Decreased von Willebrand factor ristocetin cofactor activity and increased ADAMTS13 antigen increase postoperative drainage after coronary artery bypass grafting

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Abstract

OBJECTIVES: Routine coagulation tests and bleed-scores fail to identify patients at risk of excessive postoperative drainage following coronary artery bypass grafting (CABG). We sought to investigate whether lower von Willebrand factor (VWF) and higher ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) are associated with a high postoperative drainage after CABG.

METHODS: In the prospective cohort study, VWF antigen (VWF:Ag), VWF ristocetin cofactor (VWF:RCo), VWF collagen-binding (VWF:CB), ADAMTS13 antigen (ADAMTS13:Ag) and ADAMTS13 activity were measured on the day of elective on-pump CABG in 232 consecutive patients without a prior history of haemorrhagic diathesis, including von Willebrand disease (95% discontinued aspirin preoperatively). Postoperative drainage and blood product use were recorded.

RESULTS: A comparison of extreme drainage quartiles \((n = 56)\) showed that individuals with the highest drainage volumes have mean VWF:RCo lower by 15% \((p < 0.0001)\), median VWF:Ag lower by 19% \((p < 0.0001)\), ADAMTS13:Ag higher by 8% \((p = 0.0002)\), ADAMTS13 activity higher by 9% \((p = 0.01)\) and fibrinogen lower by 14% \((p = 0.03)\) than those with the lowest drainage. Linear regression analysis showed that preoperative VWF:RCo \((b = -4.83, p = 0.002)\) and fibrinogen \((b = -61.52, p = 0.04)\) are the only independent predictors of postoperative drainage. Multivariate logistic regression demonstrated that preoperative VWF:RCo in the lowest quartile and ADAMTS13:Ag levels in the highest quartile increased the risk of high \((\geq 1000 \text{ml})\) drainage \((\text{odds ratio [95\% confidence interval]} = 4.88 [1.83–13.02], p = 0.001 \text{and} 3.77 [1.49–9.52], p = 0.005; \text{respectively})\).

CONCLUSIONS: Patients undergoing elective CABG with lower preoperative VWF:RCo are at risk of having larger postoperative drainage, which suggests a novel contributor to increased perioperative bleeding in cardiac surgery.

Keywords: Coronary artery bypass grafting • Chest-tube drainage • von Willebrand factor • ADAMTS13

INTRODUCTION

Excessive postoperative bleeding is a grave complication after coronary artery bypass grafting (CABG) and affects the morbidity and mortality [1, 2]. Up to 15% of procedures requiring cardiopulmonary bypass (CPB) are complicated with postoperative haemorrhage [3]. Transfusions of allogenic blood products after CABG are associated with reduced survival [4]. Risk factors for early postoperative blood loss after cardiac surgery include surgical factors, platelet dysfunction and/or loss secondary to CPB exposure, drug-induced impairment of platelet aggregation and plasma coagulation factor deficiencies [5–8]. Although numerous studies attempted to address the issue, foreseeing perioperative bleeding complications in cardiac surgery remains extremely difficult. Routine coagulation tests, including activated partial thromboplastin time (APTT), prothrombin time or platelet count, fail to identify patients at high risk of excessive postoperative drainage [9, 10]. Only one bleeding-risk score is available for patients undergoing cardiac surgery (The Papworth Bleeding Risk Score, BRiSc); however, its applicability for elective CABG patients is disputable [11].

Data on the associations between postoperative bleeds after CABG and von Willebrand factor (VWF) are sparse. VWF is a multimeric glycoprotein whose plasma concentrations depend partly on the balance between its release from endothelial cells and removal from the circulation. Healthy individuals with the O blood group have a shorter VWF survival than those with other groups [12].

High-molecular-weight VWF multimers contain many platelet-binding sites and are biologically the most active [13]. VWF multimer size is regulated by the specific cleaving protease, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). Increased ADAMTS13 levels lead
to enhanced VWF proteolysis and the subsequent loss of large VWF multimers, predisposing to bleeding [14]. It has been reported that ADAMTS13 activity decreases, and VWF antigen and VWF collagen-binding (VWF-CB) activity increase immediately after CABG [15].

