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Review

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Acquired von Willebrand Syndrome Associated with Cardiovascular Diseases

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The blood glycoprotein von Willebrand factor (VWF) plays an important role in hemostasis and thrombosis. VWF is produced and secreted as large multimers by endothelial cells and megakaryocytes. It is then cleaved in a sheer-stress dependent manner by a specific protease, ADAMTS13, into multimers consisting of 2–80 subunits. Among VWF multimers, high molecular weight (HMW) multimers play important roles in platelet aggregation. Therefore, their loss induces a hemostatic disorder known as von Willebrand disease (VWD) type 2A. Various cardiovascular diseases, such as aortic stenosis, hypertrophic obstructive cardiomyopathy (HOCM), and several congenital structural diseases, as well as mechanical circulatory support systems, generate excessive high shear stress in the bloodstream. These cause excessive cleavage of VWF multimers resulting in a loss of HMW multimers, known as acquired von Willebrand syndrome (AVWS), a hemostatic disorder similar to VWD type 2A. Bleeding often occurs in the gastrointestinal tract since a fragile angiodysplasia develops associated with these diseases. Radical treatment for AVWS is to remove the pathological high shear causing AVWS.

Key words: **Aortic stenosis, Heyde's syndrome, von Willebrand factor, Acquired von Willebrand's syndrome, ECMO, Left ventricular assist device**

The Function of von Willebrand Factor and its Regulation by a Specific Protease ADAMTS13

VWF is produced and secreted from endothelial cells and megakaryocytes as large multimers[1]. It is constitutively secreted from endothelial cells and also stored in Weibel-Palade bodies[2] that undergo regulated secretion by various stimuli such as exercise[3, 4], inflammation[5, 6], infection[5], pregnancy[7], and mental stress[8, 9]. Therefore, the plasma concentration of VWF is increased by these conditions.

The level of plasma VWF antigen (VWF:Ag) is relatively expressed using that of standard plasma at 100 IU/dL (1 IU/mL). In some cases, this is expressed as a percentage of the standard (100% as a control). It is noted that VWF:Ag increases in an age-dependent manner[10]. The VWF:Ag of 80-year-old people is 1.5–2.0 times the VWF:Ag of 40-year-old people on average[11]. VWF:Ag also varies among individuals. In middle-aged people, VWF:Ag is widely distributed in 60–180%[12]. Furthermore, VWF is modified by ABO-type glycosylation as found in the erythrocyte plasma membrane. The plasma VWF:Ag level of persons with O-type is approximately 70% of that with other blood types, on average[11].

VWF is present not only in plasma, but also partially in the sub-endothelial tissues of blood vessels[1]. While VWF in such tissues plays an important role[13-15], plasma VWF is also important for the regulation of thrombosis and hemostasis since excessive cleavage of VWF causes acquired von Willebrand syndrome (AVWS)[16] as described in this review. VWF is also stored in the α-granules of platelets and secreted upon their activation[17].

VWF has several functional domains (**Fig. 1A**).

