DDAVP Enhances Platelet Adherence and Platelet Aggregate Growth on Human Artery Subendothelium

The effect of intravenous 1-deamino (8-D-arginine)vasoressin (DDAVP) administration on platelet interaction with human artery subendothelium was investigated with flowing blood from five normal individuals and 12 patients with von Willebrand’s disease (vWD). Three of the patients were diagnosed as vWD subtype I, four as subtype Ila, and five as subtype IIb. DDAVP administration to normals enhanced platelet adherence, in parallel with increasing plasma levels of factor VIII-related antigen (FVIIIR:Ag) and ristocetin cofactor activity (FVIIIR:RCF). Platelet aggregate formation was transiently increased within 90 minutes. Platelet adherence in patient blood before DDAVP infusion was subnormal. In patients with subtype I, administration of DDAVP normalized the bleeding time, enhanced the platelet adherence, and transiently improved the platelet aggregate formation. The platelet adherence was more corrected than would have been expected on the basis of the FVIIIR:Ag and FVIIIR:RCF levels. In patients with subtype Ila, infusion of DDAVP increased the FVIIIR:Ag levels approximately threefold, without affecting the FVIII:RCF levels, and in only two of four patients was a transiently enhanced platelet adherence with a corresponding shortening of the bleeding time observed. In patients with subtype IIb, administration of DDAVP increased the FVIIIR:Ag levels about threefold and the FVIIIR:RCF levels five to tenfold, but decreased the platelet adherence significantly. The bleeding time values were not normalized. A close association between the bleeding time values and corresponding platelet adherence values before and after DDAVP infusion was observed. Normalization of the bleeding time was paralleled with normalization of platelet adherence. We conclude that DDAVP improves the primary hemostasis by causing enhanced FVIII-vWF-mediated platelet aggregation. DDAVP has little or no effect on the bleeding time in patients with subtype Ila and subtype IIb, because the platelet adherence is not normalized.

THE SYNTHETIC ANALOGUE of the antidiuretic hormone 1-deamino(8-D-arginine)vasoressin (DDAVP) increases the plasma levels of factor VIII procoagulant activity (FVIII:C), factor VIII-related antigen (FVIIIR:Ag), and ristocetin cofactor activity (FVIIIR:RCF). Platelet aggregate formation was transiently increased within 90 minutes. Platelet adherence in patient blood before DDAVP infusion was subnormal. In patients with subtype I, administration of DDAVP normalized the bleeding time, enhanced the platelet adherence, and transiently improved the platelet aggregate formation. The platelet adherence was more corrected than would have been expected on the basis of the FVIIIR:Ag and FVIIIR:RCF levels. In patients with subtype Ila, infusion of DDAVP increased the FVIIIR:Ag levels approximately threefold, without affecting the FVIII:RCF levels, and in only two of four patients was a transiently enhanced platelet adherence with a corresponding shortening of the bleeding time observed. In patients with subtype IIb, administration of DDAVP increased the FVIIIR:Ag levels about threefold and the FVIIIR:RCF levels five to tenfold, but decreased the platelet adherence significantly. The bleeding time values were not normalized. A close association between the bleeding time values and corresponding platelet adherence values before and after DDAVP infusion was observed. Normalization of the bleeding time was paralleled with normalization of platelet adherence. We conclude that DDAVP improves the primary hemostasis by causing enhanced FVIII-vWF-mediated platelet aggregation. DDAVP has little or no effect on the bleeding time in patients with subtype Ila and subtype IIb, because the platelet adherence is not normalized.

