von Willebrand Disease and Cardiopulmonary Bypass: A Case Report

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The anesthetic management of patients undergoing cardiac surgery on cardiopulmonary bypass can be challenging. Contact of blood with extracorporeal surfaces results in altered coagulational integrity and increased risk of bleeding. Patients with preexisting bleeding disorders are particularly vulnerable. In this article we discuss the anesthetic management of a patient with von Willebrand disease (vWD) undergoing mitral valve replacement on cardiopulmonary bypass. vWD describes a number of different von Willebrand factor disorders, associated with variable degrees of bleeding, which require an individualized approach. The extent of the surgery, the patient-specific vWD coagulopathy, and clinical indicators guided our therapy, which included desmopressin, cryoprecipitate, and vWF/Factor VIII concentrate.

Keywords: Antihemophilic factor/von Willebrand factor complex [human], cardiopulmonary bypass, desmopressin, von Willebrand, vWF/FVIII.

In 1926, Finnish physician Erik von Willebrand reported symptoms of an unknown bleeding disorder in a large family from the Aland Islands, off the coast of Finland. This newly discovered malady, unlike hemophilia, affected both sexes. It became known as von Willebrand disease (vWD), which is the most common genetic coagulation disorder affecting 1% to 2% of the population worldwide. Gingival bleeding and epistaxis are frequently encountered in the affected individuals.1

vWD is a result of either quantitative or qualitative defects in the von Willebrand factor (vWF). The vWF is produced in the endothelial cells and bone marrow megakaryocytes and consists of multimers that are stored in platelet alpha granules and in Weibel-Palade bodies of endothelial cells. The vWF plays a crucial role in both primary and secondary hemostasis. In primary hemostasis, vWF facilitates platelet adhesion to sites of vascular injury by binding to platelets at the glycoprotein Ib (GPIb) receptor. To achieve secondary hemostasis, vWF binds and stabilizes factor VIII (FVIII), thus preventing its circulating clearance and reabsorption.2

vWD is divided into 3 types. Types I and III are characterized by partial and complete quantitative deficiencies respectively, whereas type II is caused by qualitative defects. Type II is further subdivided into IIA, IIB, IIN, and IIM, which relate to specific multimer size defects and the mechanisms of multimer loss. Type III is the most severe form of vWD and is characterized by very low or no detectable levels of vWF.2 Most forms of vWD are inherited through the autosomal recessive trait with the exception of type IIN and type III.3

Review of Disease Types
vWD type I accounts for 80% of all cases and is associated with mild to moderately severe vWF deficiency with a parallel decrease in FVIII. The vWF is functionally intact with a normal multimer component. Type I is frequently manifested by mucous membrane bleeds. Type IIA is characterized by the loss of large and intermediate multimers with the resultant decrease in vWF platelet-related function. Type IIB is often referred to as a “gain of function” defect. The vWF increasingly binds to a platelet’s GPIb receptor. The loss of large multimers and accelerated clearance of vWF/platelet complexes leads to thrombocytopenia. Type IIM involves impaired binding of vWF to GPIb on the platelet surface. Type IIN is an X-linked recessive disorder where the main feature is a decreased affinity of vWF for FVIII. This subtype resembles mild to moderate hemophilia A. Lastly, type III, an autosomal recessive inherited disorder, is the most severe form of the disease with virtually nonexistent vWF and severely depressed FVIII (Table 1). Spontaneous hemorrhages may occur. Patients with vWD may exhibit symptoms ranging from mucocutaneous bleeding, a hallmark of decreased circulating vWF, to soft tissue and joint bleeds, associated with low FVIII levels.1,3

