Shear Rate-Dependent Impairment of Thrombus Growth on Collagen in Nonanticoagulated Blood From Patients With von Willebrand Disease and Hemophilia A

By Edith Fressinaud, Kjell S. Sakariassen, Chantal Rothschild, Hans R. Baumgartner, and Dominique Meyer

Thrombus formation on collagen fibrils was quantified at venous (100/s) and arterial (650/s and 2,600/s) wall shear rates in blood from patients with various subtypes of von Willebrand disease (vWD) and with hemophilia A (HA). Nonanticoagulated blood was drawn directly from an antecubital vein over purified type III collagen fibrils exposed in parallel-plate perfusion chambers. Blood-collagen interactions were differentiated and quantified by morphometry as platelet adhesion, thrombus height, thrombus volume, and deposition of fibrin strands. Sixteen patients with vWD, including four type III, six type I, four type IIa, and two type IIb, were compared with 26 normal subjects and nine patients with HA, including six severe HA and three mild HA. Platelet adhesion and thrombus formation at 2,600/s were significantly decreased in blood from patients with vWD type III, IIa, and IIb, but not in blood from patients with type I and in HA. The abnormal thrombus formation was apparently not related to the decreased levels of factor VIII (F.VIII), because thrombus height and volume were normal in severe and mild vWD.

Nonanticoagulated blood was perfused directly from an antecubital vein over purified type I collagen fibrils exposed in parallel-plate perfusion chambers. Blood-collagen interactions were differentiated and quantified by morphometry as platelet adhesion, thrombus height, thrombus volume, and deposition of fibrin strands. Sixteen patients with vWD who had not received plasma concentrates or 1-deamino-8-D-arginine vasopressin for at least 1 week before study. This group consisted of 26 healthy male and female volunteers, 22 to 57 years old, not having ingested aspirin for a period of at least 1 week before study.

Sixteen patients with vWD who had not received plasma concentrates or 1-deamino-8-D-arginine vasopressin for at least 1 month were studied. Six normal subjects and nine patients with HA were included as additional controls, because vWD patients with virtually undetectable levels of vWF in plasma have decreased F.VIII levels that are within the range of those in patients with mild HA. In this study of patients with vWD and HA using native blood and collagen as reactive surface, we emphasize the crucial role of vWF in thrombus formation at high shear rates and that of F.VIII at intermediate and low shear conditions.

MATERIALS AND METHODS

Subjects

The studies were performed after obtaining informed consent from all subjects. This group consisted of 26 healthy male and female volunteers, 22 to 57 years old, not having ingested aspirin for a period of at least 1 week before study.

vWD. Sixteen patients with vWD who had not received plasma concentrates or 1-deamino-8-D-arginine vasopressin for at least 1 month were studied. Six patients have the classical form of the disease (type I) with vWF antigen (vWFAg) levels of 15 ± 3 U/dL, ristocetin cofactor activity of vWF (vWFRCO) levels of 8 ± 2 U/dL, and F.VIII levels of 19 ± 3 U/dL (Table 1). Four patients have the severe form of the disease (type III) with a bleeding time greater than 30 minutes, undetectable levels of vWFAg and vWFRCO, and F.VIII levels of 7 ± 1 U/dL (Table 1). Four patients have characteristic findings of type IIa, with a bleeding time greater than 15 minutes, markedly decreased levels of vWFRCO (< 3 U/dL for three patients and 13 U/dL for the fourth), vWFAg levels of 34 ± 8 U/dL, and F.VIII levels of 38 ± 20 U/dL (Table 1). Two other patients with type IIb have a bleeding time of 18 and 15 minutes, vWFAg levels of 25 and 36 U/dL, vWFRCO levels of 6 and
vWF AND F. VIII IN THROMBUS FORMATION

Table 1. Characteristics of the 16 Patients With vWD (type I, III, IIA, and IIB) and of the Nine Patients With HA

