Bleeding Time and Bleeding: An Analysis of the Relationship of the Bleeding Time Test With Parameters of Surgical Bleeding

By Raffaele De Caterina, Maria Lanza, Giampiero Manca, Giuliana Buti Strata, Stefano Maffei, and Leonardo Salvatore

The bleeding time is currently the only clinically available comprehensive test to explore primary hemostasis. It is currently performed mostly as a screening procedure before surgery, to detect otherwise unknown defects in platelet-vessel wall interactions, but its use in this specific setting has been severely questioned by recent reanalyses of previously published literature. We studied the relationship of the bleeding time from a standardized cutaneous incision with other parameters of bleeding derived from the analysis of the bleeding time curve and prospectively investigated possible correlations of these alternative parameters, as well as of the bleeding time, with a number of indices of actual bleeding during or after coronary bypass surgery. Four parameters (bleeding time, total bleeding, peak bleeding rate, and time to peak bleeding) were derived from the analysis of bleeding time curves measuring blood losses from a standardized cutaneous incision at 30-second intervals in 118 subjects. Parameters from the bleeding time curve were subsequently obtained in duplicate as a preparative assessment in 40 patients with a negative bleeding history and no recent intake of non-steroidal anti-inflammatory drugs who were undergoing elective pure coronary bypass surgery performed by the same operator. These parameters were correlated in simple linear regression analysis with estimates of surgical bleeding (chest tube drainage, transfusion requirements, percentage of hematocrit, percentage of platelet level decrease, and times to hematocrit and platelet level nadir) and then, in multiple regression analysis, with indices of operation complexity (number of bypasses, total duration of the operation, and duration of the extracorporeal circulation). Bleeding time was significantly correlated, among parameters derived from the bleeding time curve, with total bleeding and peak bleeding rate, but not with time to peak bleeding. Bleeding time, total bleeding, and peak bleeding rate were similarly affected by acute interventions with intravenous aspirin (500 mg) and sublingual nitroglycerin (0.3 mg). None of these parameters, which were obtained in duplicate in each patient preoperatively, was significantly related to actual indices of bleeding at surgery. Thus, in patients with a negative history of bleeding and no recent intake of non-steroidal anti-inflammatory drugs, higher values for bleeding time and bleeding time-related parameters are not associated with higher indices of perioperative and postoperative bleeding at coronary bypass surgery. Therefore, we do not recommend the use of the test in this setting to predict perioperative or postoperative bleeding.

THE BLEEDING TIME is a widely used and popular test to explore primary hemostasis.1 The most common use of the bleeding time is as a preoperative screening of potentially dangerous platelet disorders. Because surgery entails a major challenge to hemostasis, which may be fatal in case of hemorrhagic defects, it makes sense to search for preoperative screening of potentially dangerous bleeding. Indeed, the risk of bleeding from platelet disorders is not reflected by alterations of commonly used coagulation tests such as the prothrombin time (PT) and the partial thromboplastin time (PTT). Because the bleeding time is prolonged in congenital or acquired platelet defects, it has been common reasoning for years that the test could provide a screening for hemorrhagic tendencies from otherwise occult platelet disorders. However, doubts about the predictive value of the bleeding time with respect to surgical bleeding have appeared more and more often in the recent past.2,3 In 1990, an exhaustive review of published reports on the test concluded, among other points, that no evidence exists that the bleeding time is indeed a predictor of surgical losses during or after surgical operations and that no evidence exists that efforts in standardizations have resulted in any significant enhancement in the utility of the test.4 Although most other reviews appearing at the same time or after this publication have substantially agreed with these conclusions,3,5,7 they have not necessarily shared an overall skepticism on the possible clinical usefulness of the test.3,5,8 Also, it has been pointed out that the lack of data assessing predictive value of the bleeding time test with respect to individual patients does not in and of itself negate the possibility that the bleeding time is a predictor of bleeding in certain conditions.8 The bleeding time, it has been said, might predict bleeding, but so far there is no proof of it. There is still space, therefore, for further development of the field, including further advancements in method development and better selection of the clinical settings in which to administer the test. More recent encouraging reports have indeed, at least partially, refueled the discussion.9,13

We hypothesized that the main reason for the lack of a relationship between the cutaneous bleeding time and surgical bleeding lies in the multiple determinants of surgical bleeding, which might obscure, by their preponderant weight, the possible predictive capacity of the bleeding time test. However, an additional reason may lie, on the other hand, in the intrinsic variability of the test itself, which is therefore amenable to possible further improvements.