MATERIALS AND METHODS

Patient Population and Normal Subjects

Seventeen patients with vWD were investigated at the Hemophilia and Thrombosis Centre “Angelo Bianchi Bonomi,” Milan, Italy, and one patient with vWD was investigated at the Department of Haematology, University Hospital Utrecht, The Netherlands.
The patients were characterized as subtype I (three cases), subtype IIa (six cases), subtype IIb (six cases), and as vWD subtype III (three cases). The characterization was performed on the basis of ristocetin-induced platelet aggregation in platelet-rich plasma, FVIII-vWF-related properties, and multimeric structure of plasma FVIII-vWF and von Willebrand factor (vWF) in the platelets, and family history.\textsuperscript{12,13,14} Patients with vWD subtype I have little FVIII-vWF, with a parallel decrease in FVIII:C, FVIIIR:Ag, and FVIIIR:RCF. The multimeric pattern is normal. Patients with vWD subtype IIa lack multimers with high and intermediate molecular weight. FVIII:C and FVIIIR:Ag are normal or slightly decreased; FVIIIR:RCF is low or absent. Patients with vWD subtype IIB lack the largest multimers of FVIII-vWF, and FVIII:C and FVIIIR:Ag are normal or slightly decreased. FVIIIR:RCF is low, but the platelet aggregation of platelet-rich plasma with low doses of ristocetin is increased. Patients with vWD subtype III have nondetectable or minute amounts of FVIII-vWF-related properties. The family history and FVIII-vWF determinations usually indicate that these patients are homozygous recessive. Detailed descriptions of the Italian patients have recently been reported\textsuperscript{4,5,6,15-17} (Tables 1 and 2). The Dutch patient has nondetectable FVIII-vWF-related properties in plasma and is characterized as vWD subtype III on the basis of the family data.\textsuperscript{18}

Five normal individuals from the staff of the Hemophilia and Thrombosis Centre in Milan volunteered as controls. Patients and normals were informed about the experimental nature of the investigation before obtaining voluntary consent. All experimental procedures were performed according to the Declaration of Helsinki. None of the individuals had been subjected to any medication for at least 14 days before the start of the investigation.

\textbf{Intravenous DDAVP Administration}

Intravenous administration of DDAVP (Minirin, Valeas, Milan, Italy) in patients and normals was performed at the Hemophilia and

