Changes in von Willebrand Factor During Cardiac Surgery: Effect of Desmopressin Acetate

By Mark Weinstein, J. Anthony Ware, Joseph Troll, and Edwin Salzman

Patients who receive desmopressin acetate (dDAVP) after cardiopulmonary bypass bleed less during operation and in the first 24 hours after operation than do patients who receive a placebo. To study the mechanism of improved hemostasis in bypass patients, we examined the relationship between von Willebrand factor (vWF) and blood loss in 70 cardiopulmonary bypass patients, one-half of whom received desmopressin intraoperatively. vWF concentration and multimeric composition were analyzed before and after bypass, after drug treatment, and 24 hours after operation. Before operation, patients with valvular disease had lower percentages of vWF high-mol-wt multimers (HMWMs) than did healthy subjects or patients with coronary artery disease, but subsequent blood loss, vWF activity, and bleeding times were not related to this finding.

VON WILLEBRAND FACTOR (vWF), an oligomeric glycoprotein, circulates as a family of disulfide-linked multimers with mol wt ranging from 1 to 15 to 20 x 10^6 daltons. The concentration and size of the protein affect its ability to mediate platelet–sub endothelial matrix interaction. Levels of vWF below ~0.5 U/mL or a severe depletion of the larger mol wt forms are associated with bleeding diatheses.1 Desmopressin acetate (1-deamino-8-D-arginine vasopressin, dDAVP) is generally believed to improve hemostasis in patients with these abnormalities of vWF by stimulating release of the protein from endogenous storage pools.2 Infusion of desmopressin into normal individuals3 or patients with hemophilia4 raises both the vWF concentration and the relative proportion of high-mol-wt multimers (HMWMs).

Recently, we4 and other researchers5 reported that desmopressin reduces blood loss following cardiac operations performed with the aid of cardiopulmonary bypass. We also observed that the reduction was most marked in patients with a relatively low concentration of vWF preoperatively. Although this observation provides indirect evidence that blood loss following cardiopulmonary bypass is related to vWF, it is not yet clear whether benefit from desmopressin is mediated by an increase in vWF concentration, a change in multimeric composition, or some other variable. The purpose of the present investigation was to determine what effect cardiopulmonary bypass has on vWF concentration and composition, to examine whether the beneficial effect of desmopressin on hemostasis results from alteration of parameters related to vWF, and to determine if patients with excessive (>2 L) postoperative hemorrhage can be identified preoperatively by measurement of vWF concentration and/or composition.

MATERIALS AND METHODS

A description of the patient population, randomization process for the selection of patients to receive a placebo or desmopressin, methods for sample acquisition, and techniques for measurement of intraoperative blood loss were previously reported.4 In brief, 70 cardiac patients were randomly divided into two groups: 35 received desmopressin (purchased as Stimate from Armour Pharmaceutical, Tarrytown, NY) and 35 were treated as a placebo. The drug or placebo was administered following neutralization of heparin by protamine after disconnection from the extracorporeal circuit. Blood samples were drawn at 1 day prior to surgery, immediately after bypass, 90 minutes after drug treatment, and 24 hours post operation (Fig 1). The samples were obtained through a flushed arterial line and then placed in test tubes containing a one-tenth vol 3.8% sodium citrate/20 U/mL hirudin/0.5 mg leupetin/200 U/mL Trasylol. In a few patients, no preoperative samples were acquired. Intraoperative blood loss, measured from the time of administration of the drug or placebo, and blood loss in the first 24 hours after operation were determined by weighing sponges and measuring the suction drainage. Bleeding times, determined by the template method,6 were measured before the operation and 118 ± 40 minutes (mean ± SD) after the drug or placebo was given (on arrival in the recovery room).

To assess the effect of age on plasma vWF levels and vWF multimer distribution, plasma samples were also acquired from 50 healthy individuals, aged 25 to 75 years, who had no history of heart disease. Blood was collected from these subjects as part of a routine screening procedure at the time of their enrollment in a local health maintenance organization.

Blood samples were centrifuged at 1,000 g for 10 minutes at 4°C. The platelet-poor plasma (PPP) was withdrawn and centrifuged a second time at 10,000 g for 2 minutes in a microtube. Aliquots (0.2 mL) of PPP were frozen and stored at −70°C until analyzed.

vWF antigen concentration was determined by electromunnoas-

From the William B. Castle Hematology Research Laboratory, Department of Medicine, Boston City Hospital and Boston University School of Medicine; and the Departments of Surgery and Medicine and the Dana Research Foundation, Beth Israel Hospital and Harvard Medical School, Boston. Submitted October 8, 1987; accepted January 30, 1988.