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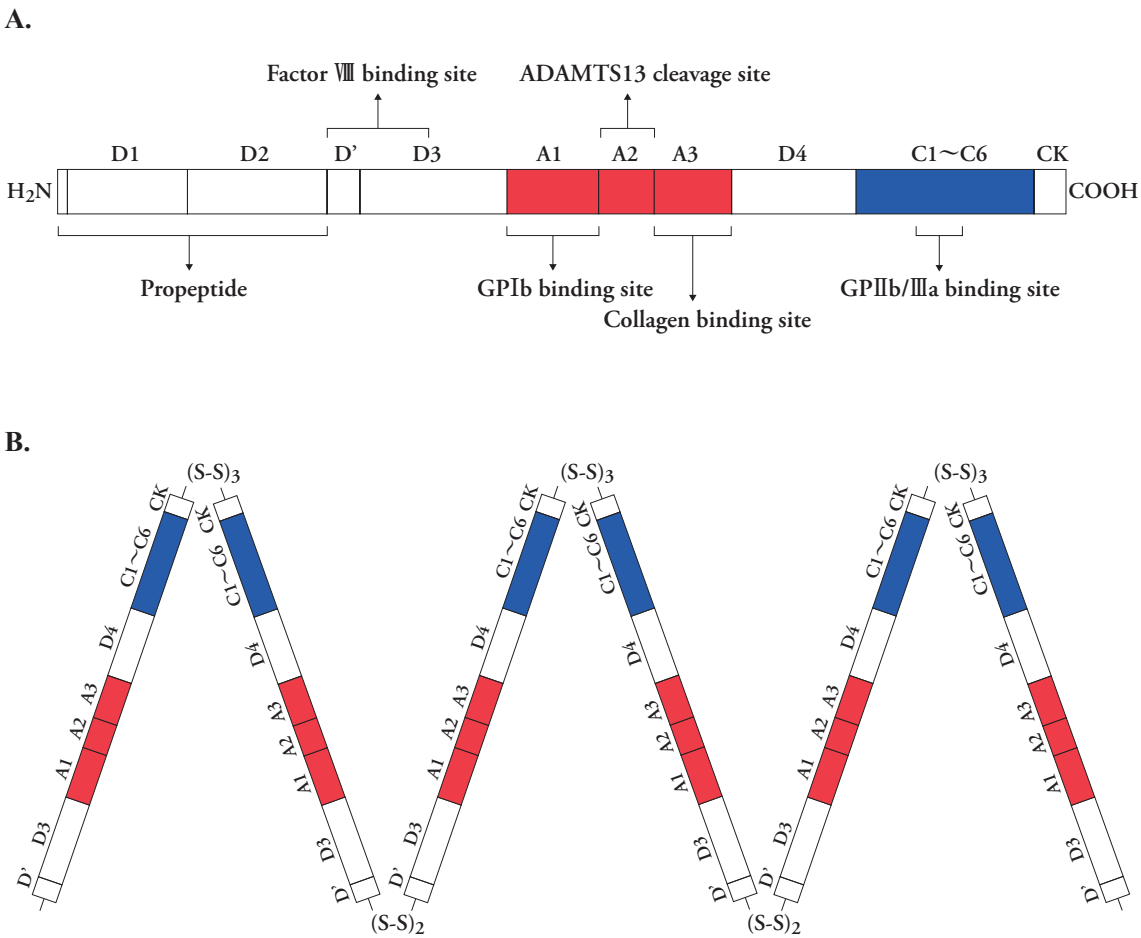


Fig. 1. The structure of von Willebrand factor (VWF)

A) Schematic structure of VWF monomer with its functional domains. Binding sites are indicated for FVIII (D' and D3 domains), GPIb (A1 domain), collagen (A3 domain) and GPIIb/IIIa (C1 domain). An ADAMTS13 cleavage site is located in the A2 domain. B) The VWF multimer structure. The subunits of pro-VWF is initially dimerized by disulfide bonds between C-terminal cysteine knot (CK) domains of each subunit in endoplasmic reticulum and then multimerized by at least two disulfide bonds in D'D3 domains concomitantly with the removal of short peptide in the C-terminal region in the Golgi apparatus.

When endothelial cells are lost because of vascular damage, VWF binds to collagen fibers in the subendothelial tissues through its A3 domain[18]. Attached VWF changes its conformation in response to the shear stress of blood flow to interact with the glycoprotein Ib (GPIb) complex on the platelet surface through its A1 domain[19]. By this interaction, platelets start rolling along the vessel wall and finally attach firmly through their collagen receptors, GPIa/IIa (integrin $\alpha 2\beta 1$) and GPVI. During the process, platelets are activated and release self-agonists such as thromboxane A_2 produced by arachidonic acid breakdown, and ADP stored in dense-core granule by regulated exocytosis, resulting in the local enhancement of platelet activation. On the surface of activated platelets, GPIIb/IIIa (integrin αIIbβ3) that is abundantly present on platelets changes its conformation to allow it to bind its ligands, VWF and fibrinogen[20, 21]. A part (~30%) of GPIIb/IIIa is also stored on the α-granule membrane and transported to the surface upon platelet activation[22, 23]. VWF is a multimer and fibrinogen is a heterohexamer consisting of two sets of α, β, and γ subunits[24], both of which contain multiple binding sites for activated GPIIb/IIIa. Activated platelets are bridged with these ligands by protein–protein interaction, resulting in the formation of platelet aggregates. Thus, VWF plays a critical role in platelet thrombosis at multiple steps. Furthermore, VWF forms a complex with coagulation factor VIII (FVIII) through its D3 domain[25]. This interaction is critical for the stable