We hypothesized that lower preoperative VWF antigen/activity and increased ADAMTS13 antigen/activity are associated with a higher chest-tube drainage following CABG, and that preoperative testing of these parameters could help identify subjects at risk of postoperative bleeding.

MATERIALS AND METHODS

Patients

From October 2008 to December 2009, we recruited 294 consecutive individuals with stable angina, scheduled for isolated elective CABG. The exclusion criteria were: a history of any cardiac surgery (n = 8), myocardial infarction (MI) or percutaneous coronary intervention (PCI) followed by dual antiplatelet therapy within 1 month prior to enrolment (n = 13), current anticoagulant therapy (n = 2), renal failure (serum creatinine >177 µmol/l) (n = 7), haematocrit <30% (n = 5), prior history of bleeding diathesis (n = 2) and incomplete laboratory or clinical data (n = 25). A final analysis comprised of 232 patients. Perioperative MI (PMI) for patients with MI within 24 h after CABG was defined as the serum creatinine kinase MB fraction (CK-MB) increase to the level greater than or equal to five times the upper limit of normal, and new Q waves had to be present, or the CK-MB value had to be ≥10 times the upper limit of normal (with or without Q waves), and no symptoms were required. The CK-MB level of 17 U/l was considered the upper normal value.

The study was powered to have an 80% chance of detecting a 15% intergroup difference in VWF:Ag using a P-value of 0.05, based on the values of these parameters in the published articles [16]. To demonstrate such a difference or greater in this variable, 50 patients were required in each group. Continuous variables were presented as mean ± standard deviation or median and quartiles, as appropriate. Categorical variables were presented as percentages. The Shapiro–Wilk test was used to test the normality of continuous variables. To examine the differences between two independent groups, Student’s t-test or Mann–Whitney U-test were used, as appropriate. The χ2 test or Fisher’s exact test was used, as appropriate, for categorical variables. To assess linear correlation between variables, the Pearson correlation coefficient (Pearson’s r) for normally distributed variables or Spearman’s rank correlation coefficient (Spearman’s rho) for non-normally distributed variables were calculated. Relationships between postoperative drainage volume and other parameters (age, sex, presence of peripheral artery disease, diabetes mellitus, arterial hypertension, history of MI, dyslipidaemia, baseline creatinine, blood glucose, total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, high-sensitivity CRP, smoking, body mass index (BMI), blood group, baseline left ventricle ejection fraction, history of PCI, chronic obstructive pulmonary disease, administration of aspirin (acetyl-salicylic

Laboratory investigations

Fasting blood samples were collected from an antecubital vein with minimal stasis at 6–8 AM on the day of CABG. Plasma samples were centrifuged within 30 min of collection, frozen and stored in aliquots at −80°C until assayed. Fibrinogen was determined using the Clauss method and C-reactive protein (CRP) by immunoturbidimetry. VWF ristocetin cofactor (VWF:RCO) was determined turbidimetrically (Siemens, Erlangen, Germany). Intra- and inter-assay coefficients of variation were 6.9 and 7.5%, respectively. The detection threshold for the assay was 5 IU/dl. VWF antigen (VWF:Ag) was measured by latex immunoassay on a STAR coagulation instrument (Diagnostica Stago, Asnières, France), with a detection limit of 2 IU/dl. Intra- and inter-assay coefficients of variation were 5.2 and 5.5%, respectively. VWF-CB was assessed by ELISA using type III collagen (Sigma) diluted in acetic acid, with a limit of detection of 4 IU/dl. Intra- and inter-assay coefficients of variation were 6.1 and 6.7%, respectively. ADAMTS13 antigen (ADAMTS13:Ag) and activity (ADAMTS13 activity) were measured by fluorogenic assays (Technoclone, Wien, Austria). Intra- and interassay coefficients of variation were 5.8 and 6.5% for antigen and 7.3 and 7.8% for activity, respectively. For both tests, lower limits of detection were 5 IU/dl. Normal reference ranges for VWF and ADAMTS13 parameters are 50–150 IU/dl.