Supported by Grants No. HL 22355 and HL 13754 from the National Institutes of Health, Bethesda, MD.

Address reprint requests to Mark Weinstein, PhD, Boston City Hospital, Thorneide 308, 818 Harrison Ave, Boston MA, 02118.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1988 by Grune & Stratton, Inc.

Fig 1. Time line of operation, sample acquisition, and blood loss measurements.

say, and vWF activity was measured by the ristocetin cofactor assay. To quantify vWF multimer distribution, autoradiograms were prepared from plasma samples separated by electrophoresis on sodium dodecyl sulfate (SDS) agarose gels. Prior to electrophoresis, samples were adjusted to a final vWF antigen concentration of 15 U/dL by dilution with veronal-buffered saline. A 25 μL aliquot of this solution was combined with 38 μL of 8 mol/L urea/0.02 mol/L Tris HCl, pH 8.0/2 mmol/L acid EDTA/2% SDS, and 8 μL of the mixture was applied to each sample well. After electrophoresis, the gel was overlaid with 125I-anti-vWF. The radiolabeled antibody was prepared from anti vWF antibody (Accurate Chemicals, Westbury, NY) labeled with 125I by the iodogen procedure (Pierce, Rockford, IL), affinity purified on vWF-Sepharose, and absorbed with Sepharose-bound plasma from a patient with severe von Willebrand disease (vWD). At least two control samples for each gel were electrophoresed, and each patient sample was examined on a minimum of two different gels.

HMWMs were arbitrarily defined as those with a mol wt greater than multimers at the optical density maximum of the autoradiograph of vWF from normal pooled plasma (Fig 2). The integrated optical density of HMWMs in normal pooled plasma was 30% ± 4% (SD) (n = 47) of the total integrated optical density area. The mol wt of multimers included in this area is estimated to be >8 x 10^6 daltons given that at least 14 multimer bands of mol wt lower than that at the peak optical density can be observed on gels and assuming that the mol-wt difference between multimer bands is 6 x 10^6 daltons. To compare the HMWM distribution of patient plasma to that of control pooled plasma and to minimize slight differences in multimer patterns that occurred from gel to gel, patient samples analyzed on a given gel were compared with a normal pool sample electrophoresed on that same gel. In the first step of analysis, the densitometric tracing of the patient’s multimer pattern was aligned with the control plasma pattern such that lower mol wt bands of both were in register. The optical density maximum of normal pool vWF multimers was determined, and a perpendicular line was drawn from that point to the base line. The intersection of the perpendicular line with the baseline was used as a reference point on a given patient’s densitometric tracing. The integrated optical density area encompassing multimers with mol wt greater than those at the reference point position was determined as a fraction of the patient’s total multimer area. This ratio was then divided by the HMWM ratio of the control plasma to give the normalized HMWM ratio. As an example of this analytical method, if the ratio of HMWM integrated optical density area to total area for a patient was 0.15 and that of the control plasma was 0.3, the patient would have a normalized HMWM ratio of 0.5, or one-half the integrated optical density of multimers >8 x 10^6 daltons as the control plasma.

The mean of duplicate normalized HMWMs ratio determinations was generally within 15% of individual values. If the range was >15%, the sample was run a third time and the values were averaged.

Fig 2. (A) Quantification of HMWMs from autoradiograms. To compare patient multimer distribution to that of the normal pool, the integrated optical density area of HMWMs (A') of a given sample was divided by total integrated optical density of that sample (A' + B'). This ratio was divided by the ratio obtained from a sample of normal pooled plasma run on the same gel to give the normalized HMWM ratio. (B) Autoradiograph and densitometric scan of vWF from a preoperative patient with valvular disease (V); normal pool plasma (N); and from a patient 90 minutes after infusion of desmopressin, (D).
Fibrinogen, IgG, α1-antitrypsin, C-reactive protein, and fibronectin were quantified by radial immunodiffusion. Statistical analysis was done by Student’s t test for comparison of means of parametric data from desmopressin and placebo-treated patients. Results are given as means ± SD. Relationships between parameters were analyzed using the least-squares method of linear regression.