Diagnosis
The diagnosis of vWD is made on the basis of a vWD assay, which includes coagulation factor VIII (FVIII:C) activity, vWF antigen (vWF:Ag), and ristocetin cofactor activity (vWF:RCOF). The latter test is most sensitive in the diagnosis of vWD. The vWF:RCOF examines the ability of vWF to agglutinate platelets in the presence of
ristocetin, an antibiotic similar to vancomycin, and reflects the interaction between vWF and GPIb. The vWF:Ag measures the vWF production defects. The ability of vWF to protect FVIII from degradation is reflected in FVIII:C activity. The vWF:RCoF/vWF:Ag ratio of less than 0.6 is considered abnormal and indicates the presence of qualitative defects, that is, vWD type II. Diagnostic and laboratory evaluation of vWD is presented in Table 2. These tests are warranted in patients with a history of unusual bleeding, especially after a tooth extraction, an abnormal coagulation profile, or both. Coagulation tests, such as prothrombin and partial thromboplastin time (PTT), are sensitive to FVIII levels. However, the FVIII level is not always decreased in vWD and the aforementioned tests may appear normal. The diagnosis of vWD should be made with caution in patients with type O blood because vWF and FVIII levels are naturally decreased in this population.  

Table 1. Pathophysiology and Treatment of von Willebrand Disease

<table>
<thead>
<tr>
<th>vWF type</th>
<th>Pathophysiology</th>
<th>First-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Partial quantitative vWF defect</td>
<td>DDAVP</td>
</tr>
<tr>
<td></td>
<td>All multimers are present</td>
<td></td>
</tr>
<tr>
<td>Type IIA</td>
<td>Qualitative defect. ↓ platelet-dependent vWF function. Loss of HMWM</td>
<td>DDAVP (mild bleeding)</td>
</tr>
<tr>
<td></td>
<td>vWF:RCoF</td>
<td>vWF/FVIII</td>
</tr>
<tr>
<td>Type IIB</td>
<td>“Gain of function” defect, ↑ vWF binding to platelet GPIb, ↑ clearance of the complex, loss of HMWM, ↓ platelet numbers</td>
<td>vWF/FVIII</td>
</tr>
<tr>
<td>Type IIM</td>
<td>↓ vWF dependent platelet adhesion</td>
<td>No HMWM loss</td>
</tr>
<tr>
<td></td>
<td>No HMWM loss</td>
<td>DDAVP</td>
</tr>
<tr>
<td>Type IIN</td>
<td>↓↓ vWF affinity for FVIII</td>
<td>No HMWM loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DDAVP</td>
</tr>
<tr>
<td>Type III</td>
<td>Complete quantitative defect of vWF</td>
<td>vWF/FVIII</td>
</tr>
</tbody>
</table>

Table 2. von Willebrand Disease Classification and Laboratory Values

<table>
<thead>
<tr>
<th>Condition</th>
<th>vWF:RCoF (IU dL−1)</th>
<th>vWF:Ag (IU dL−1)</th>
<th>FVIII</th>
<th>Ratio of vWF:RCoF/vWF:Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>&lt; 30c</td>
<td>&lt; 30c</td>
<td>↓ or normal</td>
<td>&gt; 0.5 to 0.7</td>
</tr>
<tr>
<td>Type IIA</td>
<td>&lt; 30c</td>
<td>&lt; 30–200c,d</td>
<td>↓ or normal</td>
<td>&lt; 0.5 to 0.7</td>
</tr>
<tr>
<td>Type IIB</td>
<td>&lt; 30c</td>
<td>&lt; 30–200c,d</td>
<td>↓ or normal</td>
<td>Typically &lt; 0.5 to 0.7</td>
</tr>
<tr>
<td>Type IIM</td>
<td>30–200</td>
<td>30–200</td>
<td>↓</td>
<td>&gt; 0.5 to 0.7</td>
</tr>
<tr>
<td>Type IIN</td>
<td>&lt; 3</td>
<td>&lt; 3</td>
<td>↓↓</td>
<td>Not applicable</td>
</tr>
<tr>
<td>“Low vWF”</td>
<td>30–50</td>
<td>30–50</td>
<td>Normal</td>
<td>&gt; 0.5 to 0.7</td>
</tr>
<tr>
<td>Normal</td>
<td>50–200</td>
<td>50–200</td>
<td>Normal</td>
<td>&gt; 0.5 to 0.7</td>
</tr>
</tbody>
</table>

Abbreviations: vWF, von Willebrand factor; RCoF, ristocetin cofactor; Ag, antigen; ↓ = decreased; ↑ = increased.