Clinical management

All patients underwent standardized anaesthesia and received median sternotomy. CPB was performed at moderate hypothermia (oesophageal temperature, 32°C) using a non-pulsatile roller pump (Jostra Medizintechnik AG, Hirrlingen, Germany) and a 40-µm arterial blood filter (Jostra Medizintechnik AG), with blood flow at 2.0–2.4 l/min/m² and mean arterial pressure at 40–60 mmHg. Intermittent antegrade warm blood or cold crystalloid cardioplegia was used. Anticoagulation was achieved by administration of heparin (500 IU/kg) before the onset of CPB, and was monitored using the activated clotting time, which had to be >400 s during CPB and return to normal, after anticoagulation was reversed by protamine at the end of CPB. For the left internal mammary artery harvesting, the left pleural space was opened. Meticulous surgical haemostasis was a priority in all cases. All procedures were performed by 14 experienced surgeons, who perform over 100 procedures yearly. None of the patients received aminocaproic acid, aprotinin or desmopressin acetate. Tranexamic acid was administered in two doses (2 g i.v. after sternotomy, and 2 g i.v. after the end of CPB) in all cases. The BRiSc score (range, 0–5) was calculated for all patients [11]. The volume of postoperative drainage was measured until the removal of drains (48 h postoperatively if the output was <30 ml/h for at least three consecutive hours and no air leakage was observed). Packed red blood cells (RBCs) were administered when haemoglobin level dropped to <7 g/dl, or haematocrit was <25%; platelet concentrate (PC) was transfused if there was an ongoing bleeding of >200 ml/h and platelet count was <75 × 10³/µl; fresh frozen plasma (FFP) was transfused when there was an ongoing bleeding. Rethoracotomy was indicated if the total drainage exceeded 500 ml in the first postoperative hour, 300 ml for 2 consecutive hours or >1200 ml during the first 6 h.

Statistical analysis

The study was powered to have an 80% chance of detecting a 15% intergroup difference in VWF:Ag using a P-value of 0.05, based on the values of these parameters in the published articles [16]. To demonstrate such a difference or greater in this variable, 50 patients were required in each group. Continuous variables were presented as mean ± standard deviation or median and quartiles, as appropriate. Categorical variables were presented as percentages. The Shapiro–Wilk test was used to test the normality of continuous variables. To examine the differences between two independent groups, Student’s t-test or Mann–Whitney U-test were used, as appropriate. The χ² test or Fisher’s exact test was used, as appropriate, for categorical variables. To assess linear correlation between variables, the Pearson correlation coefficient (Pearson’s r) for normally distributed variables or Spearman’s rank correlation coefficient (Spearman’s rho) for non-normally distributed variables were calculated. Relationships between postoperative drainage volume and other parameters (age, sex, presence of peripheral artery disease, diabetes mellitus, arterial hypertension, history of MI, dyslipidaemia, baseline creatinine, blood glucose, total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, high-sensitivity CRP, smoking, body mass index (BMI), blood group, baseline left ventricle ejection fraction, history of PCI, chronic obstructive pulmonary disease, administration of aspirin (acetyl-salicylic
acid, ASA), angiotensin-converting enzyme inhibitors, beta-blockers, statins and insulin, EuroSCORE I, type of cardiopulmonary solution, aortic cross-clamping time, CPB time, number of performed anastomoses, postoperative MI, intensive care unit length of stay, number of intubation days, baseline haematocrit, RBC and Hb level, baseline platelet count, APTT, fibrinogen levels, VWF:RCo, VWF:Ag, CBA:VWF, ADAMTS13:Ag and ADAMTS13 activity) were analyzed by linear regression (all parameters were tested in a simple regression, and a P-value of ≤0.05 was used as the entry criterion for the multiple regression). The independent predictors of high drainage (defined as ≥1000 ml) were identified using a forward stepwise multivariate logistic regression (a P-value of ≤0.05 in a simple regression was used as the entry criterion for the multiple models). Odds ratios in multivariate models were adjusted for age, sex, CPB time and ASA administration. A strong significant correlation between any two parameters (r > 0.5) excluded one of the parameters from the multiple linear and logistic models. Statistical analysis was performed with STATA 10.0 (StatSoft, Tulsa, OK, USA). Two-sided P-values <0.05 were considered statistically significant.