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Bleeding Time (min)</th>
<th>vWFAg (U/dL)</th>
<th>vWFRCo (U/dL)</th>
<th>VIII:C (U/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I (n = 6)</td>
<td>12</td>
<td>24</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>14</td>
<td>8</td>
<td>14</td>
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<td>9</td>
<td>9</td>
<td>15</td>
<td>27</td>
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<td>9</td>
<td>10</td>
<td>7</td>
<td>15</td>
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<td></td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 ± 1*</td>
<td>15 ± 3*</td>
<td>8 ± 2*</td>
<td>19 ± 3*</td>
</tr>
<tr>
<td>Type III (n = 4)</td>
<td>&gt; 30</td>
<td>&lt; 0.5</td>
<td>&lt; 3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>&lt; 0.5</td>
<td>&lt; 3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>&lt; 0.5</td>
<td>&lt; 3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>&lt; 0.5</td>
<td>&lt; 3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>&lt; 0.5</td>
<td>&lt; 3</td>
<td>7 ± 1*</td>
</tr>
<tr>
<td>Type IIA (n = 4)</td>
<td>15</td>
<td>57</td>
<td>13</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>32</td>
<td>&lt; 3</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>17</td>
<td>&lt; 3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>29</td>
<td>&lt; 3</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>34 ± 8*</td>
<td>38 ± 20*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IIB (n = 2)</td>
<td>18</td>
<td>25</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>16</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>HA</td>
<td>ND</td>
<td>187 ± 52*</td>
<td>167 ± 58*</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Severe (n = 6)</td>
<td>ND</td>
<td>96 ± 13*</td>
<td>100 ± 18*</td>
<td>9 ± 3*</td>
</tr>
<tr>
<td>Mild (n = 3)</td>
<td>ND</td>
<td>50-200</td>
<td>50-200</td>
<td>50-200</td>
</tr>
<tr>
<td>Controls (n = 26)</td>
<td>2-9</td>
<td>50-200</td>
<td>50-200</td>
<td>50-200</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not done.

*Mean values ± SEM.

14 U/dL and F VIII levels of 20 and 24 U/dL (Table 1). For all these patients, analysis of the multimeric structure of vWF12 and responsiveness of platelet-rich plasma to different ristocetin concentrations13 confirmed the diagnosis.

HA. Nine patients with HA were studied: six with a severe form (F VIII, < 1 U/dL) and three with a mild form (F VIII, 9 ± 3 U/dL) (Table 1). Levels of vWFAg were 187 ± 52 U/dL in the first group and 96 ± 13 U/dL in the second. The vWFRCo levels were 167 ± 56 and 100 ± 18 U/dL, respectively (Table 1).

Bleeding Time

The bleeding time was performed on the patients' forearms using a standardized template device (Simplate II; General Diagnostics, Organon Teknika Co, Durham, NC).

Blood Samples

Platelet counts and hematocrit (Hct). After venepuncture with a 19-gauge needle, blood was collected into EDTA before each perfusion experiment for platelet count and Hct. Platelet counts were measured by an electronic counting device (Coulter Counter Model S-Plus; Coulter Electronics Inc, Hialeah, FL).

The average value for platelet count in normal subjects was 262 ± 10^3/L (range, 175 to 398 × 10^3/L); in patients with vWD type I, 293 ± 10^3/L (176 to 401 × 10^3/L), type III, 358 ± 10^3/L (299 to 403 × 10^3/L), type IIA, 247 ± 10^3/L (188 to 315 × 10^3/L), type IIB, 81 and 175 ± 10^3/L in mild HA, 247 ± 10^3/L (154 to 329 × 10^3/L); and in severe HA, 186 ± 10^3/L (124 to 269 × 10^3/L). The average values for Hct were 42% (35% to 51%) in control subjects; 44% (37% to 52%) in patients with vWD type I, 41% (37% to 47%) in type III, 40% (36% to 43%) in type IIA, 45% (39% to 49%) in type IIB; 43% (30% to 47%) in mild HA, and 43% (32% to 54%) in severe HA.

Assay of F.VIII and vWF. Before each perfusion experiment, blood was also collected into 1/10 volume of 0.11 mol/L trisodium citrate. F.VIII activity was assayed by a one-stage clotting technique14; vWFAg by enzyme-linked immunosorbent assay (ELISA)15; and vWFRCo using formalin-fixed platelets.14 The concentration of these three parameters was expressed in units per deciliter using pooled normal plasma from 20 donors calibrated against the NIBSC (National Institute for Biological Standards and Control, London, UK) First International Reference Preparation for Factor VIII-related activities in plasma.

Thrombogenic Surface

The thrombogenic surface consisted of purified fibrillar human type III collagen that was coated onto plastic cover slips. Type III collagen was purified from a pepsin extract of lyophilized human placenta by selective salt precipitation.16 The final preparation appeared more than 95% pure as judged by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and densitometry scanning. Fibrils were obtained by dialysis for 48 hours17 and collagen concentration was measured by hydroxyproline assay.18 This preparation is nonprocoagulant and induces optimal platelet aggregation in platelet-rich plasma at 4 U/g/mL.9 The fibrillar collagen suspension of 0.7 to 1.2 mg/mL was sprayed onto plastic cover slips (Thermanox TM; Miles Lab, Naperville, IL) to a final density of about 20 μg/cm^2, as previously described.19 The collagen-coated cover slips were stored at 22°C for about 16 hours before they were used in perfusion experiments.