To verify these hypotheses, we first determined the relationship between the bleeding time and estimates of bleeding from the cutaneous incision in an attempt to exploit addi-
tional information available from the current performance of the bleeding time test and to search for additive/alternative parameters that might reduce test variability and possibly offer more direct and accurate predictors of surgical bleeding. We then analyzed the relationship of the bleeding time and of related parameters with several estimates of surgical bleeding in the course of one single type of operation (elective, pure coronary bypass surgery) performed by the same surgeon to test the impact of these further efforts at standardization on the prediction of surgical bleeding.

MATERIALS AND METHODS

Patients. Duplicate measurements of the bleeding time were performed in a cohort of 118 patients (subset 1: 97 men and 21 women; age [mean ± SD], 58.1 ± 9.8) admitted to a cardiological clinic for the evaluation of a chest pain syndrome or as a preoperative assessment in 40 further patients with angiographically proven coronary artery disease scheduled for elective aorto-coronary bypass surgery (subset 2: 33 men and 7 women; age, 62.3 ± 7.2). The only inclusion criteria for subset 1 patients was the absence of any history of intake of non-steroidal anti-inflammatory agents for 3 days and of aspirin-containing medications for 10 days before the test. These patients were allocated to the assessment of performance of the test, i.e., the intraoperator and interoperator variability of the bleeding time and related parameters with parameters of surgical bleeding if they fulfilled the following criteria: patients were scheduled for elective coronary bypass surgery by the same cardiac surgeon in the absence of any history for non-steroidal anti-inflammatory drug intake in 65 cases. Patients finally selected for the prospective study of surgical bleeding prediction represented 40 of 112 patients among subset 1 patients, 10 (7 men and 3 women; age, 51.7 ± 4.0 years) were studied before and 5 minutes after an intravenous injection of 50 mg of acetyl-salicylic acid (in the form of lysine salt; Aspégic; Lirca Synthelabo, Milan, Italy), a dose consistently producing in our hands complete abolition of platelet aggregatory responses to 1 mmol/L arachidonic acid and greater than 98% inhibition of thromboxane generation in serum. Ten similar patients (8 men and 2 women; age, 55.4 ± 2.5 years) were studied before and 5 minutes after a sublingual administration of 0.3 mg of nitroglycerin as a tablet (Trinitrina; Carlo Erba, Milan, Italy).

Coronary bypass surgery. Coronary bypass surgery was performed by the same experienced cardiac surgeon using left internal mammary artery for the left anterior descending coronary artery and saphenous vein with or without the right mammary artery for other bypasses, the number of which was determined according to conventional criteria derived from coronary angiography. The time of entire duration of surgery and the time of the extracorporeal circulation were carefully recorded. Cardio-pulmonary bypass was performed using standard techniques with a membrane oxygenator, the performances of which, in terms of platelet activation (as determined by the increase of platelet factor 4 and β-thromboglobulin), had been
Previously assessed\(^1\) with heparin anticoagulation and subsequent administration of protamine sulfate. A cold potassium blood cardioplegic solution was used to induce and maintain ischemic arrest. Iced saline topical cooling and systemic hypothermia at 28°C were administered. The mediastinum was drained with one tube.

Assessment of surgical bleeding. The amount of perioperative and postoperative blood losses were determined by computation of the following parameters: (1) the amount of blood collected through the chest tube drainage; (2) the amount of blood transfusions administered (these were either whole blood or plasma and were administered according to an integrated estimate by the operator of perioperative and early postoperative losses); (3) the percentage of the maximum postoperative hematocrit (Hct) decrease; (4) the time to Hct nadir; (5) the percentage of the maximum postoperative platelet level decrease; and (6) the time to platelet level nadir. For computation of parameters 3 through 6, Hct and platelet count were performed three times on the operation day and then daily for at least 1 week.

Statistical analysis. Estimates of intraoperative and interoperative variability of the bleeding time and related parameters were obtained by calculating the percentage of the coefficient of variation \(CV = [SD/mean] \times 100\) of the duplicate measurements. These estimates were compared between each other by analysis of variance and the protected Fisher least significant difference test. Linear regression analysis was used to correlate the means of the two determinations for all the bleeding time parameters used among each other and with the various parameters of surgical bleeding. These were also in turn correlated with the number of bypasses applied in each patient, the duration of the operation, and the duration of the extra-corporeal circulation. Multiple regression analysis was also performed to assess the possible independent effect of bleeding time parameters and parameters related to the length of operation on one side and estimates of surgical bleeding on the other.\(^1\) Comparison of the bleeding time curves before and after drug interventions was performed by the Kolgomorov-Smirnov statistics. The level of significance was set at \(P < .05\).