existence of FVIII. Therefore, severe von Willebrand disease (VWD) such as VWD type 3 (see below) causes a loss of FVIII and concomitantly causes hemophilia-like symptoms[26].

VWF monomers form multimers by covalent disulfide binding between C-terminal regions in the endoplasmic reticulum and between N-terminal regions in the Golgi apparatus, followed by removal of the propeptide domain (**Fig. 1B**)[27]. Subsequently, VWF is secreted as so-called unusually large VWF (UL-VWF) multimers[28]. Extracellularly, they are cleaved in a shear stress-dependent manner in the A2 domain by a specific zinc-containing metalloprotease, ADAMTS13,[29] which is secreted mainly from hepatic stellate cells (Ito cells) in the liver[30]. The trigger for the cleavage is the change in VWF conformation. Thus, in healthy plasma, VWF is present as multimers consisting of 2–80 subunits. Notably, larger multimers show stronger activity for platelet aggregation, namely hemostatic activity[31].

A genetic deficiency of ADAMTS13 causes the emergence of non-physiological UL-VWF multimers and induces thrombotic thrombocytopenic purpura (TTP) due to excessive thrombus formation in the microcirculation[32]. In comparison, genetic mutations in the VWF A2 domain, which increase susceptibility to cleavage by ADAMTS13, cause reduced HMW multimers and induce a hemostatic disorder classified as VWD type 2A (see below). A similar reduction in HMW multimers develops in various conditions such as cardiovascular diseases with excessive high shear stress, and autoimmune diseases that develop a hemostatic disorder, AVWS.

Mechanism of Development of AVWS

VWD is a hereditary disease caused by deficiency or dysfunction of VWF[33]. VWD is classified into several types: type 1 characterized by reduced VWF:Ag, type 2 by a qualitative change in VWF and type 3 by a complete loss of VWF[33]. Type 2 is divided into four subtypes:[33] Type 2A is characterized by a selective deficiency of HMW multimers, type 2B shows increased affinity to GPIb on the surface of platelets, type 2M shows a decreased binding affinity of VWF to platelets without selective reduction of HMW multimers, and type 2N is characterized by a decreased binding affinity for FVIII.

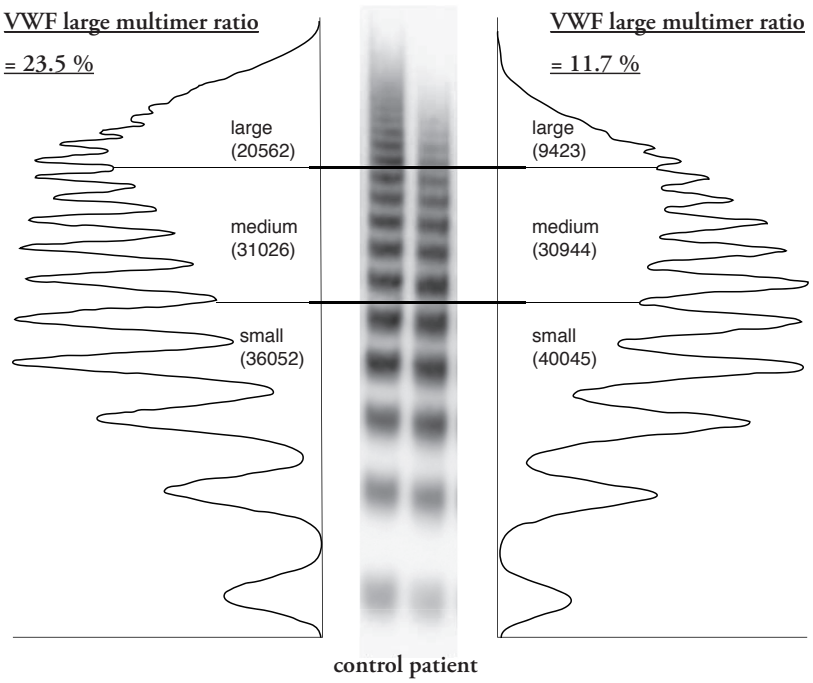
Similar VWF dysfunctions occur even without genetic mutations, which are designated as AVWS[34]. Lymphoproliferative diseases such as multiple myeloma and malignant lymphoma, myeloproliferative diseases such as polycythemia vera, malignant tumors, autoimmune diseases such as systemic lupus erythematosus, and some drugs such as griseofulvin and ciprofloxacin cause AVWS type 2 due to various causes such as autoimmunity and the absorption of VWF multimers[35-42]. It is, however, noted that the incidence of these is quite low. Hypothyroidism is sometimes accompanied by AVWS due to low protein production according to the nature of the disease[43]. The reduction of VWF:Ag is mild and hypothyroidism is not thought to be related to a bleeding disorder. The hypothyroidism-induced low expression of VWF is recovered when thyroid function becomes normal[43].