Ex Vivo Perfusions and Fixation

Ex vivo perfusions. Nonanticoagulated blood was drawn by a pump directly from an antecubital vein (Butterfly 19-gauge; Abbott Hospital Products North, Chicago, IL) over type III collagen fibrils on a plastic cover slip positioned in a parallel-plate perfusion chamber. The pump was placed distally to the chamber.20 Shear rates at the collagen surface of 100/s, 650/s, and 2,600/s were maintained for 5 minutes at a constant flow rate of 10 mL/min in three parallel-plate perfusion chambers having different geometric dimensions of the blood flow channel.21

Postperfusion was performed for 20 seconds with buffer consisting of 130 mmol/L NaCl, 2 mmol/L KCl, 12 mmol/L NaHCO3, 2.5 mmol/L CaCl2, and 0.9 mmol/L MgCl2, pH 7.4, at the same flow rate. Subsequently, fixing (2.5% glutaraldehyde in 0.1 mol/L cacodylate, pH 7.4) was perfused for 40 seconds, followed by removal of the cover slip from the chamber and immersion into freshly prepared fixative at 4°C for 60 minutes.19 The cover slips were then stored for up to 1 week in 0.1 mol/L cacodylate buffer containing 7% sucrose before they were embedded in Epon.

Morphometric evaluation. Evaluation of semithin sections of thrombotic deposits was performed on Epon-embedded sections (0.8-μm thick) prepared at an axial position of 1 mm downstream from the flow inlet at the cover slip and perpendicular to the direction of the blood flow.20 The sections were stained by toluidine blue and basic fuchsin. All these procedures have been described in detail by Sakariassen et al22 and Muggli et al.18 The morphometric analysis was evaluated according to Baumgartner and Muggli,22 where platelet adhesion is quantified as the percentage of the total surface covered with adherent platelets (contact and spread platelets) and with fibrin (fibrin deposition). Thrombus dimensions were assessed by computer-assisted morphometry by measuring the height and area of all thrombi higher than 2.5 μm (IBM computer and DlASYS program; Heinz Meyer Datalab, Thöringen, Switzerland).23 Data were expressed as average thrombus...
height (in micrometers) and average thrombus volume per unit surface area (\( \mu m^3/\mu m^2 \)).

**Statistical Analysis**

The results were expressed as mean ± SEM. P values < .05 were considered significant based on Student’s t-test.

**RESULTS**

**Platelet Adhesion**

Platelet adhesion was measured as the percent of the surface covered with platelets.

- **Wall shear rate of 100/s.** Platelet adhesion in blood from vWD (all subtypes) and from severe and mild HA was not significantly different from control values (Fig 1 and Table 2).

- **Wall shear rate of 650/s.** Platelet adhesion in blood from patients with vWD type III was slightly decreased, at the limit of significance (\( P < .05 \)); it was also slightly decreased in blood from the two patients with vWD type IIB. It was normal in vWD type I and type IIA and in severe and mild HA (Fig 1 and Table 2).

- **Wall shear rate of 2,600/s.** Platelet adhesion in blood from patients with vWD type III and IIA was significantly lower than that from normal controls (\( P < .003 \) and \( P < .0001 \), respectively; Fig 1 and Table 2). It was also markedly decreased in blood from the two patients with vWD type IIB. Platelet adhesion was slightly decreased in type I vWD, but this was not statistically significant. Platelet adhesion was within the normal range in mild HA and slightly, but not significantly, increased in severe HA (Fig 1 and Table 2).

**Thrombus Dimensions**

Thrombus dimensions were measured as height and volume of thromb.

- **Wall shear rate of 100/s.** The average thrombus volume (Table 2) and thrombus height were within the normal range for all groups of patients (Figs 2 and 3), except for severe HA, in which the thrombus height was significantly reduced (\( P < .05 \)).

  - **Wall shear rate of 650/s.** The average thrombus height in vWD type III and IIA was significantly reduced as compared with control subjects (\( P < .005 \)), and markedly decreased in vWD type IIB (Fig 2). The average thrombus volume (Table 2) was also decreased (\( P < .009 \) in type III, \( P < .05 \) in type IIA) (Fig 3). Thrombus height and volume were slightly but not significantly decreased in type I vWD (Figs 2 and 3).

  - In severe HA, there was also a significant reduction in thrombus height (\( P < .003 \)) and in thrombus volume (\( P < .009 \)) (Table 2), whereas in mild HA thrombus dimensions were within the normal range (Figs 2 and 3).

