

Review Article

The Role of von Willebrand Factor in Coagulation

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ABSTRACT

Perfusionists should be able to verify diagnosis and recognize the forms of von Willebrand disease (vWD) which may require specific coagulation management during open heart procedures. von Willebrand factor (vWF) plays two distinct and important roles in clot formation subsequent to vascular injury. First, it promotes platelet binding to subendothelial surfaces and other platelets (platelet aggregation). Secondly, it also functions as a transport molecule for factor VIII, protecting factor VIII from proteolysis, thus preserving its catalytic role in the coagulation cascade. von Willebrand disease is a heterogeneous group of bleeding disorders which vary in molecular basis, symptomatology, and diagnostic parameters. The great majority of vWD patients will not greatly complicate management of hemostasis during cardiac surgery. Type I vWD patients, comprising 75% of cases, require only intraoperative DDAVP infusion, with cryoprecipitate available if necessary post-surgically. Type II patients vary in response to DDAVP, and may require infusion of cryoprecipitate or purified concentrates of vWF and factor VIII. DDAVP is contraindicated in vWD Type IIB since it has been shown to induce severe thrombocytopenia.

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LITERATURE REVIEW

INTRODUCTION

von Willebrand disease (vWD) is believed to be the most common inherited bleeding disorder, with a prevalence that may exceed 125 per million population (1). While the instances when a perfusionist will encounter a vWD patient are relatively rare, an understanding of the condition and appropriate measures for effective hemostasis are essential. Often, the operating room staff will have had little collective experience with vWD, and knowledge of how to proceed will be incomplete at best. The perfusionist may be called upon to provide guidance which can avert unnecessary morbidity or mortality. This paper will provide an overview of von Willebrand factor (vWF) and vWD, and a reference for perfusionists on appropriate procedures when a vWD patient must undergo cardiopulmonary bypass surgery.

Blood coagulation is a complex process characterized by dynamic equilibrium affected by blood vessels, platelets, and procoagulant and thrombolytic plasma proteins. Hemophilia, a disorder of this coagulation process has been noted for centuries. Furthermore, it was one of the first diseases recognized as being congenital (2).

In the 1920s the Finnish physician Erik Adolph von Willebrand began describing a congenital bleeding disorder which, while similar to hemophilia, bore certain distinguishing characteristics. Throughout the century, evidence began to accumulate that von Willebrand's disease is characterized by abnormal platelet function, while in contrast hemophilia A involves reduced levels of factor VIII procoagulant activity (VIII:C).

It is now known that von Willebrand factor and factor VIII are transported in plasma as a complex. This fact has been the source of much confusion about the structure and function of the two proteins. Work over the past decade has done much to clarify the distinctions and describe the interrelationship between factor VIII and vWF. In addition, a fairly wide spectrum of disorders, under the "umbrella" of von Willebrand disease have recently been identified. This paper will describe the role of vWF in blood coagulation, the disorders resulting from qualitative or quantitative abnormalities of this constituent, and effective therapy for management of hemostasis during surgery.

SYNTHESIS, STORAGE AND SECRETION OF VWF

It is now known that vWF is synthesized in vascular endothelial cells and in megakaryocytes (Figure 1). The initial molecule is called a precursor unit (pro-vWF) which undergoes post-translational modifications to form a larger, mature vWF subunit. These subunits then combine to form as many as 16 different multimers—discrete species of varying molecular weight, all considered forms of vWF (3).

Following synthesis, vWF is stored in endothelial cell organelles called Weibel-Palade bodies (85%) (4) and also in alpha granules of platelets (5). A variety of substances have been shown to stimulate the release of vWF from endothelial cells, notably thrombin, fibrin and 1-deamino-8-D-arginine-vasopressin

(DDAVP) (6). vWF is released from platelet alpha granules when platelets are activated by collagen, ADP, catecholamines, and thrombin (Figure 1).

The role of the two different storage sites for vWF becomes intuitively clear given an understanding of the role of vWF in hemostasis (described below). In general, endothelial cells release vWF from damaged areas of vascular walls promoting initial platelet adhesion. Thereafter, release of vWF from platelet alpha granules fosters platelet attachment to fibrin strands.

