Role of von Willebrand factor in vascular disease

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Summary
Plasma levels of von Willebrand factor (VWF) are increased in patients with cardiovascular risk factors. Various studies aimed to elucidate the relation of VWF with thromboembolic cardiovascular events, ischaemic stroke as well as with peripheral arterial occlusive disease. In the general population, there is only a weak association between VWF levels and future cardiovascular events or stroke. In contrast, VWF levels are predictive in patients with documented vascular disease. Those patients with increased VWF suffer a higher incidence of major adverse cardiac events including death. The extent of the VWF release and its levels independently predict clinical outcome in patients with acute coronary syndromes. Elevated VWF levels have also been observed in patients with atrial fibrillation compared to controls and predict outcome. This may at least in part be attributable to the association of VWF with underlying cardiovascular risk factors. Hence, VWF correlates with Framingham and CHA2DS2-VASc stroke risk stratification score and can be used as a marker in patients with AF. However, VWF is not only a predictor; it also plays a crucial role in thrombogenesis. This fact has made VWF a promising target for research into new antiplatelet therapies that specifically inhibit VWF. This review focuses on the role of VWF in ACS, ischaemic stroke and peripheral arterial disease and the relevance of therapeutic interventions targeting VWF for ACS patients.

Pathophysiological role of VWF in thrombus formation

Binding to platelets requires initial plasma VWF activation leading to a structural change so that the A1 domain can bind to the platelet receptor GPIb-IX-V complex on the platelet surface (24, 25). Additionally, binding of VWF to platelet GPIb seems to generate procoagulant platelet-derived-microparticles (PMPs) that further enhance thrombus formation (26). Presumably, VWF’s main role lies more with platelet adhesion than aggregation (27). This assumption is illustrated by the example of VWFb disease, which is characterized by spontaneous binding of VWF to circulating platelets, leading to haemorrhagia rather than thrombosis.

A second platelet receptor for VWF, GPIIb/IIIa, does not bind VWF unless platelet activation has occurred. The platelet-GPIIb/IIIa-VWF interactions appear to contribute to the irreversible binding of platelets to the subendothelium and play a leading role in platelet aggregation, especially under high shear conditions (2). However, under extreme shear rates (>10000/s) VWF binding seems to be entirely dependent on GPIIb (28).

Plasma VWF binds also to several types of collagen, most importantly collagen type IV, in the subendothelial connective tissue (29). Collagen binding appears to induce a

Von Willebrand factor (VWF) plays a crucial role in platelet adhesion and aggregation, the main initial steps in haemostasis after vascular injury and also under conditions of high shear rate as it happens in lesions in the coronary arteries (1, 2). The VWF molecule is composed of 50–100 monomers and can reach an ultimate size of up to 20 MDa. Each VWF subunit has binding sites for:

- factor VIII,
- platelet glycoprotein Ib (GPIb),
- GPIIb/IIIa,
- heparin and
- collagen,

some of which are dependent on the shear-induced conformational change (3, 4).

VWF is almost exclusively produced by endothelial cells (5). Additionally, VWF can be found in platelet α-granules without any exchange with plasma VWF in vitro or in vivo (6). Plasma levels of VWF are raised in different states of endothelial damage and have therefore been proposed as useful markers of endothelial dysfunction (7). Finally, VWF supports blood coagulation by acting as a carrier protein and stabilizer for factor VIII (8). Accordingly, VWF is a well-characterized marker of cardiovascular risk and VWF plasma levels are increased in patients with ACS (9).

Considering the role of VWF in thrombogenesis, therapies that specifically inhibit VWF are of particular interest as potential new anti-platelet drugs. This educational review condenses previously published data on acute coronary syndromes (10) and extends it by reviewing literature on VWF levels in atrial fibrillation, stroke and peripheral arterial occlusive disease.

Plasma and subendothelial VWF

VWF can be produced and released by endothelial cells by a variety of stimuli in vitro and in vivo (11–18) such as:

- hypoxia,
- inflammatory cytokines,
- thrombin,
- leukocyte elastase,
- histamine,
- endothelin,
- adrenaline, and
- especially vasopressin.