\begin{table}[h]
\centering
\caption{Hematocrit, Platelet Count, and Bleeding Time Values in the Normal Subjects and the Patient Population}
\begin{tabular}{|c|c|c|c|}
\hline
 & Hematocrit & Platelet Count & Bleeding Time \\
 & \% & \times 10^9/L & (min) \\
\hline
Normal subjects & & & \\
Z.R. & 43 & 2.5 & 5 \\
A.M. & 36 & 4.3 & 3 \\
L.G. & 40 & 3.7 & 6 \\
M.B. & 40 & 1.9 & ND* \\
G.A. & 37 & 2.1 & ND \\
\hline
vWD subtype I & & & \\
Gia.P. & 45 & 3.1 & 12 \\
Giu.P. & 36 & 3.2 & 22 \\
C.I. & 48 & 2.4 & 13 \\
\hline
vWD subtype IIa & & & \\
A.C. & 34 & 2.7 & >30 \\
L.M. & 34 & 4.5 & >30 \\
L.P. & 29 & 2.1 & >30 \\
C.P. & 40 & 2.5 & >30 \\
G.P. & 27 & 3.6 & >30 \\
A.M. & 48 & 2.9 & 8 \\
\hline
vWD subtype IIb & & & \\
A.F. & 48 & 2.0 & 16 \\
P.D. & 50 & 1.4 & 19 \\
C.C. & 49 & 2.0 & 13 \\
M.C. & 40 & 1.7 & >30 \\
E.C. & 42 & 2.6 & 21 \\
N.C. & 32 & 3.2 & >30 \\
\hline
vWD subtype III & & & \\
B.B. & 28 & 4.1 & >30 \\
B.Z. & 45 & 1.5 & >30 \\
A.Z. & 49 & 2.1 & >30 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{FVIII-Related Properties (U/dL) Before and After DDAVP Infusion}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|c|c|c|}
\hline
\hline
\multicolumn{5}{|c|}{Before DDAVP} & \multicolumn{5}{|c|}{30 min After DDAVP} & \multicolumn{5}{|c|}{90 min After DDAVP} \\
\hline
Normal subjects & & & & & & & & & & & & \\
Z.R. & 166 & 76 & 132 & 532 & 288 & 272 & 296 & 346 & 284 \\
A.M. & 123 & 146 & 196 & 348 & 224 & 336 & 346 & 352 & 360 \\
L.G. & 69 & 61 & 89 & 288 & 182 & 312 & 302 & 202 & 300 \\
M.B. & 61 & 82 & 88 & 92 & 146 & 104 & 130 & 180 & 220 \\
G.A. & 98 & 104 & 124 & 210 & 156 & 260 & 172 & 272 & 256 \\
\hline
vWD subtype I & & & & & & & & & & & & \\
Gia.P. & 12 & 8 & 6 & 82 & 38 & 22 & 90 & 61 & 14 \\
Giu.P. & 23 & 9 & 6 & 122 & 31 & 20 & 100 & 41 & 16 \\
C.I. & 21 & 18 & <6 & 126 & 36 & <6 & 128 & 50 & <6 \\
\hline
vWD subtype IIa & & & & & & & & & & & & \\
A.C. & 52 & 61 & <6 & 136 & 122 & <6 & 346 & 244 & <6 \\
L.M. & 61 & 76 & <6 & 274 & 228 & <6 & 324 & 276 & <6 \\
L.P. & 32 & 19 & <6 & 380 & 117 & <6 & 288 & 106 & <6 \\
C.P. & 34 & 48 & <6 & 324 & 216 & <6 & 384 & 312 & <6 \\
G.P. & 70 & 48 & <6 & & & & & & & \\
A.M. & 53 & 63 & <6 & & & & & & & \\
\hline
vWD subtype III & & & & & & & & & & & & \\
A.F. & 10 & 43 & 8 & 93 & 116 & 100 & 116 & 178 & 108 \\
P.D. & 46 & 74 & 21 & 300 & 187 & 131 & 308 & 338 & 128 \\
C.C. & 46 & 24 & 8 & 192 & 84 & 45 & 316 & 220 & 136 \\
M.C. & 44 & 33 & 13 & 246 & 106 & 44 & 323 & 202 & 108 \\
E.C. & 42 & 51 & 10 & 225 & 150 & 112 & 380 & 344 & 184 \\
N.C. & 63 & 53 & 14 & & & & & & & \\
\hline
\end{tabular}
\end{table}

*Patient not infused with DDAVP.
Thrombosis Centre in Milan. DDAVP is licensed in Italy for use in the treatment of vWD.

DDAVP was diluted in 100 mL saline and infused intravenously at a dose of 0.4 μg/kg body weight during a period of 30 minutes. Mild facial flushing occurred during and immediately after infusion, but no other side effects were observed.

**Bleeding Time Measurements and Blood Collection**

The primary bleeding time in patients and three of the five normals was measured before and 30 and 90 minutes following the start of DDAVP infusion by means of an automated template device (Simplate II, General Diagnostics, Morris Plains, NJ). Blood samples were collected in parallel with the bleeding time measurements by clean venipuncture through 19-gauge needles into 1/10 vol 110 mmol/L trisodium citrate or 1/10 vol 130 mmol/L trisodium citrate. Blood anticoagulated with 110 mmol/L citrate was used for perfusion studies, and blood anticoagulated with 130 mmol/L citrate was used to assay FVIII-vWF-related properties. Whole blood for determination of hematocrit and platelet count was anticoagulated with 2 mmol/L EDTA. The hematocrit, platelet count, and bleeding time values are summarized in Table 1. Previous experience has indicated that DDAVP has no effect on the hematocrit and platelet count in blood from these patients (unpublished results).

