mechanism for the elevated vWF in cardiovascular disorders is therefore still uncertain. Although a
cytokine-mediated increase in synthesis is likely to be the common pathway, the possibilities that high vWF levels in vascular disorders may be due to a combination of increased secretion from stored pools, increased synthesis de novo or release from endothelial cell damage still remains. The initiating stimulus for vWF release or synthesis in patients with vascular disease is also uncertain, and may include various cardiovascular risk factors (smoking, hyperlipidaemia, etc.), oxygen free radicals or hypoxia secondary to ischaemia.

14. Conclusion

Many case-controlled studies support the hypothesis that high concentrations of vWF are an index of atherosclerosis or of an increased risk of thrombogenesis or both. Concerns remain, however, whether the elevations in vWF in vascular disorders are relevant or simply an epiphenomenon. Recent reports also suggest that raised vWF levels have important prognostic implications in ischaemic heart disease and peripheral vascular disease. vWF may therefore be a good marker for endothelial dysfunction in a variety of vascular disorders. Further research is indicated to explore the predictive value of this marker in population studies and perhaps therapeutic approaches in (and the value of) modulating vWF levels or function. However, some of these future directions also await a better understanding of the transcriptional and translational regulation of vWF biosynthesis and of vWF secretion.

15. Note added in proof

Increased vWF due to smoking is reversible upon cessation [119]. This further supports the hypothesis that increased vWF precedes atherosclerosis and that levels fall by treatment of risk factors.

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