Along this line, blockade of nitric oxide enhances the stimulated release of VWF in humans (15, 19). Levels of VWF can also vary in pregnancy, exercise (20), and after alcohol consumption. They are also influenced by the ABO blood group system (21). Of note, VWF levels increase in the general population by approximately 0.15 U/ml for each 10 years of age, although this estimate is based only on data from women (22). Cardiovascular risk factors that increase VWF have been reviewed extensively by Blann (23). Furthermore, it is highly probable that VWF release might differ in various vascular beds, such as the lung or the skin (23).
conformational change within the factor VIII-binding domain (VWF is carrier protein for factor VIII) and lowers the affinity for factor VIII (FVIII). Without VWF, the half-life of FVIII is shortened 10–20 fold due to proteolytic inactivation by activated protein C and its cofactor protein S (30). Consequently, released FVIII may locally support fibrin clot formation (31). The clinical importance of FVIII for thrombin generation is illustrated by bleeding as it happens in patients with haemophilia A and von Willebrand disease.

ADAMTS-13

A further example for the importance of VWF is illustrated by ADAMTS-13. This metalloproteinase enzymatically converts ultralarge VWF multimers to smaller forms (32). The failure to cleave large multimers promotes thrombosis (33). Indeed, patients with ADAMTS-13 deficiency have an increased thrombosis risk (34).

The physiologic importance of ADAMTS-13 can be illustrated by the association of thrombotic thrombocytopenic purpura (TTP) with antibodies against, or congenital deficiency of, ADAMTS-13.

VWF and CAD

Predictive value in healthy subjects

Raised levels of VWF are predictive of stroke and vascular events among patients with atrial fibrillation (35). The VWF levels in AF patients are not altered by warfarin and aspirin treatment (36). Correspondingly, many studies have investigated the association between VWF levels and the development of cardiovascular disease in a prospective manner. In demonstrating the risk increase due to high levels of VWF the present literature is equivocal. Several case control studies were able to show a significant increase of coronary arterial disease (CAD) in patients with elevated VWF (ARIC and VIP study, PRIME study with 3-fold increased risk for severe CAD in the highest compared to the lowest quartile).

However, the very well powered Reykjavik study reported only an odds ratio of 1.23 for the highest versus the lowest quartile of VWF. Taken together, these data indicate that plasma VWF levels are at best a weak independent predictor of future CAD in initially healthy subjects (37). However, the fact that the association between VWF and CAD risk disappears after adjustment for conventional risk factors, in particular diabetes mellitus, does not exclude the possibility that these factors exert their deleterious effect via VWF increase, but rather may simply reflect the high degree of correlation among them. This is demonstrated by the observation that successful treatment and consecutive reduction of risk factors decrease VWF levels (38–40).

VWF in coronary artery disease

Increased VWF concentrations were found in plasma from patients with acute myocardial infarction (AMI) compared to control subjects (41, 42). Furthermore, detection of VWF in fresh, human coronary thrombi suggests a causative role of VWF in platelet thrombus growth (43, 44). The unweighted mean (±SD) of published VWF data (41, 45–58) shows that patients with AMI (196 ± 39%; n = 877) have markedly increased VWF values as compared to UAP (156 ± 41%; n = 345) and CAD (140 ± 30%; n = 300) patients, as well as healthy controls (110 ± 17%; n = 394).

There is a well-established association between VWF levels and the future risk of myocardial infarction in vascular disease patients (59). These results are corroborated by numerous studies that also describe an association of VWF levels and re-infarction and mortality risk (47).

High concentrations of VWF have been shown to be independently associated with both re-infarction and mortality in MI survivors younger than 70 years (60). Similar results could be found in other studies. For example in the large SHEEP study it was shown that higher VWF concentrations are a strong predictor in AMI recurrence (odds ratio for re-infarction 2.3.) (61).

Taking these results together, it appears that while the association between VWF levels and coronary events in the general, apparently healthy population is weak, this association becomes much stronger in patients with preexisting vascular disease, in particular MI survivors.

As VWF is normally proteolytically degraded by the enzyme ADAMTS13, it is natural to consider the possibility that ADAMTS13 activity is itself abnormal in the setting of ischaemic cardiovascular disease.

ADAMTS-13 levels were shown to be reduced in patients with acute myocardial infarction (62). On the other hand, a recently published case control study demonstrated an increased MI risk in patients with higher ADAMTS-13 levels (63). This discrepancy remains unexplained and merits further investigation.

VWF Levels

Changes in STEMI

VWF levels show a typical time course during an acute cardiovascular event. In the setting of STEMI, VWF levels become elevated at 24 hours and peak at 48–72 hours before returning to baseline at around day 14 (52). For instance the extent of VWF release, i.e. the difference between baseline and 24 hour VWF values during the index event, is not only associated with the incidence of acute heart failure, but significantly correlates with 30-day mortality in patients with STEMI (64). The VWF rise in patients with STEMI patients treated with fibrinolysis significantly correlated with death or MI at 30 days (65). Patients with AMI have increased VWF levels compared to patients with unstable angina pectoris (55, 66). The combined evaluation of VWF and troponin I in this patient group has provided information on the long-term prognosis: high VWF and/or high troponin I are significantly associated with an increase in the composite end-point death, AMI, recurrent angina, and revascularization after one year follow-up (67).