**Assays of FVIII-vWF–Related Properties**

FVIII:C was measured in a one-stage clotting assay, FVIIIIR:Ag by electroimmunodiffusion using rabbit anti-FVIII-vWF serum raised against human FVIII-vWF, and FVIIIIR:RCF with formalin-fixed platelets and 1.0 mg ristocetin/mL. The lower detection limit of these assays was <1, <3, and <6 U/dL for FVIII:C, FVIIIIR:Ag, and FVIIIIR:RCF, respectively. Reference plasma for FVIII:C, FVIIIIR:Ag, and FVIIIIR:RCF was fresh frozen plasma pools (1/10 vol 130 mmol/L trisodium citrate) from 40 normal subjects, stored at ~80°C, and calibrated in U/dL against the First International Plasma Standard for FVIII-vWF (National Institute for Biological Standard and Controls, London, UK).

**Perfusion Studies With Whole Blood**

Perfusion studies with whole blood were performed at 37°C with steady flow in an annular perfusion chamber, according to Baumgartner. The distance between the outer wall of the chamber and the surface of the artery mounted on the rod was 0.6 mm and the length of the rod was 77.0 mm. Segments of a human umbilical artery denuded of endothelium were everted and mounted on rods and subsequently exposed for 3 minutes to flowing blood at a flow rate of 107 mL/min, corresponding to a wall shear rate of 2,500 sec⁻¹. The artery segments were about 1.0-cm long, and the endothelium was removed by brief air exposure, similar to that reported for the human renal artery. Prior to a perfusion run, the arteries were treated for 1 hour with 0.1 mol/L aspirin (A 5376, Crystalline, Sigma, St. Louis, MO), dissolved in 0.2 mol/L Tris-HCl buffer, pH 7.35, in order to inhibit prostaglandin I₂ (PGI₂) production, and subsequently washed 4 times with the Tris-HCl buffer. PGI₂ inhibits platelet adherence and platelet aggregate formation in flowing blood on subendothelium of the rabbit aorta.

**Morphological Studies**

Platelet–subendothelium interaction was quantified with morphometric evaluation according to Baumgartner et al. Following perfusion, the artery segments were fixed in 2.5% glutaraldehyde and 2.0% osmium tetroxide, dehydrated with graded ethanol, and finally embedded in epon. Sections about 1-μm thick were stained at 70°C for 2 minutes with basic fuchsin and methylene blue.

Light microscopic evaluation of platelet interaction with the subendothelium at a magnification of 1,000× was performed with a specially constructed eye-piece micrometer in the ocular (E. Leitz, GMBH, Wetzlar, FRG). The platelet interaction with the subendothelium was divided into platelet adherence and platelet aggregate formation. Platelet adherence (the sum of contact (C) and spread platelets (S)) was expressed as percentage of subendothelial surface covered by adhering platelets, and finally corrected for the 1-μm thickness of the section. Platelet aggregate formation was defined as the percentage of spread platelets covered with aggregates of more than two platelets.

**Perfusion Studies With Reconstituted Blood**

In a few experiments, purified plasma FVIII-vWF was added to normal plasma in order to mimic the high plasma levels observed after administration of DDAVP. FVIII-vWF was purified from human cryoprecipitate according to the method of van Mourik and Mochtar, with some minor modifications. In these experiments, the platelet–subendothelium interaction was studied by means of 111In-radiolabeled platelets, under flow conditions similar to those described for whole blood. 111In-oxine was obtained from Byk Mallinckrodt, Petten, The Netherlands. The platelets were treated with 10 μmol/L aspirin and washed 3 times, as previously reported. Aspirin treatment inhibits platelet aggregate formation on subendothelium, but does not affect the platelet adherence. Moreover, the platelet count was kept subnormal (1.2 × 10¹¹/L) in order to minimize platelet aggregate formation at physiologic red cell concentration. Thus, the radioactivity associated with the artery segment may be taken as indicative of adherent platelets.