RESULTS

Analysis of vWF concentration in preoperative samples. The mean preoperative vWF concentration of patients examined in this study, 1.8 ± 0.8 (SD) U/mL, was high as compared with the mean of 1.07 ± 0.76 (SD) U/mL for our normal subjects (Fig 3A). However, given the age of the patient population, 62 ± 12 (SD) years, and the observation that average vWF concentration increases with age, the mean and range of vWF concentrations observed in our patients may not be abnormal. To test this hypothesis, vWF concentration was examined as a function of age in cardiac surgical patients and normal subjects. Although age contributed significantly to the regression equation for normal individuals (P < .001), age could not fully account for the higher mean vWF antigen level of the patient group (P < .05).

The degree of correlation between preoperative vWF antigen concentration and total blood loss during and after operation was determined by linear regression analysis (Fig 4). With the exclusion of an outlier blood loss value of 7.5 L, the correlation coefficient for patients receiving a placebo was 0.318. For those receiving desmopressin, r = -.022 (Fig 4). In both instances, the correlations between the two parameters are not statistically significant. However, of 22 patients not treated with desmopressin who had vWF levels below the population mean, 11 lost more than 2 L blood intraoperatively and during the first 24 hours postoperatively ("high blood loss patients") (Fig 4). Only one of the ten placebo patients who had vWF antigen levels above the mean lost >2 L blood. Patients who received desmopressin lost 1.3 ± 0.5 L blood during and after operation as compared with 2.2 ± 1.4 L for untreated patients. Together, these results suggest that blood loss and low preoperative levels of vWF tend to be associated in patients who received a placebo but not in those treated with desmopressin.

A recent report demonstrated that a group of patients with type O blood have lower average levels of vWF antigen than do those with other blood types. In the present study, 52% of our patients with vWF <1.8 U/mL had type O blood. This was not significantly different from the general population, of which 45% have blood type O. Only 3 of the 11 patients with blood loss >2 L had type O blood. Thus, in this study, blood type was not correlated with high blood loss.

Comparison of vWF antigen concentration prebypass and postbypass: Evidence for vWF release during bypass. vWF concentration was analyzed in samples acquired within 10 minutes after bypass. At this time, patients had not yet received desmopressin or placebo. vWF concentration decreased for most patients during bypass (Fig 3B) and the change in vWF concentration was directly related to the initial vWF level (r = .8, Fig 5). However, 14 patients with low preoperative vWF levels, 10 with valvular disease and 4 with coronary artery disease, had vWF concen-
During Cardiac Surgery

During bypass, vWF concentration decreased, IgG generally decreased during bypass, antitrypsin and vWF secretion during bypass, fibronectin, fibrinogen, α2-antitrypsin, and IgG generally decreased during bypass postbypass that were higher than their initial concentrations. This suggests that sufficient amounts of C., C.eled one of the eight who had preoperative levels of vWF < 0.8. Patients with blood loss >2 L (●); patients with blood loss <2 L (○).

The direction of change in vWF concentration during bypass in patients who had low preoperative vWF levels was associated with subsequent blood loss. Patients who had low preoperative vWF levels and a decrease in vWF concentration during bypass tended to have greater blood loss than did similar patients whose vWF concentration increased during this period (Fig 5). In patients who were to receive a placebo, of the eight who had preoperative levels of vWF <1.8 U/mL and an increase in vWF concentration during bypass, only one bled >2 L. In contrast, of 12 placebo patients who had preoperative vWF levels <1.8 U/mL and who had a decrease in vWF concentration during bypass eight bled >2 L.

Similarly, for patients who eventually received desmopressin, an increase in vWF postbypass (before dDAVP was given) was associated with reduced total blood loss (after dDAVP). Among these patients, five with preoperative vWF concentrations <1.8 U/mL and whose vWF levels increased during bypass had an average blood loss of 963 ± 142 mL. In comparison, for the group who had a decline in vWF postbypass (n = 14), blood loss was 1,549 ± 453 mL (P < .02). These results suggest that factors that influence vWF concentration during bypass, irrespective of drug treatment, are related to total blood loss.

The correlation coefficient of the line relating postbypass vWF antigen concentration to total blood loss for all patients receiving a placebo was 0.365, indicating a weak association between postbypass vWF concentration and blood loss.