RESULTS

Baseline data

A total of 232 CABG patients, mostly hypercholesterolaemic, hypertensive and overweight men with prior MI, were studied (Table 1). Mean preoperative VWF:RCo was 100.4 ± 24.5 IU/dl, mean VWF:Ag was 95.9 ± 28.6 IU/dl and mean VWF:CB was 99.5 ± 28.6 IU/dl. Mean preoperative ADAMTS13:Ag was 102.4 ± 13.8 IU/dl, and mean ADAMTS13 activity was 106.8 ± 21.2 IU/dl. Mean preoperative VWF:RCO was 100.4 ± 24.5 IU/dl, mean VWF:Ag 99.5 ± 28.6 IU/dl and mean VWF:CB was 99.5 ± 18.4 IU/dl. Mean preoperative ADAMTS13:Ag was 102.4 ± 13.8 IU/dl, and mean ADAMTS13 activity was 106.8 ± 21.2 IU/dl. Median VWF:RCO/VWF:Ag was 1.06 (0.87–1.23). Seventy-three (32%) patients had O blood group; however, they did not differ from those with non-O blood groups with respect to VWF:Ag levels (91.0 ± 79.6 ml; P = 0.33, r = 0.33, P = 0.33). VWF:Ag and ADAMTS13 parameters were similar. However, none of the cardiovascular risk factors, including age and medication, showed associations with any of the VWF and ADAMTS13 parameters studied. Similarly, there were no associations between VWF and ADAMTS13 parameters and the BriSC score.

Peri- and postoperative data

All subjects underwent on-pump CABG (Table 2). As few as 11 (5%) patients continued aspirin administration. None of the studied individuals received clopidogrel. Sixteen (7%) subjects suffered from PMI, and 8 (4%) died before discharge, including 4 (2%) with PMI (Table 2). The subjects who died, compared with the remaining group, had lower VWF:RCo (by 17%, P = 0.02); VWF:Ag and ADAMTS13 parameters were similar. However, none of the deaths were due to haemorrhage.

The median postoperative chest-tube drainage volume was 675 (475–905) ml. Drainage volumes were higher in men than in women by 26% (P < 0.0001). Rethoracotomy for excessive drainage was performed in 14 (6%) subjects, in whom median drainage volume was almost 3-fold higher than in the remaining subjects (1900 [1510–2400] vs 650 [460–870] ml; P < 0.0001, respectively). Packed RBCs were administered in 146 (63%) patients, and 46 (20%) subjects received more than 2 units. Neither patients undergoing rethoracotomy, nor those who received RBC transfusion, did differ from the remaining subjects in terms of the VWF or ADAMTS13 parameters. Blood groups O vs non-O did not differ with regard to postoperative drainage (data not shown).

Comparison of extreme drainage quartiles

A comparison of extreme chest-tube drainage quartiles (<475 ml [n = 56] and >905 ml [n = 56]) showed that individuals with the drainage volumes in the highest quartile have mean VWF:RCo lower by 19% (P < 0.0001), median VWF:Ag lower by 19% (P < 0.0001), ADAMTS13:Ag higher by 8% (P = 0.0002), ADAMTS13 activity higher by 9% (P = 0.01) and fibrinogen levels lower by 14% (P = 0.03) (Table 3). Similar trends were observed in tertile (drainage volumes, <440 ml [n = 74] and >830 ml [n = 74]) and quintile analyses (drainage volumes, <440 ml [n = 44] and >980 ml [n = 42]) (data not shown).