**Statistical Analysis**

Statistical calculations were performed with a HP Hewlett-Packard 65 (Advanced Product Division, Cupertino, CA). Linear regression analysis, power curve fit analysis, t statistic for two means, and standard error (SE) were performed with the programs STAT 1-22A, STAT 1-23A, STAT 1-30A, and STAT 1-02A, respectively.

**RESULTS**

**Normal Individuals**

Administration of DDAVP to normal individuals gave a two to fourfold increase of all FVIII-vWF–related properties (Table 2). The bleeding time values were not affected (Fig 1A), but the platelet adherence was significantly enhanced (P < .025) after DDAVP infusion, and remained so for 90 minutes (Fig 1B).

A transient increase of platelet aggregate growth was also observed (Fig 1C), but these values dropped toward the preinfusion level within 90 minutes.

**Patients With vWD Subtype I**

DDAVP normalized the bleeding time in all patients with vWD subtype I (Fig 1D). The plasma levels of FVIII:C and FVIIIIR:Ag increased, respectively, four to eightfold and two to fivefold, but in only two of the three patients did FVIIIIR:RCF increase three to ten-
In patient C.I., FVIIIR:RCF remained below the detection limit of the method (<6 fold (Table 2). In all patients, however, the subnormal platelet adherence was enhanced by DDAVP administration, reaching levels above the normal range (Fig 1E). The platelet aggregate formation was transiently enhanced after DDAVP infusion, similar to what was observed in normals (Fig 1F).

**Patients With vWD Subtype Ila**

DDAVP infusion in four patients with vWD subtype Ila increased the plasma levels of FVIII:C and FVIIIR:Ag, respectively, five to elevenfold and six to sevenfold (Table 2). The plasma level of FVIIIR:RCF, however, was not affected and remained below the detection limit. In patient L.M., the bleeding time was transiently normalized, and in patient C.P., a transiently shortened bleeding time was measured (Fig 2A). This was in parallel with a slightly enhanced platelet adherence in the blood from both patients, although not normalized (Fig 2B). In patient L.P., the bleeding time and the platelet adherence were not affected. In the blood of patient A.C., the platelet adherence decreased after DDAVP infusion and the bleeding time remained >30 minutes at 30 minutes after infusion and dropped to 22 minutes at 90 minutes after infusion.

In the blood of the patients G.P. and A.M. (not treated with DDAVP), the platelet adherence was, respectively, 6% (bleeding time: >30 minutes) and 13% (bleeding time: 8 minutes). Thus, all patients with vWD subtype Ila had subnormal platelet adherence before DDAVP infusion.

Platelet aggregate formation was not morphometrically scored because of the low percentage of spread platelets (S), which makes the estimation of platelet aggregate formation impractical and unreliable.

**Patients With vWD Subtype IIb**

DDAVP infusion in five patients with vWD subtype IIb increased the plasma levels of FVIII:C, FVIIIR:Ag, and FVIIIR:RCF (Table 2). FVIII:C and FVIIIR:Ag reached values similar to those seen after DDAVP infusion in normal subjects, especially at 90 minutes postinfusion. FVIIIR:RCF increased five to tenfold above the values found before DDAVP administration, but reached a level about half of that observed in normal subjects after DDAVP infusion. The bleeding time was not normalized, but was shortened in patients M.C. and E.C. (Fig 2C). In patients A.F. and P.D., the bleeding time was longer following DDAVP infusion. Before infusion, platelet adherence in blood from all patients was impaired. After DDAVP treatment, the platelet adherence transiently decreased in four of five patients (Fig 2D). For the patient group as a whole, this decrease in platelet adherence reached significance (P < .050). The bleeding time values were not well correlated with the results of the platelet adherence studies. Patient N.C., not treated with DDAVP, had a baseline platelet adherence of 4% (bleeding time: >30 minutes).

Platelet aggregate formation was not morphometrically evaluated because of the low percentage of spread platelets.