A 53-year-old man (188 cm, 98 kg) presented to the cardiothoracic surgical service for mitral valve replacement. The patient had a 3-year history of severe mitral valve regurgitation and had been symptomatic with shortness of breath and palpitations while walking 1 block. Preoperative transesophageal echocardiogram revealed a
moderately dilated left ventricle, left atrial enlargement, and an ejection fraction of 65% with reversal of flow in the pulmonary veins. Medical history included hypertension and panic attacks, controlled with benazepril and paroxetine respectively. In addition, the patient had a history of type 1 vWD. The diagnosis was made 3 years ago when, after cardiac catheterization, the patient developed uncontrolled bleeding and required hospitalization. Preoperative vWD assay (expressed in percent of normal) was consistent with type 1 vWD and the results were as follows: FVIII:C of 36%; vWF:Ag of 47%; and vWF:RCoF of 26%. Coagulation studies included the following results: platelet count, 186,000; prothrombin time, 13.4 seconds; PTT, 32.6 seconds; and international normalized ratio of 1.01. On physical examination a loud systolic/diastolic murmur was appreciated over the entire precordium. Chest x-ray and bilateral lung fields were unremarkable.

Per the hematologist’s recommendation, the patient received intravenous (IV) desmopressin (20 µg) 2.5 hours preoperatively. In the operating room, standard monitors were applied, 100% oxygen was administered via face mask, and an arterial line was placed. The patient’s baseline vital signs were as follows: blood pressure, 108/60 mm Hg; pulse, 60/min; respiration, 19/min; SaO₂, 98%. Intravenous anesthesia induction was achieved with fentanyl, 500 µg; lidocaine, 100 mg; propofol, 80 mg; and midazolam, 4 mg. Tracheal intubation was facilitated with cisatracurium (20 mg) intravenously. Anesthesia was maintained with isoflurane (0.2% to 0.9% end tidal) in an oxygen/air mixture (Fio₂ = 0.5). Central venous and pulmonary artery access was obtained via the right internal jugular vein, without evidence of hematoma. Baseline activated clotting time (ACT) was 105 seconds. A routine antifibrinolytic IV infusion of aminocaproic acid was initiated at 1 g/h after a loading dose of 10 g. After full heparinization (ACT of 375 seconds), cardiopulmonary bypass (CPB) was instituted. Anesthesia was maintained with a propofol infusion at 25 µg/kg/min and isoflurane through CPB. Blood was scavenged from the surgical field through the suction cannulae and returned to the CPB machine for oxygenation and recirculation. The surgical course was uneventful. The patient received a 31-mm Medtronic Mosaic tissue valve.

After the termination of the aortic cross clamp, rewarming began and an additional midazolam (5 mg) IV was administered for amnesia. The patient was placed on IV norepinephrine at 1 µg/kg/min and dobutamine at 5 µg/kg/min to augment afterload and cardiac contractility respectively, while weaning off CPB. Nitroglycerin at 0.3 to 1 µg/kg/min was infused to offset excessive increases in afterload and to improve coronary artery perfusion. The CPB was successfully discontinued and protamine (4 mg/kg) was administered, yielding an ACT of 115 seconds. Total operative time was 4 hours 16 minutes with CPB time of 1 hour 58 minutes. After cessation of CPB, the surgeons reported excessive oozing of blood in the surgical field. A second dose of desmopressin (20 µg) IV was infused. Fresh frozen plasma (2 U) and cryoprecipitate (20 U) were administered to replace clotting factors, FVIII and vWF in particular. Because functional platelets are required for primary hemostasis, 3 U of platelets were transfused. Packed red blood cells (3 U) were also given to maintain a goal hematocrit of 30 mg/dL. After the lapse of 30 minutes, oozing of blood in the field continued, which raised a concern of inadequate hemostasis. Estimated postbypass blood loss was 400 mL over 20 to 30 minutes. The decision was made to administer the vWF/FVIII concentrate antihemophilic factor/von Willebrand factor complex [human] (Grifols Biologicals Inc) 60 international units (IU)/kg IV. Following antihemophilic factor/von Willebrand factor complex [human] (Alphanate) administration, the oozing of blood diminished significantly and hemostasis was deemed adequate for surgical closure. The patient was transported to the intensive care unit in stable condition. The patient was extubated later that day. During the first 24 hours no signs of bleeding were observed from the surgical site and the combined output from 2 chest tubes was 340 mL of serosanguinous drainage. On postoperative day 1 a unit of packed red blood cells was transfused for a hematocrit of 28 mg/dL. The patient was discharged home on postoperative day 5 without anticoagulant medications.