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Therapeutic influence

Interestingly, administration of either enoxaparin or pegylated (PEG)-hirudin is able to blunt the VWF rise in patients with unstable angina pectoris compared to unfractionated heparin or dalteparin, and is associated with a more favorable clinical outcome (68). Similarly, use of enoxaparin following fibrinolytic therapy reduces the VWF rise in patients with STEMI, and also is associated with a reduction in death or subsequent MI at 30-day follow-up (65). However, two other studies could not confirm the beneficial effects of enoxaparin compared to dalteparin and unfractionated heparin in patients with ACS (69, 70).

Prospects of measuring VWF levels

Recent studies provide evidence that not only VWF but also platelet plug formation under high shear rates, as measured by the platelet function analyzer (PFA-100®), is predictive of the degree of myocardial necrosis, myocardial blood flow, and future events in patients with ACS (55, 71, 72).

Influences of VWF

VWF and PCI

After a successful percutaneous coronary intervention (PCI), it may be relevant that stent implantation is associated with endothelial damage and concurrent VWF release (73). Therefore, it is possible that this mechanically-induced increase in VWF may exacerbate the pro-thrombotic state of ACS patients, despite restored normal epicardial flow.

Consistent with this hypothesis is the observation that stenting with drug eluting devices is associated with a reduced inflammatory response as well as diminished VWF antigen levels in the coronary circulation (74).

Thrombolysis and VWF

Thrombolytic agents have an established role in the management of patients with acute myocardial infarction. Given that VWF is a key factor in coronary thrombus formation, interaction of the thrombolytic agents with VWF seems to be crucial. Although the clinical benefits of thrombolytic therapy in the management of ST-elevation myocardial infarction are well established, thrombolysis in AMI patients leads to some degree of endothelial cell damage as evidenced by a slight increase in VWF levels peaking between three hours (streptokinase) to 72 hours (rt-PA) post lysis (51, 75). Furthermore, VWF undergoes degradation during thrombolytic therapy in AMI patients. The degree of degradation depends on the type and dose of thrombolytic agent (being greater for streptokinase than for recombinant tissue plasminogen activator or urokinase). VWF degradation has been speculated to be a potential causative factor for bleeding complications occurring in treated patients.

VWF levels in stroke

Non-valvular atrial fibrillation is associated with an approximately 5-fold increase in stroke risk (76). Thrombogenesis in patients with atrial fibrillation may be reflected by VWF plasma levels. Sato et al. found a significant correlation between VWF and severity, outcome and ischemic infarct size and levels were higher in the AF group than in the non AF group (77). A significant relation between VWF Ag and the occurrence of ischemic stroke (OR 2.20) in nonvalvular AF patients was also shown by Yip et al. (78). Baseline plasma levels of VWF were described as predictors of the occurrence of ischemic stroke in patients with chronic non valvular atrial fibrillation (NVAF) (79).

Although ischemic stroke is associated with accentuated platelet function, it remains unclear whether this applies to all subtypes of cerebral infarction. Interestingly, Bath et al. reported that VWF was also significantly increased in hemorrhagic stroke and no difference was found regarding VWF levels in cortical or lacunar ischemic stroke as compared to controls (80). Results of this study also suggested that the increase of VWF in all types of stroke may reflect an acute phase response. Nomura et al demonstrated that the VWF activities increased at 1 month after admission as compared to the acute stage (81). In contrast, Bongers et al. described that VWF Ag levels were similar to controls three months post stroke (82). Although these data may indicate that VWF levels remain elevated for one month following stroke, Yip et al. failed to show a change of VWF levels at any time point after ischaemic stroke in patients with non valvular atrial fibrillation (78).

In patients with subarachnoidal haemorrhage, VWF elevation in plasma occurred in the early stage of subarachnoidal haemorrhage (83). In addition, VWF levels were different in the cerebrospinal fluid compared to the control group and emerged as an independent prognostic factor for cerebral vasospasm and ischaemic complications. Its elevation correlated clinically with a poor neurological condition.

A biological marker for the refinement of the stroke risk stratification in AF patients has long been under investigation. The authors of the SPAF trial showed that VWF levels correlated with two stroke risk stratification scores, i.e. CHADS and Framingham (84).