**Patients With vWD Subtype III**

The three patients investigated with vWD subtype III were not infused with DDAVP. Values of hematocrit, platelet count, and bleeding time are given in...
Table 1. None of these patients had detectable amounts of FVIII:C, FVIIIIR:Ag, and FVIIIIR:RCF in plasma, and their platelet adherence values were therefore considered as the basic adherence level. The platelet adherence in the blood of these patients was subnormal, being 4% (B.B.), 7% (B.Z.), and 8% (A.Z.), compared with a range of 17%–25% in normal subjects.

Platelet aggregate formation was not scored because of the low percentage of spread platelets. Infusion of DDAVP in these patients had no effect on the FVIII-vWF-related properties and their prolonged bleeding time.2

Platelet Adherence v Bleeding Time

The percentage platelet adherence in blood from all normals and patients before and after DDAVP treatment, was correlated with the plasma level of FVIIIIR:Ag by means of power curve fit analysis (Fig 4). Values of $r^2$ were 0.54 and 0.72, respectively. In patients with vWD subtype I, however, the platelet adherence was more enhanced than in normals when related to the plasma levels of FVIIIIR:Ag. Patients with vWD subtype IIa and subtype IIb showed increased FVIIIIR:Ag levels in plasma, without any effect on the platelet adherence.

In a few experiments, the plasma level of FVIIIIR:Ag was increased in vitro by the addition of

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**Fig 2.** Bleeding time values (A) and platelet adherence (B) to human artery subendothelium in blood from patients with vWD subtype IIa before (0 minutes) and 30 and 90 minutes following the start of DDAVP infusion. Bleeding time values (C) and platelet adherence (D) to human artery subendothelium in blood from patients with vWD subtype IIb before (0 minutes) and 30 and 90 minutes following the start of DDAVP infusion. For further details see legend to Fig 1.
Adherence so 25
vwD-1 .
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SM (x 10^11/cm^3)

Fig 4. Correlation between platelet adherence to human artery subendothelium and plasma levels of FVIIIR:RCF (U/mL) measured before and 30 and 90 minutes following the start of DDAVP infusion. The percentage adherence was measured in blood from normal subjects (●), patients with vWD subtype I (○), subtype IIa (□), subtype IIb (x), and vWD subtype III (●). Power curve fit analysis revealed, for normals and subtypes I, IIa, and IIb, r^2 values of, respectively, 0.54, 0.72, 0.05, and 0.11. Experimental conditions are given in Materials and Methods.

![Graph](image1)

Various amounts of purified FVIII-vWF to normal plasma. Concentrations of FVIIIR:Ag that were in the same range as those in plasma of normal individuals 30 and 90 minutes after DDAVP infusion were produced. The platelet–subendothelium interaction was measured with ^{111}In-labeled platelets and was found to be correlated with the amount of plasma FVIIIR:Ag; r^2 = 0.90 on power curve fit analysis (Fig 5). A similar tendency was observed with DDAVP-containing blood (Fig 4).

Correlation between the percentage platelet adherence and the FVIIIR:RCF values was observed in normal individuals before and after DDAVP infusion by means of linear regression analysis, with r^2 = 0.61 (Fig 6). In one patient (C.I.) with vWD subtype I, the platelet adherence reached values above the normal range 30 and 90 minutes following DDAVP infusion, without any detectable FVIIIR:RCF (Table 2 and Fig 1E). In contrast, patients with subtype IIb had normal amounts of FVIIIR:RCF 30 and 90 minutes following DDAVP administration, but without any effect on platelet adherence (Table 2 and Fig 2D).

**DISCUSSION**

Intravenous administration of DDAVP in normals and patients with vWD subtype I enhanced platelet adherence to, and the growth of, small platelet aggregates on the damaged vessel wall. In patients with vWD subtype I, the enhanced platelet adherence was associated with normalization of the primary bleeding time. In patients with vWD subtype IIa, DDAVP had little effect on platelet adherence or bleeding time. In patients with vWD subtype IIb, DDAVP decreased the platelet adherence significantly and had a poor effect on bleeding time.