ROLE OF VWF IN HEMOSTASIS

There is now considerable evidence demonstrating that vWF serves two critical functions in the process of clot formation subsequent to vascular injury (Figure 1). First, it is a mediator of platelet adhesion to collagen and other subendothelial surfaces, and it promotes platelet-platelet aggregation. As will be seen, the initial platelet plug cannot form in the absence of vWF. Second, vWF is complexed noncovalently to procoagulant factor VIII in plasma. By protecting VIII:C from proteolytic digestion, vWF may regulate VIII:C levels (and thus procoagulant function) in plasma (7). It is hypothesized that factor VIII serves as a cofactor in the activation of factor X by factor IXa (8). Once activated, Factor X catalyzes the conversion of prothrombin to thrombin. Reduction of VIII:C levels will therefore severely limit the synthesis of fibrin. Thus, vWF plays a direct role in platelet adhesion, and an indirect role in the coagulation cascade which ultimately forms fibrin.

The role of vWF in stimulating platelet aggregation subsequent to vascular injury has been gradually clarified over the past 20 years. Experiments (9) have demonstrated that platelets do not attach normally to subendothelial surfaces in patients with vWD. This defect can be corrected by infusion of vWF-rich plasma (10). Studies have demonstrated that vWF does in fact bind to collagen and other subendothelial tissues (11) which are exposed to plasma when a blood vessel is injured.

It is hypothesized that, subsequent to vessel wall damage, endothelial cells release vWF which binds to collagen and other subendothelial tissue (see Figure 1). The vWF molecules (now bound to subendothelial surfaces) can then bind to adhesion proteins on the surfaces of activated platelets (12). Activated platelets also release vWF from alpha granules. This fosters formation of platelet aggregates (platelet-platelet binding) and platelet-fibrin interactions (13).

VWD AND HEMOPHILIA A

For several decades, von Willebrand disease researchers were unable to distinguish the bleeding diathesis described by von Willebrand in the 1920s from hemophilia A, at least with regard to their molecular basis. Symptomatically, there were some important differences noted. Hemophilia A was characterized by hemarthrosis (joint bleeding) and soft tissue hemorrhage while von Willebrand disease patients presented with mucocutaneous bleeding: bruising, epistaxis, oral bleeding and metromenorrhagia. It has since been determined that hemophilia