RESULTS

Baseline values of bleeding time and related parameters in 66 patients of subset 1 receiving double measurements and allocated to the study of intraobserver variability are reported in Table 1. Bleeding time was not related in our study to baseline Hct values \((R = .05)\) in the narrow range of Hct values for our patients (33% to 47%).

Correlations of bleeding time with bleeding parameters derived from the analysis of the bleeding time curve. The bleeding time proved to be correlated significantly with the total bleeding rate and the peak bleeding rate, but no relationship was found with time to peak (Fig 2). The trend to a clear relationship between the bleeding time, the total bleeding rate, and the peak bleeding rate was also evident from analysis of the curves before and after acute pharmacologic interventions with drugs reported to prolong the bleeding time, such as aspirin and nitroglycerin (Table 2 and Fig 3). These interventions prolonged bleeding time and increased total bleeding and peak bleeding rate, but did not affect the time to peak. Interestingly, the global analysis of bleeding time curves before and after pharmacologic interventions proved to be statistically more powerful in detecting differences (Kolgomorov-Smirnov statistics on complete data shown in Fig 3).

Assessment and comparisons of the variability of the various parameters derived from the analysis of the bleeding time curve. The coefficients of variation between duplicate measurements for the bleeding time and related parameters are shown in Fig 4. Despite the theoretical attractiveness of alternative bleeding parameters, they proved to be affected by greater variability than the bleeding time itself, both when duplicate measurements were performed by the same operator (intraoperator variability) and when these were performed by different operators (interoperator variability).

Correlations of the bleeding time and related parameters with estimates of surgical losses. There was no relationship between any of the bleeding time parameters and any of the parameters of surgical bleeding at simple linear regression analysis (Table 3). The bleeding time in patients with lower and higher than median values for all indices of bleeding

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**Table 1. Baseline Values of the Bleeding Time and Related Parameters in Averaged Duplicate Measurements in 66 Coronary Artery Disease Patients**

<table>
<thead>
<tr>
<th></th>
<th>Bleeding Time (min)</th>
<th>Total Bleeding (mg)</th>
<th>Peak Bleeding Rate (mg/30 s)</th>
<th>Time to Peak Bleeding (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>5.7</td>
<td>13.7</td>
<td>3.2</td>
<td>1.0</td>
</tr>
<tr>
<td>SD</td>
<td>1.8</td>
<td>10.3</td>
<td>1.8</td>
<td>0.4</td>
</tr>
<tr>
<td>% CV</td>
<td>32</td>
<td>75</td>
<td>56</td>
<td>40</td>
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\(^1\) For personal use only.
parameters and parameters related to the complexity of the surgical procedure (duration of the operation, duration of the extracorporeal circulation, and the number of bypasses [dependent variables]). The bleeding time or related parameters did not explain part of the residual variability after taking into account parameters of surgical complexity. For example, in multiple regression analysis of chest tube drainage (independent variable) versus the number of coronary artery bypasses, the addition of the bleeding time as a second dependent variable did not improve the $R^2$ value significantly ($0.205$ before and $0.208$ after) and did not decrease the standard error of the estimate ($45.8$ before and $46.5$ after), indicating a lack of improvement in the prediction of the estimate. This was also shown by the absence of any significant trend towards a relationship between bleeding time parameters and parameters of actual bleeding at surgery taking into account relatively homogeneous groups of operations (Fig 5). Also, correction of the bleeding time values for the packed red blood cell volume, as recently suggested by one group, did not improve the relationship between the bleeding time and indices of operative bleeding. Indeed, the coefficient of correlation ($R$) between postoperative bleeding, as assessed by chest tube drainage, cumulative transfusion units, Hct decrease, time to Hct nadir, percentage of platelet level decrease, or time to platelet level nadir, versus the mean of the two bleeding time determinations corrected for the preoperative Hct still remained clearly nonsignificant ($R = 0.17, 0.06, 0.14, 0.08$, and $0.15$ for each of these correlations, respectively).