- **Wall shear rate of 2,600/s.** Thrombus dimensions were significantly reduced in all types of vWD (\( P < .01 \) to \( P < .05 \) for thrombus height and thrombus volume) (Figs 2 and 3). There was also a significant reduction of thrombus height (\( P < .03 \), Fig 2) and of thrombus volume (\( P < .03 \), Fig 3) in type I vWD, even though there was no significant decrease in platelet adhesion (Table 2).

  - In mild HA, thrombus height and thrombus volume were within the normal range, whereas they were slightly, but not significantly, increased above the normal range in severe HA (Figs 2 and 3).

**Fibrin Deposition**

Fibrin deposition was measured as the percent of the surface covered with fibrin.

- **Wall shear rate of 100/s.** In vWD type I, fibrin deposition on collagen was comparable with that of the controls (Fig 4). In all other types of vWD and in severe and mild HA, very little fibrin was deposited on the surface, but the decrease was not statistically significant because of the relatively large dispersion of fibrin deposition in the control group (Fig 4).

- **Wall shear rate of 650/s.** The deposition of fibrin was only significantly reduced (\( P < .05 \)) in severe HA as com-
pared with the normals (Fig 4). In all types of vWD and in mild HA, the difference in deposition was not significant (Fig 4).

Wall shear rate of 2,600/s. No significant differences in fibrin deposition between the low range in controls and the various groups of patients were observed (Fig 4). The average value of the control group was 5%.

**DISCUSSION**

It is apparent that both F.VIII and vWF are required for optimal thrombus formation at arterial blood flow conditions. However, the requirement for F.VIII is apparent at relatively low arterial wall shear rates (≤650/s), whereas the requirement for vWF is more pronounced at higher arterial wall shear rates (≥650/s). Thus, the F.VIII-vWF complex in plasma supports thrombus formation by different mechanisms that are shear rate dependent. However, the experiments are not conclusive in regard to whether F.VIII and vWF increase the growth rate and/or the stabilization of the thrombi, and to what extent vWF in plasma and in platelets supports thrombus formation.

At a high shear rate of 2,600/s, which is in the range of

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Table 2. Platelet Adhesion and Thrombus Volume in Blood From Controls and Patients With vWD and HA

<table>
<thead>
<tr>
<th></th>
<th>Platelet Adhesion (%)</th>
<th>Thrombus Volume (μm³/μm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shear Rate (s⁻¹)</td>
<td>100</td>
</tr>
<tr>
<td>vWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>18.0 ± 3.1 (n = 6)</td>
<td>45.9 ± 6.6 (n = 5)</td>
</tr>
<tr>
<td>Type III</td>
<td>18.8 ± 1.4 (n = 3)</td>
<td>28.9 ± 8.5* (n = 4)</td>
</tr>
<tr>
<td>Type IIA</td>
<td>24.4 ± 4.7 (n = 3)</td>
<td>47.8 ± 2.0 (n = 4)</td>
</tr>
<tr>
<td>Type IIB</td>
<td>12.1 and 14.2 (n = 2)</td>
<td>37.2 and 29.8 (n = 2)</td>
</tr>
<tr>
<td>HA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>23.4 ± 0.9 (n = 3)</td>
<td>41.9 ± 14.1 (n = 3)</td>
</tr>
<tr>
<td>Severe</td>
<td>10.7 ± 2.7 (n = 5)</td>
<td>54.5 ± 7.0 (n = 6)</td>
</tr>
<tr>
<td>Controls</td>
<td>17.2 ± 2.0 (n = 22)</td>
<td>54.1 ± 2.7 (n = 23)</td>
</tr>
</tbody>
</table>

Experimental conditions are indicated in Fig 1. These values indicate the mean ± SEM and are those of Fig 1 for platelet adhesion and Fig 3 for thrombus volume.

*P < .05.  †P < .003.  ‡P < .009.  §P < .003.  ||P < .0001.
those at the apex of stenosed arteries, platelet adhesion was significantly decreased in all types of vWD, except type I. However, all subtypes, including type I, had a striking decrease in thrombus formation. These results are compatible with a role for vWF in thrombus formation at wall shear rates of stenosed arteries, particularly in view of the impaired thrombus formation but normal platelet adhesion in the patients with vWD type I. F.VIII is apparently not involved in thrombus formation under these experimental conditions, because both adhesion and thrombus dimensions were normal in our patients with mild and severe HA.