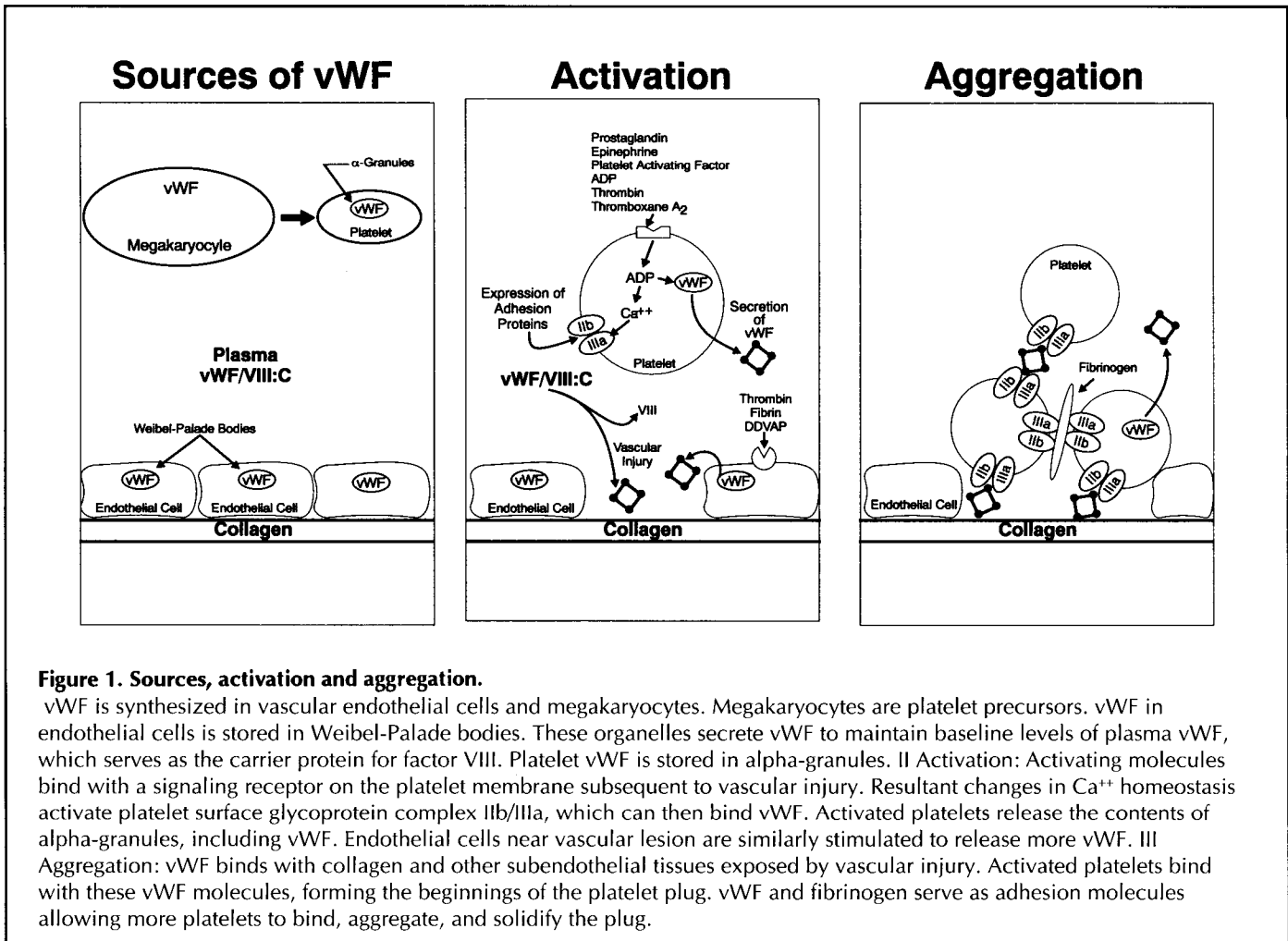


Figure 1. Sources, activation and aggregation.

vWF is synthesized in vascular endothelial cells and megakaryocytes. Megakaryocytes are platelet precursors. vWF in endothelial cells is stored in Weibel-Palade bodies. These organelles secrete vWF to maintain baseline levels of plasma vWF, which serves as the carrier protein for factor VIII. Platelet vWF is stored in alpha-granules. II Activation: Activating molecules bind with a signaling receptor on the platelet membrane subsequent to vascular injury. Resultant changes in Ca^{++} homeostasis activate platelet surface glycoprotein complex IIb/IIIa, which can then bind vWF. Activated platelets release the contents of alpha-granules, including vWF. Endothelial cells near vascular lesion are similarly stimulated to release more vWF. III Aggregation: vWF binds with collagen and other subendothelial tissues exposed by vascular injury. Activated platelets bind with these vWF molecules, forming the beginnings of the platelet plug. vWF and fibrinogen serve as adhesion molecules allowing more platelets to bind, aggregate, and solidify the plug.

A is specifically due to reductions in VIII:C activity, which limits fibrin formation. vWD by contrast is a genetic inability to synthesize quantitatively or qualitatively adequate vWF. von Willebrand disease will often be accompanied by reduced VIII:C levels but the symptoms are almost always characteristic of platelet (as opposed to coagulation cascade) dysfunction.

Early evidence of a molecular distinction between the two disorders was based on differential results of therapy. For instance, there were reports that treatment with VIII:C rich plasma fraction I-O, while somewhat helpful, did not work as completely for vWD patients as for those with hemophilia A (14). This was an indication that the blood constituent missing in vWD was distinct from VIII:C.

The advent of immunologic methodology allowed investigators to positively distinguish between vWF and VIII:C. Experiments demonstrated that hemophilia A patients had normal levels of vWF antigen, while vWD patients had little or none (15).

DIAGNOSIS OF VWD

Prolonged skin bleeding time is a primary diagnostic characteristic of vWD. The more severe cases will always present

with prolonged bleeding time whereas mild or moderate cases may have normal bleeding times.

A functional test for vWF which is still utilized was reported by Howard and Firkin in 1971 (16). The test is based on the fact that ristocetin, an antibiotic, induces platelet agglutination in normal individuals. It was shown that ristocetin-induced platelet aggregation was normal in patients with most hemophilic disorders, but markedly reduced or absent in vWD patients. The test may be referred to as ristocetin-induced platelet aggregation in platelet-rich plasma (RIPA). A variation of this principle is the assay for ristocetin cofactor activity (RCA). RIPA and RCA will be decreased in vWD with several exceptions noted below and in Table 1.

von Willebrand factor antigen (vWF:Ag) can be quantitatively measured by any of a variety of immunoassay techniques (15). vWF:Ag levels will often be below normal in vWD, however, normal or near normal levels have been seen in vWD patients so this test should not be considered definitive for diagnosis.