DISCUSSION

First described in 1901 by Milian, the bleeding time has been practiced for several decades in the way described in

| Table 2. Values of the Bleeding Time and Related Parameters in Single Measurements Before and After Treatment With Intravenous Aspirin (500 mg, n = 10) or Sublingual Nitroglycerin (0.3 mg, n = 10) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Before ASA                      | After ASA                       | Before NTG                     | After NTG                       |
| Bleeding Time (min)             | Total Bleeding (mg)             | Peak Bleeding Rate (mg/30 s)   | Time to Peak Bleeding (min)     |
| Mean                            | 6.2                             | 20.3                           | 4.5                             | 1.2                           |
| SD                              | 1.9                             | 14.2                           | 1.9                             | 0.3                           |
| % CV                            | 31                              | 70                             | 42                              | 26                            |
| $P$ (before v after)            | <.05                            | <.05                           | <.05                            | NS                            |
| Before NTG                      | 7.4                             | 23.9                           | 4.5                             | 1.2                           |
| SD                              | 1.0                             | 11.4                           | 1.9                             | 0.4                           |
| % CV                            | 14                              | 48                             | 42                              | 33                            |
| $P$ (before v after)            | <.05                            | <.05                           | <.05                            | NS                            |

Abbreviations: ASA, aspirin; NTG, nitroglycerin; NS, not significant.
Subsequent important modifications attempted at standardizing the procedure were introduced by Ivy et al.\textsuperscript{19} and Mielke et al.\textsuperscript{14} The test is currently performed by means of disposable devices producing an incision of relatively consistent depth and length and measuring the time intercurring from the incision to the arrest of the hemorrhage after periodic blotting of the wound. Practically unquestioned as to its clinical usefulness until the mid-1980s, despite the lack of appropriately controlled studies addressing the issue of its predictive ability with regard to the risk of actual bleeding, the validity of the bleeding time as an useful clinical test has been seriously questioned by a number of investigator\textsuperscript{s}\textsuperscript{17} and, particularly, by the accurate and complete reanalysis of the literature up to 1986 by Rodgers and Levin.\textsuperscript{4} Under discussion is not so much the value of the test as an epidemiologic or pharmacologic tool to explore primary hemostasis, but rather its practical usefulness in predicting bleeding episodes in patients with a previously negative history of bleeding in situations in which the hemostatic system is seriously challenged, such as during major surgery. As clearly formulated,\textsuperscript{17} the focus of the dispute is whether the bleeding time is useful to “predict clinically significant bleeding sufficiently in advance of its occurrence to allow helpful intervention” and to “provide information not already available by means of other tests that would in any event have been performed.”\textsuperscript{13} The evidence gathered so far is largely negative in this regard. In particular, it has been stressed that at present there is no evidence that the utility of the bleeding time has been enhanced by recent advances in standardization and that there is no evidence that the bleeding time is a predictor of the risk of hemorrhage.\textsuperscript{4} These two statements are someway interconnected. It may be that a lack of clinical usefulness to predict bleeding is caused by variability intrinsic to the test as performed so far. If so, attempts at further improving the methodology of the test are fully justified. This is even more so because no practical alternatives to the bleeding time as a screening procedure for defects of primary hemostasis are on the horizon.

**Fig 3.** Modifications of the bleeding time curves after the intravenous administration of aspirin (500 mg, A) or the sublingual administration of nitroglycerin (B). Values at each time point represent the mean ± SEM of determinations in 10 different subjects for each drug studied. The curves before and after each pharmacological interventions differ more (P < .01 at Kolgomorov-Smirnov statistics) than the bleeding time (P < .05 at Student’s t-test for paired data). Note the clear increase in the size of the curves after each pharmacologic intervention (increase in total bleeding), with an increase in the bleeding time and the peak bleeding rate, but not in the time to peak.

**Fig 4.** The variability in the practical performance of the bleeding time test, as related to the measurement of bleeding time and related parameters. The percent coefficient of variation for the four parameters derived from the analysis of the bleeding time curves (CV, as an indices of the variability of the measurements) in the two measurements obtained in each patient by the same operator (intraobserver variability) or by two different operators (interobserver variability) are shown.
We first sought to determine whether the bleeding time is actually a correlate of bleeding from the cutaneous incision. This was investigated by carefully measuring the amount of blood loss in each 30-second interval of the present state-of-the-art technique, which allowed us to construct, for each bleeding time determination, a curve of blood loss over time.

A similar attempt had been previously described with similar patterns and comparably similar baseline results, but before the introduction of the template to standardize the cutaneous incision. However, the relatively low correlation coefficients between the bleeding time and some of the alternative parameters derived from the analysis of the bleeding time curve (see Fig 2) also suggested the existence of bleeding determinants during the test procedure not assessed by the bleeding time. Therefore, determination of parameters of actual bleeding during the bleeding time procedure might offer better correlates with blood losses at surgery. Pharmacologic interventions increasing the bleeding time (aspirin and nitroglycerin in our case) also increase the total amount of bleeding.