Correlations and linear regression

Postoperative drainage volumes correlated inversely with VWF: RCo (r = −0.33, P < 0.0001; Fig. 1A), VWF:Ag (r = −0.31, P < 0.0001;
Table 3: VWF and ADAMTS13 in the comparison of extreme drainage quartiles

<table>
<thead>
<tr>
<th>Variable</th>
<th>The lowest quartile (n = 56)</th>
<th>The highest quartile (n = 56)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets, 10^3/µl</td>
<td>228.0 (202.0–276.0)</td>
<td>210.5 (178.0–254.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Fibrinogen, g/l</td>
<td>4.30 (3.30–5.49)</td>
<td>3.72 (3.01–4.71)</td>
<td>0.03</td>
</tr>
<tr>
<td>VWF:RCO, IU/dl</td>
<td>106.30 ± 26.97</td>
<td>85.98 ± 21.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VWF:Ag, IU/dl</td>
<td>101.77 ± 27.05</td>
<td>82.42 ± 18.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ADAMTS13:Ag, IU/dl</td>
<td>99.26 ± 13.32</td>
<td>108.26 ± 11.25</td>
<td>0.0002</td>
</tr>
<tr>
<td>ADAMTS13 activity, IU/dl</td>
<td>98.40 (89.75–111.00)</td>
<td>108.05 (99.80–121.10)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data shown as mean ± SD or median (IQR), or number (percentage).


Fig. 1B) and fibrinogen (r = −0.17, P = 0.03), and positively with ADAMTS13:Ag (r = 0.24, P = 0.0003; Fig. 2A) and ADAMTS13 activity (r = 0.19, P = 0.004; Fig. 2B). The number of FFP transfusions correlated inversely with VWF:RCO (r = −0.21, P = 0.001) and VWF:Ag levels (r = −0.19, P = 0.004), and positively with ADAMTS13:Ag (r = 0.22, P = 0.001). The number of PC transfusions correlated inversely with VWF:RCO (r = −0.20, P = 0.003). No correlations between packed RBC transfusions and VWF–ADAMTS13 parameters were observed; however, the correlations with preoperative haemoglobin, haematocrit and RBC count were significant (r = −0.31, P < 0.0001; r = −0.28, P < 0.0001; r = −0.34, P < 0.0001; respectively). The linear regression model for postoperative chest-tube drainage...
volume showed that the only independent predictors of this variable were VWF:RCO and fibrinogen (Table 4).

### Logistic regression

After adjustment for potential confounders, the odds of high postoperative drainage (≥1000 ml) decreased with an increase in the baseline concentrations of VWF:RCO and increased with an increase in baseline ADAMTS13:Ag (Table 5). Similarly, VWF:RCO in the lowest quartile and ADAMTS13:Ag in the highest quartile, adjusted for confounders, increased the risk of high drainage (Table 6). For VWF:RCO, these observations were confirmed in categorized tertile (odds ratio [OR] for VWF:RCO <89 IU/dl [lowest tertile] adjusted for confounders 5.37 [1.87–15.45]; P = 0.002) and quintile (OR for VWF:RCO <79.2 IU/dl [lowest quintile] adjusted for confounders 2.90 [1.03–8.20]; P = 0.43) analyses.

### DISCUSSION

This study demonstrates for the first time that postoperative chest-tube drainage after elective on-pump CABG in subjects without a prior bleeding history is associated with preoperative balance...
between VWF and ADAMTS13, which is crucial for platelet adhesion and haemostasis. Our findings indicate that lower values of VWF:RCO (though within the reference range) increase chest-tube drainage in CABG patients, the majority of whom were not taking antiplatelet agents and had low bleeding risk based on the BRiSc score. High levels of ADAMTS13:Ag have also been found to be associated with increased drainage in CABG patients, but this variable was not the independent predictor. This study suggests that, in such patients undergoing cardiac surgery, preoperative assessment of VWF:RCO could help identify individuals prone to larger chest-tube drainage, which might have practical implications, including preoperative careful haematological evaluation and the use of haemostatic measures. The current results could be clinically relevant, since data on increased drainage predictors are inconsistent, and valid bleed-scores for elective CABG patients are lacking. Furthermore, the use of BRiSc score appears inappropriate in subjects undergoing elective CABG, because except for age and BMI, none of the risk factors were present in the studied patients.