PAOD and VWF

Few data exist about VWF and peripheral arterial occlusive disease (PAOD). The Edinburgh Artery Study examined associations of hypercoaguability markers and development and clinical progression of PAOD. Median levels of fibrinogen and VWF were higher in the group developing PAOD. However, none of the analysed haemostatic factors (including VWF) were significantly associated with progression of PAOD (85).

Tsakiris et al. assessed VWF levels before and after peripheral transluminal angioplasty in patients with PAOD with predominantly femoropopliteal disease. The authors demonstrated a trend to higher rates of VWF in patients who later developed restenosis (86). Increased concentrations of
VWF have also been seen in patients with PAOD in another study (87) and can predict poor outcome of infrainguinal bypass grafting (88).

The level of coagulation activation and endothelial stimulation was assessed in patients with intermittent claudication and critical limb ischaemia. Patients with claudication had significantly higher levels of VWF than controls and VWF levels were significantly increased in patients with critical limb ischaemia. Only 15% of patients with claudication had a history of known coronary heart disease (89).

As already mentioned, smoking, hypertension (90) or diabetes mellitus are associated with increased VWF levels. This might reflect endothelial activation. However, in this particular study no difference in smokers or patients with hypertension could be found in claudicants and patients with critical limb ischaemia. However, there were more diabetics in the critical limb ischaemia group and none in the control group.

VWF may also increase after physical exercise. Woodburn et al. investigated whether VWF levels increase during exercise that induces claudication. However, this study failed to show a significant increase in VWF levels following exercise (91).

Role of VWF as a marker and/or as a pathogenic mediator

Interestingly, there are rare diseases, which provide indirect evidence for a pathogenic role of VWF in AMI. Acute thrombotic thrombocytopenic purpura, the hallmark of which is a pronounced rise in the level of circulating ultra large VWF, is quite commonly associated with myocardial injury (92). This may lead to severe myocardial infarction, cardiogenic shock and cardiac arrest as described in recently published case reports (93–95).

Hoylaerts et al. reported a case of recurrent arterial thrombosis in a young woman linked to autoimmune antibodies enhancing VWF binding to platelets and inducing platelet activation (96). Conversely, arterial thrombosis appears to be very rare in patients with all forms of von Willebrand disease which arise from a qualitative or quantitative deficiency of VWF (97). In addition, an association between the genetic trait of AB0 blood group and myocardial infarction has been recognized for a long time (98, 99). Interestingly, the 0 allele carriage is not only linked to a significant MI risk reduction, but also is highly correlated with lower VWF antigen levels (100).

Another finding that supports an adverse association between VWF levels and cardiovascular events (MI) was described after desmopressin infusion. Since desmopressin is a potent secretagogue for VWF (101) and notably does not lead to coronary vasoconstriction, induction of a short-term prothrombotic state seems to be the underlying cause of side effect of desmopressin treatment (101–104).

VWF and drugs

VWF antagonists have been proposed as potentially advantageous, novel antiplatelet drugs (105). Heparins have been shown to bind to a site on the VWF molecule which overlaps its A1 domain responsible for GPIb binding (106, 107). So heparin administration and in particular the LMWH enoxaparin is associated with a reduction in VWF release, recurrent MI and death in the setting of acute MI (65, 108).

Some ex vivo studies indicate that GPIIb/IIIa inhibitors, mainly the monoclonal antibody c7E3Fab (abciximab), suppress the VWF mediated platelet activation (109) by a mechanism which was described to be mediated by platelet GPIb interactions with VWF under conditions of high shear stress (110). Goto et al. showed that abciximab as compared to tirofiban and eptifibatide inhibits the VWF-mediated procoagulant activities (111).

More specific antagonists of the VWF-GPIb interaction have been investigated, but none have yet achieved regulatory approval to be marketed as drugs. Recombinant peptide fragments of VWF can compete with native VWF for GPIb binding and can interfere with platelet adhesion and aggregation in vitro (112). For example, a recombinant and humanized version of 6B4-Fab-frag-

Conclusions

VWF is a useful clinical marker strongly correlating with the incidence and prognosis of acute coronary syndrome. A significant correlation also exists between VWF levels and stroke risk scores as well as angiographic scores (123). However, none of the current therapeutic interventions for myocardial infarction specifically targets VWF. Thus, VWF antagonists may represent a novel, potentially valuable addition to the known antithrombotic agents.

Conflict of interest disclosures
None.
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