Despite the reduction in vWF concentration during bypass, the mean vWF level, postbypass for all patients was still higher than that of normal individuals who did not undergo surgery (compare N. Fig 3A and B).

vWF Concentration Postmedication. Although vWF concentration rose in most patients from immediately postbypass to 90 minutes after administration of desmopressin or placebo (Figs 3C and 6), the increase was greater and more consistent for those who received desmopressin. Desmopressin-treated patients had an average increase of 0.6 ± 0.5 U/mL as compared with 0.2 ± 0.6 U/mL for the placebo group (P < .02). vWF concentration declined from postbypass levels in 11 of the 33 placebo patients but in only 3 of the 30 desmopressin-treated patients (Fig 6). In neither group of patients was the magnitude or direction of change in vWF levels related to the preoperative or postbypass concentration of vWF, indicating that for bypass patients the change in vWF concentration was not feedback regulated.

Total blood loss was not strongly correlated with vWF concentration at the 90-minute postmedication time point for either desmopressin-treated (r = .17) or placebo-treated (r = .18) patients. vWF concentration for the 11 placebo

![Graph](image-url)
patients with blood loss >2 L was 1.3 ± 0.5 U/mL, however, as compared with 1.5 ± 0.6 U/mL for the total placebo group. The latter level was significantly less than the 1.8 ± 0.5 U/mL for those treated with desmopressin (Fig 3C) (P < .02). These results indicate that although total blood loss and vWF concentration were not linearly correlated at this time, there was a tendency for low vWF concentration to be associated with high blood loss.

vWF concentration 24 hours after surgery. The influence of desmopressin on vWF concentration was no longer evident 24 hours after operation. The average vWF antigen level of 2.5 ± 0.7 U/mL for the desmopressin-treated group was nearly identical to the placebo group average of 2.4 ± 0.6 U/mL (Fig 3D).

Multimeric analysis: Preoperative studies. To determine if abnormal vWF multimer mol wt distribution might be related to subsequent intraoperative and postoperative hemorrhage, the relative proportion of HMWMs to total multimer population was analyzed. In preoperative blood samples, patients with valvular disease (n = 43), including those with aortic stenosis (n = 17) and regurgitation (n = 9), and mitral valve stenosis (n = 7) and regurgitation (n = 10), had a normalized HMWM ratio of 0.67 ± 0.17 (SD). This was significantly less (P < .001) than that of healthy subjects (n = 50) who did not have heart disease (described in the Materials and Methods section) and who had a ratio of 0.93 ± 0.17 (range from 0.60 to 1.13) or coronary artery disease patients (n = 18) who had a ratio of 0.91 ± 0.21 (Fig 7A). The HMWM deficiency was unrelated to vWF concentration. Inspection of the multimer densitometric tracing showed that the reduction in the normalized HMWM ratio of the valvular disease patients resulted from a decrease in the amount of large vWF oligomers rather than an increase in the proportion of low-mol-wt species.

Despite reduced levels of HMWMs, valvular disease patients did not differ from the healthy population or coronary artery disease patients in their ratio of ristocetin-platelet aggregation activity to vWF antigen, or in their average bleeding times. The ristocetin cofactor activity/vWF antigen ratio of patients with valvular disease was 1.05 ± 0.43 (n = 44) as compared with 1.34 ± 0.9 (n = 18) for coronary artery disease patients and 1.16 ± 0.5 (n = 12) for healthy subjects.

Considered as a group, the 11 placebo patients who lost >2 L blood did not have a consistent preoperative deficiency of HMWMs (Fig 7A). The seven high blood loss placebo patients with valvular disease had a normalized HMWM ratio of 0.52 ± 0.16 as compared with 0.67 ± 0.13 for the other 17 placebo valvular disease patients (P < .05). However, the four high blood loss coronary artery disease patients had a HMWM ratio of 1.07 ± 0.18 vs 0.75 ± 0.16 for the other three placebo coronary artery disease patients. In sum, the 11 placebo patients who lost >2 L blood had a normalized multimer ratio of 0.72 ± 0.31, whereas the other placebo patients had a value of 0.70 ± 0.16 (Fig 7A). Thus, unlike the association between high blood loss and low preoperative vWF antigen levels (Fig 3A), preoperative multimer distribution was not related to excessive hemorrhage.

vWF multimers postbypass: Further evidence of vWF release during bypass. Despite the decline in overall vWF concentration during bypass, the change in vWF multimer distribution prebypass to postbypass suggests that vWF was released during bypass in most patients. Prior to administration of desmopressin or a placebo, the normalized HMWM ratio rose from the preoperative value of 0.67 ± 0.17 to 0.95 ± 0.18 postbypass for all valvular disease patients and from 0.91 ± 0.21 to 1.02 ± 0.14 for all coronary artery disease patients (Fig 7A and B).