Discussion

The pathophysiology of coagulation abnormalities associated with CPB is multifactorial. Contact of blood with CPB tubing results in endothelial dysfunction, platelet abnormalities, and hemodilution. Activation of the intrinsic coagulation pathway leads to the consumption of clotting factors. In addition, hypothermia, platelet receptor down regulation, fibrinolysis, and the use of heparin and protamine render platelets less functional and further contribute to hemostatic instability. Pharmacological agents like nitroglycerin, which was used in this case, as well as milrinone and nitroprusside, commonly used in cardiac surgery, also contribute to decreased platelet adhesion. Both the nitric oxide donors (nitroglycerin, nitroprusside) and milrinone affect platelet aggregation through activation of cyclic guanosine monophosphate pathway and inhibition of platelet’s adenosine diphosphate by high levels of cyclic adenosine monophosphate respectively.

The goals of treatment in vWD are to correct the dual defects of hemostasis, namely, the abnormal platelet adhesion and abnormal coagulation due to decreased FVIII (Figure). First-line therapy that can potentially correct both of these deficiencies is synthetic peptide 1-deamino-8-D-arginine vasopressin, also known as desmopressin. It induces the release of vWF from endothelial cells by

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binding to vasopressin-2 receptors and activating adenylate cyclase and cyclic adenosine monophosphate-mediated signaling, thus leading to exocytosis of vWF from Weibel-Palade bodies. Mechanisms responsible for desmopressin-mediated cellular release of FVIII are still poorly understood. Desmopressin, 0.3 µg/kg, increases vWF levels 3- to 5-fold above baseline within 1 hour and lasts for 6 to 8 hours. Desmopressin therapy is most efficacious in vWD type I because vWF is functionally intact. In contrast, it is ineffective in type III and is contraindicated in type IIB because it may precipitate severe thrombocytopenia. Tachyphylaxis may result with repeated desmopressin administration. Our patient received 2 doses of desmopressin, 7 hours apart, to maintain endogenous release of vWF as well as FVIII. Clinical signs of adequate hemostasis, as well as direct FVIII level measurement, can be used to assess the effectiveness of therapy. According to Ternström et al. most clotting factors, including fibrinogen, are significantly reduced after cardiac surgery on CPB and there is an inverse correlation between fibrinogen levels and postoperative bleeding. In our case, cryoprecipitate was administered to augment hemostasis by providing high concentrations of fibrinogen as well as vWF and FVIII. Although still in use, cryoprecipitate is not considered a mainstay therapy for hemostatic disturbances associated with vWD because of the potential risk of bloodborne viral infections. In cases where rapid hemostasis has to be established and desmopressin response is unsatisfactory, vWF/FVIII concentrates manufactured from pooled plasma are the therapy of choice. As the name suggests, a vWF/FVIII concentrate provides high concentration of vWF and FVIII and is prepared by cryoprecipitation. The treatment with vWF/FVIII concentrate can be symptomatic (to treat bleeding as it occurs), prophylactic (for surgical procedures), and/or as a secondary long-term prophylaxis (to treat/prevent recurrent bleeding at the specific sites). Although any concentrate can correct vWF:RCoF activity, the bleeding time response may not be consistent because of the potential loss of high molecular weight multimers in the process of product fractionation and purification. Therefore, clinical hemostatic stability is the most important parameter in the assessment of the effectiveness of the therapy.