However, some cardiovascular diseases, such as aortic stenosis, cause AVWS[16]. Non-physiological high shear stress in blood excessively cleaves VWF multimers, resulting in AVWS with decreased HMW multimers. This pathophysiology of AVWS is similar to that of hereditary VWD type 2A.

Diagnosis of Shear Stress–Induced AVWS

A diagnosis of shear stress–induced AVWS includes the demonstration of the loss of HMW multimers. The current standard method is VWF multimer analysis. The multimers are separated by sodium dodecyl sulfate–containing agarose (not polyacrylamide) gel electrophoresis in a non-reduced condition and detected by western blot analysis with anti-VWF antibody to analyze giant molecules 500,000-20,000,000 Daltons in size. VWF multimer ladders from the lowest to the fifth, from the sixth to the tenth, and higher than the eleventh, are classified as low molecular weight (LMW), medium molecular weight (MMW), and HMW multimers, respectively (**Fig. 2**). The loss of HMW multimers is evaluated by comparison with the plasma of a healthy subject analyzed in the same gel[44].

VWF multimer analysis has not usually been evaluated quantitatively except for several studies, where 'VWF HMW multimer ratios' have been measured[16, 44, 45]. The ratio is calculated based on the densitometric analysis of a western blot of patients' plasma, defined as HMW multimer area per total VWF area[44]. Patients with aortic stenosis exhibited ratios ranging from 4–15% in a previous report[16] and 15–25% in our study[44], while an aortic stenosis severity–dependent decrease in the ratios was observed in both studies. Furthermore, the ratios of patients treated with LVAD have ranged from 20–60%[45]. Thus, the 'ratios' vary from study to study, probably due to the nature of the methods used. It seems difficult to use HMW multimer ratios for a severity classification of AVWS or as a comparison of severity across studies. To overcome the issue, we have recently proposed a value, named the VWF large multimer index,



$$\text{VWF large multimer INDEX} = \frac{\text{vWF large multimer ratio of the patient}}{\text{vWF large multimer ratio of the control}} \times 100$$

$$= \frac{11.7\ \%}{23.5\ \%} \times 100$$

$$= 49.9\ \%$$

Fig. 2. Quantification method for the calculation of the von Willebrand factor (VWF) large multimer index

This is defined as the ratio of the patient's HMW multimer ratio to the healthy subject's ratio analyzed in the same gel. With the index, a patient's high molecular weight (HMW) multimers are expressed as a percentage of those of a healthy control. The patient's plasma in this figure was from the patient with severe aortic stenosis with mean aortic pressure of 68 mmHg and peak blood flow of 5.24 m/sec.

that is defined as the ratio of the patient's HMW multimer ratio to the healthy subject's ratio that is analyzed in the same gel (**Fig. 2**)[44]. With the index, a patient's HMW multimers are expressed as a percentage of those of a healthy control. The plasma of the patient with severe aortic stenosis with mean aortic pressure of 68 mmHg and peak blood flow of 5.24 m/sec exhibits the VWF large multimer ratio 23.7% and the index 49.9% (**Fig. 2**).