The factor VIII procoagulant antigen can be measured using the same immunologic techniques (17). Typically these

Table 1. von Willebrand Disease Diagnosis and Management.

<u>Parameters</u>	<u>vWD Type I</u>	<u>vWD Type II</u>	<u>vWD Type IIB</u>	<u>vWD Normandy</u>	<u>vWD Type III</u>
Bleeding Time	prolonged	prolonged	prolonged	?	markedly pro- longed
RIPA*	decreased	markedly decreased	increased	normal	absent
RCA**	decreased	markedly decreased	decreased to normal	normal	absent
vWF Antigen	decreased	decreased to normal	decreased to normal	normal	absent
Factor VIII Antigen	decreased	decreased to normal	decreased to normal	decreased	markedly decreased'
vWF Multimers	all multimers present	large and intermediate multimers absent	large multimers absent	all multimers present	no multimers present
Management During CPB	intraoperative DDAVP, cryo if needed postop	DDAVP if effective, cryo, vWF and VIII concentrates as required	DDAVP contra- indicated; use cryo of vWF/VIII concentrates	vWF infusion pre-op to bring VIII levels to normal	cryo, vWF and VIII infusion

*RIPA = Ristocetin-induced platelet aggregation in platelet-rich plasma

**RCA= Ristocetin cofactor activity

Information in this table based on reference (30)

levels are reduced in vWD patients. Reductions in factor VIII show high correlation with reductions in vWF.

Gel electrophoresis techniques have allowed investigators to analyze the multimeric structure of vWF. Such studies have resulted in the current classification system of vWD which identifies three general subtypes of the disease - types I, II, and III. In Type I vWD, all multimers of vWF are present but in abnormally low quantity (18). This subtype may comprise as many as 75% of vWD cases. Typically, VIII:C levels are decreased in proportion to, and secondary to, the reduction in vWF. The great majority of these patients can be effectively treated with infusion of DDAVP. A small percentage of Type I patients with low platelet concentrations of vWF do not respond well to DDAVP (19).

Type II vWD is characterized by absence of the larger vWF

multimers (20). DDAVP is ineffective in normalizing bleeding time in these patients since the vWF they secrete is structurally abnormal and may be limited in its ability to promote platelet aggregation and bind with and protect VIII:C. Type IIB vWD patients comprise 5% of vWD and present a particular concern regarding hemostasis during surgery. These patients apparently translate an abnormal vWF multimer which induces spontaneous platelet aggregation and removal from plasma (21). Thus these patients may present with transient or persistent thrombocytopenia which may be exacerbated by surgery (22). Moreover, infusion of DDAVP will result in severe thrombocytopenia with circulating platelet aggregates, thus presenting an increased risk of thromboemboli (23). Type IIB vWD patients will show an enhanced (rather than reduced) platelet aggregation response to ristocetin (RIPA).

Another variant of vWD Type II, vWD Normandy, has recently been reported (24). The vWF synthesized by these patients has no binding site for factor VIII. They show normal results when tested for RIPA, vWF antigen concentration and vWF multimer pattern. Factor VIII levels are decreased, and do not respond to DDAVP. Infusion of purified factor VIII results in only a temporary increase in plasma VIII levels. Infusion of purified vWF (which is structurally normal) causes a slow rise in factor VIII levels to normal values.

A third type of vWD has been categorized variously as Type III or severe Type I. In this rare but extremely severe subtype of vWD, vWF is markedly decreased or undetectable in platelets, plasma and endothelial cells (25).

Finally, a disorder called platelet-type or pseudo von Willebrand disease should be mentioned. Functionally, it appears to mimic Type IIB von Willebrand disease (26). In this case however the genetic mutation is in the platelet itself rather than in vWF. Bleeding time is prolonged while RIPA is increased and the larger vWF multimers are reduced. DDAVP may induce thrombocytopenia.

It should be remembered that there is some heterogeneity among the three "types" of vWD in the current classification system. Certain Type I patients may also present with structurally abnormal vWF, and some Type II patients have abnormally low levels of the vWF multimers they can synthesize. There is still much confusion about the appropriate classification of Type III vWD. Perhaps when more information is available, the current system will be considered inadequate, and a new classification system will arise.