There are numerous factors that determine circulating VWF concentration and activity, including genetic polymorphisms, ABO blood group, hormones, smoking, and age [17]. Of note, increased chest-tube drainage in CABG patients with lower VWF:Ag and VWF:RCO cannot be explained by the distribution of ABO blood groups, because O blood group (in healthy subjects with 20% lower VWF:Ag) cannot be explained by the distribution of ABO blood groups. Furthermore, the use of BRiSc score appears inappropriate in subjects undergoing elective CABG, because except for age and BMI, none of the risk factors were present in the studied patients.

The issue of low aspirin use in the present CABG patients deserves a comment. The patients were recruited 4 years ago, and most of them were asked to stop aspirin administration 7–10 days prior to surgery. It has been shown that the time of aspirin withdrawal before CABG surgery influences perioperative blood loss and PC transfusion [18]. However, recent data show that aspirin therapy does not increase the postoperative drainage after CABG to such extent as clopidogrel [25]. Nevertheless, the present results cannot be likely extrapolated on CABG patients who continue aspirin and/or clopidogrel up to the day of operation.

The present study has several limitations. First, studied individuals were operated on by 14 different surgeons, and surgical haemostasis must be considered as a potential source of bias. The number of participants was limited, and included as few as 22% (n = 52) female subjects, thus, to validate the results for this subgroup, a larger study is needed. We studied only on-pump CABG patients; however, it is likely that lower VWF could increase chest-tube drainage also in patients undergoing valve surgery or other (including urgent) procedures. Because patients with acute coronary syndromes were excluded, none of the studied individuals

### Table 6: Categorized extreme quartiles of VWF parameters, compared with the remaining group, in regression analysis for high postoperative drainage (≥1000 ml)

<table>
<thead>
<tr>
<th>Variable</th>
<th>High postoperative drainage (≥1000 ml)</th>
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<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>VWF:RCO &lt;83.65 IU/dl (lowest quartile)</td>
<td>5.88 (2.87–12.04)</td>
</tr>
<tr>
<td>VWF:Ag &lt;78.15 IU/dl (lowest quartile)</td>
<td>3.76 (1.85–7.65)</td>
</tr>
<tr>
<td>VWF:CB &lt;87.95 IU/dl (lowest quartile)</td>
<td>1.65 (0.79–3.42)</td>
</tr>
<tr>
<td>ADAMTS13:Ag &gt;111.30 IU/dl (highest quartile)</td>
<td>3.76 (1.85–7.65)</td>
</tr>
<tr>
<td>ADAMTS13 activity &gt;120.00 IU/dl (highest quartile)</td>
<td>1.67 (0.81–3.42)</td>
</tr>
</tbody>
</table>

Hosmer–Lemeshow test for the final model: P = 0.42. The area under the receiver operating characteristic curve (c-statistics) for the final model was 0.84. Highest VWF:RCO, VWF:Ag and VWF:CB quartiles, and lowest ADAMTS13:Ag and ADAMTS13 activity quartiles, are not shown.

VWF:CB: von Willebrand factor collagen binding; others see Table 3.
received clopidogrel, or other potent antplatelet agents. The distribution of VWF multimers, known to display the highest haemostatic activity closely associated with the activity of ADAMTS13, was not assessed. The dynamic changes in VWF and ADAMTS13 during and directly after the surgery, as well as assessment of VWF induced platelet aggregability (using point-of-care tests, like Multiplate or PlateletWorks), were beyond the scope of this study.

In conclusion, this study shows that patients undergoing elective on-pump CABG with lower preoperative VWF:RCO are at risk of having a larger postoperative chest-tube drainage. It might be speculated that preoperative VWF:RCO measurements might help identify patients at risk of high postoperative chest-tube drainage. A larger study is needed to validate this hypothesis.

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Conflict of interest: none declared.

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