Ristocetin induces platelet agglutination in the presence of HMW multimers[46]. With pre-fixed platelets, VWF ristocetin co-factor activity (VWF:RCo) can be measured automatically by laboratory analyzer in hospitals and expressed as a percentage of that of standard plasma. Usually, VWF:RCo and VWF:Ag are well correlated to each other, with VWF:RCo/VWF:Ag ratios normally 1.0[47, 48]. For the diagnosis of VWD type 2, a VWF:RCo/VWF:Ag ratio less than 0.6[49] or 0.7[50] is used as a reference for its diagnosis. It would be feasible if this value can be used for a diagnosis. However, it is not usually used for the diagnosis of cardiovascular disease–associated AVWS at the moment. In our preliminary analysis, the VWF:RCo/VWF:Ag ratio may be less sensitive than VWF multimer analysis, although they are moderately correlated. We are conducting further analysis to elucidate the precise reasons and improve the method.

Studies to evaluate AVWS severity with suitable quantitative values for HMW multimers and simultaneous bleeding events are definitely required. This would provide us with an AVWS severity classification useful for a clinical setting.

Heyde's Syndrome; Aortic Stenosis with Gastrointestinal Bleeding

Since aortic stenosis is an age-related disease, the number of patients is drastically increasing in many countries. Generally, severe aortic stenosis is defined as a mean aortic pressure higher than 40 mmHg, with peak blood flow faster than 4 m/sec, or an aortic valve area less than 1.0 cm^2 [51]. When severe aortic stenosis is accompanied by heart failure, syncope, or angina, invasive treatment such as a surgical aortic valve replacement and a transcatheter aortic valve implantation (TAVI) is considered [52, 53].

Aortic stenosis with gastrointestinal bleeding is designated as Heyde's syndrome since Dr. Edward Heyde first described such patients [54]. The mechanism of this syndrome has recently been uncovered: the gastrointestinal bleeding is caused by a hemostatic disorder AVWS (aortic stenosis–AVWS) and gastrointestinal angiodysplasia [55]. It has been reported that 7–24% of patients with gastrointestinal bleeding of unknown origin are associated with aortic stenosis [56].

The severity of AVWS is dependent on the severity of the aortic stenosis. HMW multimer ratios in patients with severe aortic stenosis negatively correlated with the mean transvalvular gradient [16]. We have also demonstrated that VWF large multimer indices in 31 severe aortic stenosis patients are decreased depending on the severity of the aortic stenosis [44]. Importantly, in these studies, the values of HMW multimers start to be affected at around 40 mmHg of mean pressure gradient, namely 50–60 mmHg of the maximal pressure gradient, through the aortic valve. Thus, severe aortic stenosis in most patients may be associated with AVWS. It is speculated that no less than 100,000 patients with AVWS associated with aortic stenosis may exist in Japan.

The prevalence of Heyde's syndrome, namely the development of gastrointestinal bleeding in patients with aortic stenosis, is rather high. Among patients with severe aortic stenosis, 27.5–38.7% develop the syndrome, while the definition of the gastrointestinal bleeding varies from study to study [44, 57]. It is noted that the exclusion of Heyde's syndrome is difficult even when the origin of the bleeding cannot be identified by upper and lower endoscopic examinations since approximately 20% of angiodysplasia develop in the small intestine [58].

For treatment of the acute phase of bleeding, supplementation of VWF by VWF-containing blood products, such as fresh frozen plasma and cryoprecipitate containing much VWF, could transiently be effective in addition to endoscopic hemostasis [59]. For radical therapy, the stenotic aortic valve itself should be treated by surgery [16, 60] or, more recently, TAVI [61, 62]. Without proper treatment of the valve, bleeding events would become repetitive. For example, a case who initially refused surgery experienced 10 bleeding events over a period of 2 years until he was treated with a surgical aortic valve replacement [44]. AVWS, namely the loss of HMW multimers, is rapidly recovered in a couple of days after treatment of the valve [63, 64]. It is noted that the HMW multimer is not recovered when perivalvular leaks occur associated with TAVI [65]. During surgery, strong anti-coagulation is required for the use of the cardiopulmonary bypass apparatus. Since a case with a subdural hematoma associated a surgical aortic valve operation has been reported [66], supplementation of VWF may be beneficial during treatment. Further evidence is required to clarify the operation-related bleeding risk and possible prevention by supplementation.