At an intermediate shear rate (650/s), blood from vWD type III and IIB only exhibited a partial defect in platelet adhesion, but still a severe abnormality in thrombus formation. In vWD type I and IIA, there was no defect of platelet adhesion, but the formation of platelet thrombi remained abnormal. However, the deposition of fibrin was normal. vWF thus also appears essential for platelet-platelet interaction at this shear condition. Blood from severe HA patients showed platelet adhesion within the normal range, but a markedly decreased thrombus formation at this flow condition. The defective thrombus formation cannot be related to vWF, which is quantitatively and qualitatively normal in these patients. However, fibrin deposition was also significantly reduced and it is likely that the impaired formation of thrombin and/or fibrin leads to less growth and/or stabilization of platelet thrombi. Blood from patients with mild HA had normal fibrin deposition and thrombus formation, despite F.VIII levels within the range of those in vWD patients.

At the lowest shear rate tested (100/s) at which no significant difference in platelet adhesion was noticed, fibrin formation on collagen was not significantly decreased in all types of vWD and in patients with HA. However,
there is a substantially lower deposition of fibrin on collagen than on subendothelium. This may be explained by the absence of tissue factor in collagen. Thus, fibrin levels are low in our control group. However, it is interesting to note that in severe HA, in which fibrin deposition was consistently nil, a significant decrease of thrombus height existed, suggesting a role for thrombin and fibrin in thrombus growth and/or stabilization, respectively.

These results are in agreement with those of Turitto et al and Weiss et al, who showed reduced thrombus formation on subendothelium of rabbit aorta in patients with vWD type III and type IIA and with severe HA. However, we show further (1) a clear role of vWF in thrombus formation at relatively high arterial shear rates through the study of patients with vWD type I; and (2) a role of F.VIII in thrombus formation at intermediate arterial and venous shear rates through the study of patients with severe HA. Furthermore, these results were obtained with human fibrillar type III collagen, which lacks tissue factor and thus induces much less deposition of fibrin than procoagulant subendothelium. The quantitation of blood-collagen interactions was performed at an extreme upstream position to avoid the axial dependence phenomena, contrary to Weiss et al and Turitto et al, who quantitated thrombus formation at the midsection. Upstream quantitation is important in comparative studies of thrombus formation, because the size of the thrombi decreases along the axis of the surface due to rapid growing thrombi at the upstream end, which depletes the blood layers streaming adjacent to the surface for platelets farther downstream. Despite these differences in methodology, our results are in good agreement with those reported by Weiss et al and Turitto et al.

Thus, at venous and intermediate arterial shear conditions, F.VIII influences thrombus formation presumably through the generation of thrombin and fibrin. It is known that thrombin exerts two activities in the local control of thrombosis: it stabilizes the growing thrombus by catalyzing fibrinogen polymerization to fibrin and it can activate platelets independently of fibrin formation. Several groups have already commented on the possible role of thrombin in platelet recruitment. In a previous study, Sakariassen et al have found a dramatic increase of thrombus formation in nonanticoagulated blood as compared with citrated blood. Baumgartner and Sakariassen showed that heparin reduced the thrombus volume by 72% at 5 minutes of perfusion time at a wall shear rate of 650/s in rabbits. This indicates that activation of coagulation plays a pivotal role in thrombus growth and/or stability. In a successive study, Hanson and Harker tested the effect of a synthetic inhibitor of thrombin in a baboon model of arterial graft thrombosis and also showed a role for thrombin in thrombus formation at a wall shear rate of 450/s. Our studies with blood from patients with hemostatic defects confirm these observations and indicate, furthermore, that thrombin may also recruit platelets at venous shear conditions.

One function of vWF is to prevent degradation and removal of F.VIII from the circulation and possibly to carry this procoagulant protein to the site of a developing clot. The localization of vWF in plasma, platelets, and vessel wall and its multimeric structure contribute to its efficient role in hemostasis. At intermediate and high shear conditions, vWF was known to mediate platelet adhesion, but this study clearly emphasizes that vWF is also involved in platelet cohesion at these flow conditions. Because glycoprotein IIb/IIIa (GPIIb/IIIa) is required for platelet-platelet interaction, it is most likely that the binding of plasma and/or platelet vWF to this receptor is needed in vivo for optimal thrombus formation. Platelet GPIIb/IIIa has been identified as the major binding site for released platelet vWF. Several studies indicate that the interaction of vWF with GPIIb/IIIa mediates platelet thrombus formation. It would therefore be interesting to perform ex vivo perfusions with different subtypes of vWD type I containing various amounts of platelet vWF to see whether there is a correlation between the quantity and/or quality of platelet vWF and the formation of thrombi.

ACKNOWLEDGMENT

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