There are a number of available vWF/FVIII preparations with variable vWF to FVIII ratios. Antihemophilic factor/von Willebrand factor complex [human] ratio of 1.0 ± 0.28 IU/mL reflects the approximately equal content of vWF and FVIII. Originally designed to treat hemophilia, antihemophilic factor/von Willebrand factor complex [human] showed promise in off-label use in vWD. Studies done with antihemophilic factor/von Willebrand factor complex [human] and other concentrates have established their efficacy and safety for both surgical prophylaxis and bleeding episodes in patients with vWD. The recommended adult dose is 60 IU/kg. Additional doses of 40 IU/kg can be administered at 8- to 12-hour intervals as needed based on clinical indicators, such as oozing from the surgical site. Adequacy of treatment is evaluated based on the outcomes expected for healthy individuals undergoing the same procedure. In our case, because the oozing of blood in the surgical field

Figure. The Role of von Willebrand Factor in Coagulation Cascade: Mechanism of Action of von Willebrand Factor Replacement Therapies

A: vWF is released from endothelium at the site of injury. B: vWF binds to collagen level of subendothelium and to GPIb receptor on platelets, thus promoting platelet adhesion. C: Another function of vWF is to stabilize FVIII. D: Desmopressin acts on endothelium, facilitating the release of vWF. E: vWF/FVIII concentrate provides the exogenous vWF and FVIII, which then participate in the coagulation process.

Abbreviations: vWF, von Willebrand factor; FVIII, factor VIII; GPIb, glycoprotein Ib.
was ongoing and refractory to desmopressin, as well as factor and platelet therapy, an intervention with antihemophilic factor/von Willebrand factor complex [human] was warranted. Postoperatively, the patient was monitored for signs of adequate hemostasis. After a single dose of antihemophilic factor/von Willebrand factor complex [human], the patient exhibited no evidence of bleeding from the operative site or chest tubes and had a normal PTT level at 24-hour follow-up and throughout the entire postoperative course. Routine PTT measurement was used, as it reflects intrinsic pathway factor activity, including FVIII.18 Measurements of FVIII:C, vWF:Ag, and vWF:RCoF were impractical in our case because the specimens had to be sent to an outside testing facility.

Extrinsic FVIII concentrate should be administered cautiously, because high levels of FVIII have been associated with deep vein thrombosis.1,13 Rapid antihemophilic factor/von Willebrand factor complex [human] administration (>10 mL/min) can result in an altered vasomotor response. Concentrate administration has to be discontinued immediately if fever, chills, urticaria, and/or wheezing develop.16

**Conclusion**

Management of patients with vWD presents a unique challenge to an anesthesia provider because the hemostatic response in the face of surgery can be unpredictable. Understanding the underlying pathophysiology of vWD, its subtypes, and diagnostic tests is important. Collaboration with a hematologist is crucial. History of excessive bleeding, especially after tooth extraction, should be given its due attention. The course of treatment would depend on the type of vWD defect and the extent of surgery. To maintain primary hemostasis, the presence of functional vWF and platelets is necessary, whereas in secondary hemostasis FVIII is required to participate in the intrinsic clotting pathway. Desmopressin therapy is indicated in vWD types where vWF is functionally intact. The 2 types of vWD that do not warrant desmopressin infusion are type IIB and type III. The former places a patient at an increased risk for profound thrombocytopenia and the latter will render the desmopressin therapy futile. The vWF/FVIII concentrate is the treatment of choice for vWD types where desmopressin treatment is ineffective or contraindicated (see Table 1). Although antihemophilic factor/von Willebrand factor complex [human] was used in our case, other concentrates currently available in the United States offer different features that could be advantageous for patients with certain vWD types, and a hematologist should be consulted on this account. The vWF/FVIII concentrate may be used either for surgical prophylaxis or to treat bleeding as it occurs. Clinical signs of hemostatic stability are the most important variables in guiding the treatment.

**REFERENCES**


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