THE THERAPY

The principal goal of therapy in vWD is to achieve normal hemostasis. Bleeding time must be normalized by returning vWF to normal levels. The coagulation cascade must also be normalized by returning VIII:C levels to normal when necessary. The mucosal bleeding characteristic of vWD occurs because of abnormal platelet function. During CPB this primary hemostasis may be achieved by cautery or suturing. In this case correction of a VIII:C mediated coagulopathy becomes a primary concern.

In essence there are two therapeutic modalities for treatment of vWD: blood products and DDAVP. The most effective of blood products is probably cryoprecipitate which contains high concentrations of the VIII/vWF complex (27). This would seem efficacious in Type II vWD where endogenous vWF is structurally incomplete. Concentrates of factor VIII/vWF are also available. In general, infusion of VIII/vWF, whether from cryoprecipitate or concentrates, is extremely effective in normalizing VIII:C activity, due both to the addition of exogenous factor VIII and to increased endogenous factor VIII secondary to vWF administration. The infused vWF will be cleared from the circulation more quickly than VIII:C, thus bleeding time will again become increased. It should be remembered that cryoprecipitate carries the risk of transmission of viral illness. This is why DDAVP, when effective, is the therapy of choice with

cryoprecipitate as a back-up measure if necessary to stop bleeding.

As stated above, DDAVP stimulates endothelial cell release of vWF. Thus it is effective in Type I vWD except when platelet vWF is also abnormal. Effectiveness of DDAVP in Type II vWD patients is variable. Test infusions of DDAVP can identify those patients who do respond positively. Platelet function will remain abnormal in Type II patients who do not respond to DDAVP. In such instances, factor VIII levels and platelet function can be transiently normalized with cryoprecipitate. This may prove sufficient during cardiopulmonary bypass (CPB) where bleeding can also be mechanically controlled (22).

SUMMARY

In the great majority of cases, vWD will not pose a significant hemostasis problem during CPB. Administration of DDAVP and/or cryoprecipitate will transiently return VIII:C levels to normal and thus stabilize coagulation function. Platelet function can also be normalized, especially in Type I patients who comprise as much as 75% of vWD cases. Platelet-related bleeding can also be managed by cautery and suturing during this type of surgery.

Spieß and Ivankovich (28) have reported a case study which uses thrombelastography (TEG) to monitor the effectiveness of DDAVP during CPB in a vWD Type I patient. A preoperative, pre-DDAVP TEG tracing revealed a profoundly reduced maximum amplitude (MA), indicative of platelet dysfunction. Infusion of DDAVP resulted in normalized TEG tracings both during and after surgery. No excessive postoperative bleeding was reported, and cryoprecipitate was apparently not needed.

Type II von Willebrand patients may not respond effectively to DDAVP. The perfusionist should make sure that cryoprecipitate is available for a Type II patient. In centers where they are available, purified concentrates of vWF should be considered. These have recently been shown to be effective in Type II and III vWD (29).

The area of chief concern for the perfusionist is Type II B vWD, where spontaneous thrombocytopenia is a constant problem. CPB, especially long pump runs, may severely exacerbate this condition. Furthermore, administration of DDAVP in these patients has been shown to induce severe thrombocytopenia with circulating platelet aggregates. Care must be taken prior to surgery to discern whether a vWD patient is Type II B.

ALGORITHM FOR HEMOSTASIS DURING CARDIAC SURGERY IN VWD PATIENTS

When confronted with a patient who is believed to have vWD, the perfusionist should do the following:

1. Attempt to confirm the diagnosis. Review patient records for evidence of skin bleeding time tests, RIPA or RCA, vWF:Ag and/or VIII:Ag concentrations, and analysis of

vWF multimer pattern.

2. If vWF Type I is confirmed (see Table 1), DDAVP should be infused (0.3 µg/kg) intraoperatively. Ensure that cryoprecipitate is available in the event of excessive postoperative bleeding.
3. If vWF Type II (non-B) is confirmed (see Table 1) review patient records for evidence of effective DDAVP therapy in the past. If none exists suggest a trial DDAVP infusion with bleeding time tests and/or TEG tracings to verify effectiveness. If effectiveness of DDAVP can be verified, follow same procedures as for Type I vWD. If DDAVP is not effective, or if effectiveness is unknown, ensure that vWF and factor VIII are available for infusion, either in cryoprecipitate or in some concentrated form.
4. If vWD Type IIB is verified, DDAVP is contraindicated. Structurally normal vWF and factor VIII should be available for infusion.
5. If vWD Normandy is verified, vWF should be infused prior to surgery, allowing enough time for factor VIII levels to rise to normal.

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