AVWS Caused by Other Cardiovascular Diseases

In addition to aortic stenosis, several cardiovascular diseases causing excessive high shear stress are associated with AVWS.

Hypertrophic cardiomyopathy sometimes causes an intraventricular obstruction, known as hypertrophic obstructive cardiomyopathy (HOCM). HOCM is sometimes associated with an intraventricular pressure gradient of more than 50 mmHg [67]. With a mechanism similar to that of aortic stenosis, HOCM can cause AVWS [68-70].

Several congenital structural heart diseases, such as a ventricular septal defect and tetralogy of Fallot, contribute to jet flow in the cardiovascular system. In these diseases, the development of AVWS and bleeding have been reported [71-73].

Pulmonary hypertension is a critical and progressive disease, sometimes resulting in fatal outcomes. AVWS has been reported to occur in patients with pulmonary hypertension [74-76]. Some patients with pulmonary hypertension are treated with anti-coagulant therapy to prevent the progression of the disease itself [77]. Since hemoptysis is a complication of pulmonary hypertension [78], careful attention should be paid to anti-coagulation therapy for such patients although only a proportion of patients with pulmonary hypertension may suffer from AVWS. Obstructive sleep apnea is associated with AVWS [79]. This could be caused by pulmonary hypertension during apnea periods.

Mitral regurgitation also causes AVWS [80, 81]. One study reported that 13.2% of patients with mitral regurgitation developed gastrointestinal bleeding and

41.5% of the patients had at least one positive bleeding according to a questionnaire[80]. In a clinical setting, however, mitral regurgitation has hardly been considered a hemostatic disorder. Thus, the association between mitral regurgitation and AVWS needs to be further evaluated in future.

AVWS Caused by Mechanical Circulatory Support

Mechanical circulatory supports play an important role in the treatment of life-threatening cardiopulmonary failure. Extracorporeal membrane oxygenation (ECMO; another name is V-V ECMO) is used for the treatment of acute respiratory failure. Under ECMO therapy, blood is collected through the outflow cannula inserted into the jugular vein and returned through the inflow cannula in the femoral vein after oxygenation by a centrifugal pump at 2–4 L/min. Bleeding is one of the major complications and has been thought to be exclusively due to antithrombotic therapy for the prevention of thrombosis. However, it has been demonstrated that ECMO is associated with AVWS, probably due to extraordinarily high shear stress inside the pump[82]. More recently, AVWS is thought to contribute to ECMO-associated bleeding complications[82-84]. Percutaneous cardiopulmonary support (PCPS), otherwise known as V-A ECMO or extracorporeal life support (ECLS), is used for the treatment of acute circulatory failure. PCPS is also associated with bleeding and AVWS is noted as one of its major cause[85, 86]. AVWS caused by PCPS is far more severe, with much lower VWF large multimer indces, compared to that caused by aortic stenosis[86].

A left ventricular assist device (LVAD) is a powerful tool for the treatment of end-stage heart failure[87, 88]. By taking continuous flow instead of pulsatile flow, the pump has become smaller and implantable in the thoracic cavity. Since patients can be discharged from hospital after successful LVAD implantation, the number of patients is drastically increasing. Up to 2016, 18,987 patients were treated with an implantable LVAD in the world[89]. LVAD-implantation is only permitted for bridging to cardiac implantation in Japan in 2011. While heart transplantation is performed in approximately 50 cases in Japan, 174 patients were treated with an LVAD from October 2015 to September 2016 [90].