The normalized HMWM ratio increased for most patients regardless of initial vWF levels (Fig 8 as compared with Fig 5). Valvular disease and coronary artery disease placebo patient data are considered separately in Fig 8 because valvular disease patients generally have lower preoperative levels of HMWMs than do coronary artery disease patients, and the changes in multimer ratio of the two groups were dissimilar.

The average increase of HMWMs in placebo patients who bled >2 L was no different from that in placebo patients who hemorrhaged less (Figs 7B and 8). Therefore, changes in multimer distribution postbypass were less strongly correlated with blood loss than were changes in vWF concentration. Furthermore, the change in multimer distribution from preoperation to postbypass was not correlated with preoperative vWF concentration.

vWF multimers post medication. Ninety minutes after infusion of either placebo or desmopressin, the ratio of HMWM forms continued to rise regardless of medication (Fig 7C). The normalized HMWM ratio for the desmopressin group, 1.24 ± 0.18, was somewhat greater than the placebo group average of 1.16 ± 0.13 (P < .07).
The HMWM distribution of placebo patients who bled >2 L was similar to that in patients who received desmopressin and greater than the ratio of HMWMs in placebo patients who hemorrhaged less (Fig 7C). A high percentage of large multimers was not sufficient to prevent excessive blood loss.

**vWF multimers 24 hours postoperation.** Desmopressin-treated and untreated patients had similar HMWM distributions at this time, with identical average normalized ratio values of 1.07 (Fig 7D). The change in multimer distribution from 90 minutes postmedication to 24 hours postoperation was caused by an increase in lower mol wt forms rather than from an absence of larger multimers.

Fresh frozen plasma was given to 15 patients postbypass in addition to desmopressin or the placebo. Because frozen plasma contains vWF, which might affect the quantitative and qualitative analysis of the protein, we considered the data with these patients excluded. The average multimer distribution and vWF concentration were not altered.

**DISCUSSION**

The acquired hemostatic defects responsible for excessive hemorrhage during cardiopulmonary bypass are not well understood. One major contributing element is believed to be abnormal platelet function, brought about by passage of platelets through the bypass circuit. Immediately after bypass, platelets are less responsive to ADP and collagen, do not adhere well to glass beads, have a reduced number of fibrinogen binding sites, and form increased microparticles. Other researchers have shown that the prolonged bleeding time of patients with a variety of platelet functional defects can be shortened by treatment with desmopressin or cryoprecipitate. These latter studies stimulated our inquiry into the effect of desmopressin and vWF on hemostasis in bypass patients.

Although prior results suggested that cardiopulmonary bypass blood loss and vWF are related, the molecular basis for this association is obscure. Before cardiac surgery, patients had normal bleeding times and levels of vWF much higher than that necessary for adequate hemostasis. Throughout the surgical procedure, both desmopressin-treated and untreated patients had vWF levels far above the minimum required for normal hemostasis. To test the hypothesis that large, more hemostatically effective vWF multimers were released to a greater extent in patients treated with desmopressin than in patients who did not receive the drug, we analyzed multimeric composition as well as concentration of vWF in the present study.

Prior to surgery, valvular disease patients had a significantly lower ratio of HMWMs to total multimers than did either coronary artery disease patients or the healthy population. A deficiency of HMW vWF multimers in association with a cardiac abnormality also has been described in children with noncyanotic congenital heart disease. In both valvular disease and congenital heart disease, correction of the cardiac defect was followed by the appearance of a normal range of multimer forms.

Although proteolysis may be responsible for the deficiency of HMW forms, bypass patients did not have disseminated intravascular coagulation, an increased proportion of low-mol-wt vWF, or fragments of vWF below the normal mol-wt range. Turbulence or high shear stress created by blood flow through stenosed valves or other narrowed openings might also be responsible for the loss of HMW forms of vWF. HMW forms bind to platelets in vitro under rapid flow conditions.