In patients with vWD subtype I, the enhanced platelet adherence following DDAVP infusion was higher than would have been expected on the basis of the plasma levels of FVIIIR:Ag and FVIIIR:RCF. This may indicate that the FVIII-vWF released by

![Graph](image2)

**Fig 5.** ^{111}In-labeled platelet deposition on human artery subendothelium in reconstituted normal blood (●) at FVIIIR:Ag plasma levels of 1.3, 2.3, and 3.3 U/mL. The FVIIIR:Ag plasma levels were increased by adding, respectively, 1.0 and 2.0 U FVIIIR:Ag/mL of a purified FVIII-vWF preparation to normal plasma. Power curve fit analysis revealed a r^2 value of 0.90. The range of platelet deposition in reconstituted blood (platelets and red cells from normals) with plasma from patient A.Z. (vWD subtype III) is included for comparison (■). Experimental conditions are given in Materials and Methods.

![Graph](image3)

**Fig 6.** Correlation between the platelet adherence to human artery subendothelium and the plasma levels of FVIIIR:RCF (U/mL) in normal blood before and 30 and 90 minutes following the start of DDAVP infusion. Linear regression analysis revealed a r^2 value of 0.61. Experimental conditions are given in Materials and Methods.
DDAVP in this subtype has a relatively higher potency to mediate platelet adherence than in normal subjects. Another possibility may be that blood platelets from these patients need less FVIII-vWF in order to adhere normally.

In contrast to patients with vWD subtype I, normalization of the plasma levels of FVIIIIR:Ag (subtype IIa) and FVIIIIR:Ag and FVIIIIR:RCF (subtype IIb) had little effect on platelet adherence and bleeding time. Absence of parallelism between normalization of FVIIIIR:Ag and/or FVIIIIR:RCF and the bleeding time has been reported before, and normalization of the bleeding time and platelet adherence was previously reported. The perfusion model is therefore probably the best in vitro system for measuring the "von Willebrand activity" of FVIII-vWF. This was substantiated by the observation of a close association between platelet adherence and bleeding time.

Administration of DDAVP in normals and vWD subtype I leads to the appearance of multimers with higher molecular weight, as visualized by SDS-agarose electrophoresis, as well as quantitative increase of the FVIII-vWF-related properties. The quantitative increase of FVIIIIR:Ag was correlated with enhanced platelet adherence. In normals, the FVIIIIR:RCF values were also correlated to the platelet adherence, in accordance with previously reported data. Evidence that this enhanced platelet adherence is caused by FVIII-vWF itself was obtained from studies in which increasing amounts of purified FVIII-vWF were added to normal reconstituted blood.

Enhanced platelet aggregate formation was seen after DDAVP infusion in normals as well as patients with subtype I. No correlation between the transiently enhanced aggregate formation and FVIIIIR:Ag or FVIIIIR:RCF or the bleeding time values was observed. The platelet aggregate formation was transiently improved and might, at least in part, have been responsible for normalization of the bleeding time in these patients. Platelet aggregate formation on the subendothelium in blood from patients with vWD subtypes IIa and IIb could not be evaluated because too few platelets had adhered to the subendothelium. Under such circumstances, accurate evaluation of platelet–platelet interaction is impossible.

The data presented here indicate that the poor effect of DDAVP on the hemostasis in patients with vWD subtypes IIa and IIb is caused by the failure of normalization of the platelet adherence. Evidence that FVIII-vWF in subtype IIb is qualitatively different from the normal FVIII-vWF has been obtained. It therefore seems likely that DDAVP is only effective in normalizing platelet adherence and bleeding time in patients possessing FVIII-vWF that is essentially normal in function. Normal platelet function is evidently also required.

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DDAVP enhances platelet adherence and platelet aggregate growth on human artery subendothelium

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