Three-year survival rates after implantable LVAD are 59% in the world and 81.6% in Japan[89, 91]. The major complications of an implantable LVAD are infection of the drive-line that connects the implanted pump to the battery and computer outside of the body, intra-pump thrombosis and its related embolism, and bleeding. Bleeding most often occurs in the gastrointestinal tract in 10–33% of patients. To prevent pump thrombosis, antiplatelet and anticoagulation therapies are usually employed. It had been thought that LVAD-associated bleeding was due to the strong anti-thrombotic therapy. Nevertheless, LVAD-caused AVWS has been recently thought to contribute much to the bleeding[92, 93]. Bleeding occurs in not only an immediate or early phase but also even after years of LVAD implantation[92, 94]. The origin of the bleeding at an early phase could be from gastrointestinal mucosal damage, as observed in our patient who developed massive gastrointestinal bleeding at approximately 1 month after LVAD implantation from multiple ulcers and erosions of the colon[95]. In comparison, the gastrointestinal bleeding that develops at a later phase is considered to be from gastrointestinal angiodysplasia, since it would take some time, possibly several months, for the angiodysplasia to form after LVAD implantation. We have recently demonstrated that all 41 examined LVAD-treated patients exhibited far more severe AVWS compared to that in patients with aortic stenosis by quantitative analysis of AVWS[96]. Twelve patients (approximately 30%) developed gastrointestinal bleeding, where bleeding frequently occurred in patients with a VWF large multimer index below 40%[96], suggesting a critical role of AVWS in gastrointestinal bleeding in patients treated with LVAD. It is noted that four cases developed bleeding within 40 days after LVAD implantation, with 8 cases after 142 days[96]. One case developed bleeding on the 1,106th day after LVAD implantation[96].

Two kinds of rotary pumps, centrifugal and axial types, are utilized for LVAD. Sufficient blood flow is provided at ~4,000 rpm by centrifugal-type pumps and at ~8,000 rpm by axial pumps. Accordingly, axial type LVAD causes more severe AVWS than the centrifugal type[97]. Recently, it is found that platelet function is also impaired in patients treated with LVAD. This may also contribute to the bleeding associated with LVAD[98]. Thus, antiplatelet therapy, platelet dysfunction, AVWS, angiodysplasia and/or mucosal damage such erosion and ulcer are implicated in the pathogenesis of the LVAD-associated gastrointestinal bleeding (**Fig. 3**).

Much effort has been made to develop LVAD with reduced shear stress in the pump. HEARTMATE3 has achieved this by using a magnetically levitated centrifugal-flow pump[99]. However, HEARTMATE3 unexpectedly did not reduce the rate of gastrointestinal bleeding compared to the axial-flow pumps in the MOMENTUM3 trial[100]. Although the

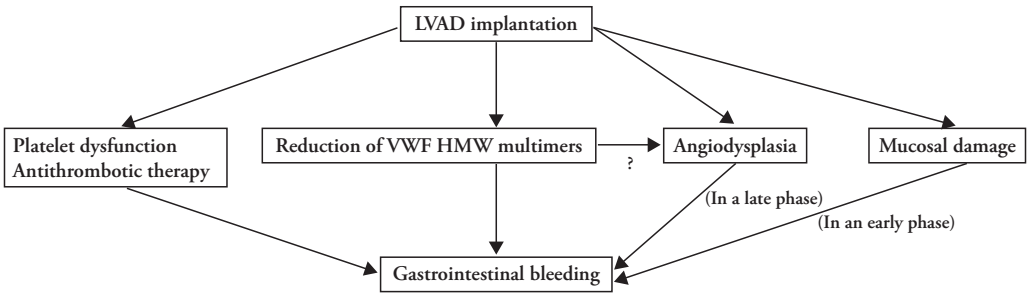


Fig. 3.
Pathogenesis of gastrointestinal bleeding associated in patients treated with an left ventricular assist device (LVAD). The gastrointestinal bleeding is caused by mucosal damage, platelet dysfunction, antithrombotic therapy, a reduction of von Willebrand factor (VWF) high molecular weight (HMW) multimers and angiodysplasia as possible causes. In an early phase, bleeding could be caused mainly by mucosal damage. In a late phase, bleeding could be caused mainly by angiodysplasia formed after LVAD implantation.

degree of reduction of HMW multimers was not shown, and therefore it is difficult to evaluate the contribution of the reduction in shear stress, it is possible that other factors may also contribute to LVAD-associated bleeding.