In the patients we examined, the decrement in HMWMs was insufficient to affect measurably either in vivo or in vitro vWF activity. However, aortic valvular disease patients have been reported to have an increased incidence of gastrointestinal bleeding, and a severe deficiency of HMWMs may contribute to this tendency.

Regardless of the type of cardiac disease, the bypass procedure affected vWF structure and concentration. The proportion of HMWMs increased for most patients during bypass. The rapidity of vWF appearance in the circulation and the greater proportion of HMWMs suggest that the protein was released from storage pools rather than synthesized de novo. Possible sources of this preformed HMW vWF are the Weibel-Palade bodies of endothelial cells and the alpha-granules of platelets. Large vWF multimers are preferentially stored in the alpha-granules and Weibel-Palade bodies, and the contents of these cellular inclusions are released by a variety of physiologic stimulants, including thrombin and fibrin. Some but not all investigators have found evidence of platelet alpha-granular release in postbypass blood.
Sufficient amounts of vWF were released during bypass to increase levels above preoperative concentrations in some patients, unlike the other plasma proteins studied. The increase was apparent primarily in patients who had relatively low preoperative levels of the factor, but the increase in HMWMs suggests that release took place in most patients. Hemodilution could mask evidence of release in patients with high preoperative vWF levels. To illustrate this point, we can assume that hemodilution reduced preoperative protein concentration by 50% and that secretion during bypass added 0.8 U/mL vWF to the circulation. An estimated hemodilution effect of 50% is reasonable, considering that the hematocrit declined by 42% ± 12% after bypass. An assumed average influx of 0.8 U/mL vWF during bypass was derived from extrapolation of change in vWF concentration v initial concentration (Fig 5). Given these assumptions, a preoperative vWF level of 1 U/mL would increase to 1.3 U/mL postbypass, whereas an initial level of 3 U/mL would decline to 2.3 U/mL postbypass.

Patients with high blood loss tended to have low vWF levels preoperatively that did not rise during bypass and postbypass levels that were ≤1.2 U/mL. The failure of these patients to increase their vWF concentration during bypass was probably caused by the removal of vWF during bypass rather than defective synthesis or release. In support of this conjecture, the absolute increase in vWF concentration between the time immediately postbypass and 90 minutes after placebo administration was the same for patients with high blood loss as for other placebo patients. If inadequate synthesis or release were the mechanism by which vWF declined during bypass, this defect would most likely persist for at least 90 minutes after bypass.

After bypass, at the time expected for maximum desmopressin effect, placebo patients had vWF levels of 1.5 ± 0.65 U/mL as compared with 1.8 ± 0.5 U/mL for the desmopressin-treated group. Although this difference was statistically significant (P < .02), it was less than the two- to four-fold increase in vWF seen in healthy individuals or in hemophilic patients treated with the drug.5 The diminished response to desmopressin postbypass could be analogous to the progressive decline in vWF release observed in some individuals who were repeatedly treated with desmopressin for a short time2 and may be caused by a decrease in vWF contained in storage pools during bypass. Alternatively, vWF could be released but be bound to platelets and/or endothelial cells.

Twenty-four hours after surgery, vWF concentration rose but the percentage of HMWMs declined as compared with the sample obtained 90 minutes after drug administration. A postoperative rise in vWF has been noted by other researchers9 and is in accord with the characterization of vWF as an acute-phase reactant.9,10 The higher proportion of lower mol wt multimers may be the result of proteolysis9 or may reflect an increased output of low-mol-wt forms of vWF.

We showed that the effectiveness of desmopressin in reducing blood loss cannot be ascribed to the appearance of HMWMs not present in patients receiving a placebo. Because the average difference in vWF concentration between placebo and desmopressin-treated patients was relatively minor and both groups had vWF levels within the range generally believed to be adequate for hemostasis, the mechanism responsible for the beneficial effects of desmopressin remains unclear. Factors not analyzed in our study that are induced by desmopressin infusion, such as a rise in factor VIII coagulant protein, or exposure of new binding sites on endothelial cells as the Weibel-Palade bodies secrete their contents, might correlate better with reduced blood loss than do the measured vWF-related parameters. The concentration of vWF shortly after bypass also may have a much greater influence on hemostasis than occurs under less traumatic circumstances. Platelet surface proteins such as the glycoproteins Ib and IIb-IIIa are less accessible to their ligands after bypass14,15 and they may also have lower affinities for vWF. If binding constants of these proteins for vWF become elevated after bypass, greater than normal levels of vWF would be required for adequate hemostasis. Desmopressin may exert its beneficial effect by causing vWF to exceed a threshold concentration necessary for proper platelet–vessel wall interaction.