We limited our study to patients without medications obviously able to prolong the bleeding time in order to have a baseline assessment of the normal distribution of bleeding time and bleeding values in the absence of foreign interventions. We also decided to perform linear regression analysis rather than receiver-operator characteristic (ROC) analysis (assessing specificity, sensitivity, and positive and negative predictive values) in the absence of any a priori criteria to set cutoff values, on the assumption that bleeding time and bleeding are both continuous variables. We tested the hypothesis that the hemostatic competence of a patient is related to the results of the bleeding time test.

We first determined the relationship among the various parameters derived from the bleeding time procedure. The significant correlation found between bleeding time on one side and total bleeding and peak bleeding rate on the other allows us to reach the conclusion that the bleeding time is indeed a measure of the total amount of blood loss from the standardized cutaneous incision. However, the relatively low correlation coefficients between the bleeding time and some of the alternative parameters derived from the analysis of the bleeding time curve (see Fig 2) also suggested the existence of bleeding determinants during the test procedure not assessed by the bleeding time. Therefore, determination of parameters of actual bleeding during the bleeding time procedure might offer better correlates with blood losses at surgery. Pharmacologic interventions increasing the bleeding time (aspirin and nitroglycerin in our case) also increase the total amount.

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of blood loss and the peak bleeding rate during the procedure. However, comparisons of the intraoperator and interoperator variabilities for the various parameters investigated indeed proved that the bleeding time is affected by a lower variability than total bleeding and peak bleeding rate. The coefficient of variation for the individual variability of the bleeding time reported by us (13%, Fig 4) is comparable to (and actually slightly better than) the 24% and 17% previously reported with the Simplet I and Simplet II devices, respectively. However, even in this case, the coefficient of variation is greater than 10%, which is larger than that found for the vast majority of laboratory tests, despite being obtained in our case by two trained operators who are likely to be better than the average physicians or technicians usually administering the test in a clinical setting.

We subsequently compared all parameters derived from the analysis of the bleeding time curve with a variety of indices of actual bleeding during surgery. To minimize some surgical determinants of variable bleeding values, we elected to study only one type of surgical operations (elective isolated coronary bypass surgery), all performed by the same surgeon. In consideration of the possibly preponderant value that length and complexity of the operation may play in determining surgical bleeding, we performed multiple linear regression analysis, including variables such as duration of the operation, duration of the extracorporeal circulation, and the number of bypasses applied. Even accounting for all these factors, no significant relationship was disclosed between any value derived from the bleeding time test and any index of actual bleeding.

This negative conclusion is in line with a number of previous attempts at correlating surgical losses with the results of the tests. Neither the selection and careful definition of alternative bleeding time parameters nor the attempts at standardizing some of the surgical variables and in choosing multiple indicators of surgical bleeding were able to revert previously expressed skeptical opinions. This conclusion is also in agreement with that of a recently reported study aimed at relating preoperative and postoperative bleeding time with surgical blood losses. In this report, postoperative, but not preoperative, bleeding time was related to postoperative blood losses after cardiopulmonary bypass. Our conclusion is at variance, on the other hand, from that of two recently reported studies. In one of these, 159 consecutive patients undergoing coronary bypass surgery were studied in a multivariate analysis to determine clinical and laboratory predictors of excessive postoperative packed red blood cell transfusion. In this study, preoperative bleeding time appeared to be an useful predictor of excessive postoperative blood transfusion, which is the only indicator of bleeding reported. Another recent report by the same group has recently reemphasized the same finding using the ratio of preoperative bleeding time to preoperative packed red blood cell volume to predict the need of postoperative blood transfusion. We have attempted to use the same index in our patients, without improving the relationship of the bleeding time versus indices of operative bleeding. A possible reason for discrepancy is the inclusion of patients with drug-induced prolongation of the bleeding time in the quoted studies.

Indeed, recent preoperative aspirin intake was associated with excessive bleeding in one of these studies. Although the aspirin-induced prolongation of the bleeding time has been well known for a long time, a demonstration of the aspirin-induced increase in postoperative blood losses has awaited the conclusion of a large-scale multicenter study. However, we feel that confirmation by other groups of the findings of the only two studies reporting a predictive value of the bleeding time on perioperative bleeding is needed to recommend the use of the bleeding time in the preoperative screening of cardiac surgery patients. Our negative conclusion pertains to patients with no history of bleeding or of recent intake of non-steroidal anti-inflammatory drugs. In this setting, duplicate performance of the bleeding time and the assessment of parameters related to it (otherwise useful, in our hands, to document the effects of drugs affecting primary hemostasis) does allow us to establish not even a trend towards significant correlations with actual bleeding.

Based on our results, we suggest not using the bleeding time test in the preoperative screening of patients undergoing coronary surgery without history of bleeding and of recent intake of non-steroidal anti-inflammatory drugs.

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