AVWS-Associated Gastrointestinal Angiodysplasia

Gastrointestinal angiodysplasia is frequently the origin of the gastrointestinal bleeding associated with cardiovascular disease-induced AVWS[55]. Angiodysplasia is an accumulation of dilated vessels in the subepithelial tissue susceptible to easy bleeding (**Fig. 4**). This lesion develops through the gastrointestinal tract from the stomach to rectum, more usually in the right colon in Western patients, while in the left colon in Japanese patients[101]. Furthermore, approximately 20% of the angiodysplasia develops in the small intestine[58]. Angiodysplasia increases in an age-dependent manner[102]. However, it develops in younger patients after LVAD implantation[103, 104]. Therefore, it is conceivable that the disease *per se* causes angiodysplasia, possibly through impaired perfusion of blood, reduced pulse pressure and/or a decrease of HMW multimers as well as for other reasons.

Angiodysplasia may be generated by the acceleration of immature angiogenesis[105]. Angiogenesis is initiated by endothelial migration and proliferation followed by maturation with surrounding pericytes and/or vascular smooth muscle cells[106]. Vascular endothelial growth factor (VEGF) induces endothelial migration and proliferation and angiopoietin-1 (Ang-1) plays a critical role in maturation through activation of its receptor Tie-2, where Ang-1 function is antagonized by another factor, Ang-2[107-109]. VEGF and Ang-2 are generated in endothelial cells in ischemia,

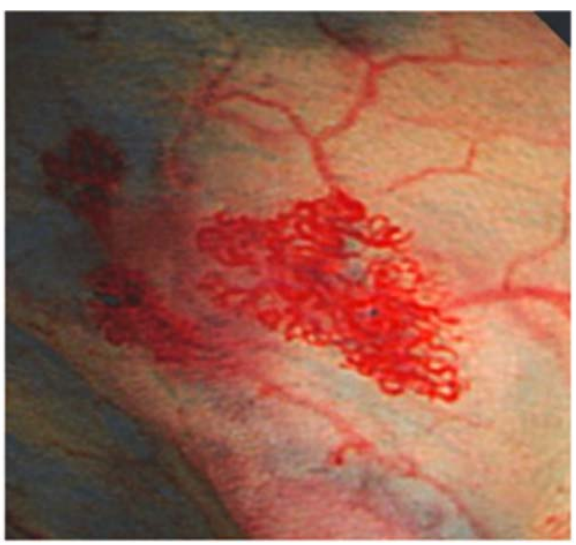


Fig. 4.
Typical angiodysplasia in the small intestine. The photo is adopted from Tamura *et al.*[44].

which may contribute to the enhancement of angiogenesis in ischemic tissue[110, 111]. Such angiogenesis-regulating factors may be involved in the formation of angiodysplasia since their expression is increased in the affected tissue[112,113]. Plasmas of LVAD-treated patients are known to strongly enhance endothelial proliferation and migration[114], suggesting the involvement of humoral factors. These may be VEGF and/or Ang2 in the tissue, the expression of which may be induced by the abnormal blood flow. Further, since VWF has an inhibitory function for angiogenesis[115], decreased HMW multimers *per se* may contribute to the formation of angiodysplasia[116-118]. Thus, much is still to be elucidated for a full understanding of the mechanism of angiodysplasia formation.

Conclusion and Perspectives

Non-physiological high shear stress generated in various cardiovascular diseases causes the hemostatic disorder AVWS by the excessive cleavage of VWF multimers.

Many issues remain to be elucidated: (1) how often and how severely does AVWS occur in each cardiovascular disease, (2) how often do bleeding events occur in each disease, (3) what severity of AVWS is a risk for bleeding, and (4) what treatment is suitable for hemostasis upon bleeding and in an operation. A severity classification, namely bleeding risk stratification, of cardiovascular disease-associated AVWS needs to be established.

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Disclosures

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