ACKNOWLEDGMENT

We thank Dr Olof McLetchie and the staff of the Harvard Community Health Plan for their cooperation. The assistance of Linda Robertson, Mary Ann Lee, and Ann Donovan is gratefully acknowledged.

REFERENCES


From www.bloodjournal.org by guest on September 24, 2017. For personal use only.
10. Weinstein MJ, Deykin DD: Comparison of factor VIII-related von Willebrand factor proteins prepared from human cryo-
precipitate and factor VIII concentrate. Blood 53:1095, 1979
quantitation of antigens by single radial immunodiffusion. Immuno-
chemistry 2:235, 1965
RR: The effect of ABO blood groups on the diagnosis of von
13. Harker LA, Malpass TW, Branson HE, Hessel EA, Slichter
SJ: Mechanism of abnormal bleeding in patients undergoing cardio-
pulmonary bypass: Acquired transient platelet dysfunction asso-
R, Edmunds LH: Loss of fibrinogen receptors from the platelet
surface during simulated extracorporeal circulation. J Lab Clin Med
105:514, 1985
15. George JN, Pickett EB, Saucerman S, McEever RP, Kunicki
T, Kieffer N, Newman PJ: Platelet surface glycoproteins. Studies on
resting and activated platelets and platelet membrane microparticles
in normal subjects and observations in patients during adult respira-
tory distress syndrome and cardiac surgery. J Clin Invest 78:340,
1986
16. Kobrinsky NL, Israels ED, Gerrard JM, Cheang MS, Wat-
son CM, Bishop AJ, Schroeder ML: Shortening of bleeding time by
1-deamino-8-D-arginine vasopressin in various bleeding disorders.
Lancet 1:1145, 1984
17. Schulman S, Johnsson H, Egberg N, Blomback M: DDAVP-
induced correction of prolonged bleeding time in patients with
18. Gerritsen SW, Akkerman J, Sixma JJ: Correction of the
bleeding time in patients with storage pool deficiency by infusion of
20. Moake JL, Turner NA, Stathopoulos NA, Nolasco LH, Hellums JD: Involvement of large plasma von Willebrand Factor
(vWF) multimers and unusually large vWF forms derived from
endothelial cells in shear stress-induced platelet aggregation. J Clin
Invest 78:1456, 1986
of the largest von Willebrand factor multimers from the plasma of
22. Kunicki TJ, Montgomery RR, Schullek J: Cleavage of human
von Willebrand factor by platelet calcium-activated pro-
von Willebrand factor induced by enzyme(s) released from polymor-
24. Peterson DM, Stathopoulos NA, Giorgio TD, Hellums JD,
Moake JL: Shear-induced platelet aggregation requires von Wille-
brand factor and platelet membrane glycoproteins Ib and IIb-IIIa.
Blood 69:625, 1987
25. McNamara JJ, Austen WG: Gastrointestinal bleeding occur-
ing in patients with acquired valvular heart disease. Arch Surg
97:538, 1968
26. Sporn LA, Marder V, Wagner DD: Inducible secretion of
large, biologically potent von Willebrand factor multimers. Cell
46:185, 1986
27. Ribes JA, Francis CW, Wagner DD: Fibrin induces release of
von Willebrand factor from endothelial cells. J Clin Invest 79:117,
1987
AG, Meade TW: Haemostatic changes following surgery. Thromb
Res 32:223, 1983
29. Cucuianu MP, Missits I, Olinic N, Roman S: Increased
ristocetin cofactor in acute myocardial infarction: A component of
the acute phase reaction. Thromb Haemost 43:41, 1980
30. Kelly DA, O’Brian FJ, Hutton RA, Tuddenham E, Summer-
field JA, Sherlock S: The effect of liver disease on factors V, VIII
and protein C. Br J Haematol 61:541, 1985
Berkowitz S, Ruggeri Z, Zimmerman TS: Proteolytic degradation of
von Willebrand factor after DDAVP administration in normal
individuals. Blood 70:173, 1987
Changes in von Willebrand factor during cardiac surgery: effect of desmopressin acetate

M Weinstein, JA Ware, J Troll and E Salzman