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 seriously 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 preoperative 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.

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Bleeding Time Test With Parameters of Surgical Bleeding

The bleeding time is a widely used and popular test to explore primary hemostasis. The most common use of the bleeding time is as preoperative screening of potentially dangerous platelet disorders. Because surgery entails a major challenge to hemostasis, which may be fatal in case of hemostatic 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.

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. Although most other reviews appearing at the same time or after this publication have substantially agreed with these conclusions, they have not necessarily shared an overall skepticism on the possible clinical usefulness of the test. 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. 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.

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, ie, the intraoperator and interoperator variability of the bleeding time and related parameters (n = 66 and n = 21, respectively; see below); the correlations of two alternative methods to estimate total bleeding from the cutaneous incision (n = 37); and the acute effect of drugs (n = 20). Patients in subset 2 were selected for the part of the study aimed at assessing correlations of the bleeding time and related parameters with parameters of surgical bleeding if they fulfilled the following criteria: patients were selected for elective coronary bypass surgery by the same cardiac surgeon in the absence of any need for other concomitant surgical correction (ie, valvular heart disease); patients had an absence of any history of bleeding; patients had values of PT and activated PTT (aPTT) within the normal range (international normalized ratio [INR] <1.2 and aPTT <32 seconds, respectively); and patients had an absence of any history of intake of non-steroidal anti-inflammatory agents for 3 days and of aspirin-containing medications in the 10 days before the test.

Reasons for this selection were the need for an assessment of baseline bleeding time performance in the absence of pharmacologic interventions and for the study of an otherwise hemostatically normal patient population to assess the correlation of test performances with actual surgical bleeding. Patients finally selected for the prospective study of surgical bleeding prediction represented 40 of 112 patients screened. Reasons for the 72 exclusions in this series were a concur-

Test procedure. Bleeding times were performed by the technique described by Mielke et al4 in which a horizontal incision (parallel to the elbow crease) on the lateral aspect of the volar surface of the forearm is made after the inflation of a sphygmomanometric cuff at 40 mmHg. Care was taken throughout all measurements to the following technical details; tests were performed on patients lying in bed in a comfortable 45° position, between 9 and 11 AM, after a light breakfast taken at 7 AM; skin was cleansed with ethyl ether and shaved, when necessary, more than 4 minutes before the incision; the incision was performed within 1 minute after the application of the cuff; and clamps were applied to the cuff to maintain the pressure in the cuff constant throughout the duration of the test. Tests were performed in duplicate in each patient on both arms in random order. All tests were performed by two opera-

ors (among the authors of the study) whose performances proved to be similar (see below). For the part of the study aimed at assessing interoperator variability, the two operators performed the tests at a minimum interval of 15 minutes on different arms in random order of operator (right arm first); for all other studies, the same operator performed the duplicate measurements on the same patient on different arms, again at a minimum interval of 15 minutes (right arm first). Incisions were performed by a disposable device (Surgicutt; Ortho Diagnostics, Raritan, NJ); the operators were aware of the possible alterations of results caused by the application of an inconsistent pressure of the device on the skin and were instructed to apply moderate pressure on the forearm, ie, sufficient to ensure a complete contact of the inferior side of the device with the skin. Whatman No. 1 filter paper (Whatman, Hillsboro, OR) was used to blot the blood oozing from the incision, and care was taken not to touch the wound directly.

Analysis of test results. Squares of Whatman No. 1 filter paper of approximately 1.5 cm × 1.5 cm were cut and weighed individually on a Mettler balance (sensitive to variations of 0.1 mg) and arranged in a rack ready for the blotting of each incision at 30-second intervals. Blotting was performed with the aid of forceps. Reweighting of the filter paper after blotting allowed the determination (by subtraction of the preblotting value) of the weight of the estimated blood loss during that time interval. This estimate was correlated to the actual amount of blood loss, as estimated alternatively by blood collection in weighed borosilicate glass microhematocrit capillary tubes (BRI, Moduloom, Henlev, Denmark),15 with the difference being exactly accounted for by the amount of water in plasma, which quickly evaporated during the drying of the blotting filter paper (the correction factor was, for all practical purposes, the plasmaic value). The estimate of blood loss allowed, for each bleeding time determination, the construction of a curve of blood accumulation over time (Fig 1A). This proved in all cases to be asymmetrical, with an early peak and a long tail. The following four parameters were defined in each curve and used for all subsequent analysis (Fig 1B): (1) the bleeding time, defined conventionally as the time up to the first blotting not giving rise to a detectable blood staining of the filter paper; (2) the total bleeding, defined as the area under the curve obtained by the sum of the estimates at each time point; (3) the peak bleeding rate, defined as the maximum weight of dried blood in the 30-second intervals; and (4) the time to peak bleeding, defined as the time up to the peak bleeding rate.

Pharmacologic interventions. 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 a complete abolishment 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
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\%).

**RESULTS**

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

<table>
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<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>% CV</th>
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<tr>
<td>Bleeding Time (min)</td>
<td>5.7</td>
<td>1.8</td>
<td>32</td>
</tr>
<tr>
<td>Total Bleeding (mg)</td>
<td>13.7</td>
<td>10.3</td>
<td>75</td>
</tr>
<tr>
<td>Peak Bleeding Rate (mg/30 s)</td>
<td>3.2</td>
<td>1.8</td>
<td>56</td>
</tr>
<tr>
<td>Time to Peak Bleeding (min)</td>
<td>1.0</td>
<td>0.4</td>
<td>40</td>
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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 (.205 before and .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 = .17, .06, .00, .14, .08, and .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>
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<tr>
<th>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)</th>
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<tbody>
<tr>
<td><strong>Before ASA</strong></td>
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<tr>
<td><strong>Bleeding Time (min)</strong></td>
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<tr>
<td><strong>Total Bleeding (mg)</strong></td>
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<tr>
<td><strong>Peak Bleeding Rate (mg/30 s)</strong></td>
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<tr>
<td><strong>Time to Peak Bleeding (min)</strong></td>
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<tr>
<td><strong>P (before v after)</strong></td>
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<tr>
<td><strong>Before NTG</strong></td>
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<tr>
<td><strong>Bleeding Time (min)</strong></td>
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<tr>
<td><strong>Total Bleeding (mg)</strong></td>
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<td><strong>Peak Bleeding Rate (mg/30 s)</strong></td>
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<td><strong>P (before v after)</strong></td>
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Abbreviations: ASA, aspirin; NTG, nitroglycerin; NS, not significant.
tive history of bleeding in situations in which the hemostatic system is seriously challenged, such as during major surgery. As clearly formulated, 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." 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. These two statements are somehow 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.

1910 by Duke. Subsequent important modifications attempted at standardizing the procedure were introduced by Ivy et al and Mielke et al. 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 investigators and, particularly, by the accurate and complete reanalysis of the literature up to 1986 by Rodgers and Levin. 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.

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 subject 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 an 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 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 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. 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of blood loss and the peak bleeding rate during the proce-
dure. However, comparisons of the intraoperator and interop-
erator 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 intraindividual variability of the
bleeding time reported by us (13%, Fig 4) is comparable to
(and actually slightly better than) the 24% and 17% pre-
viously reported with the Simplate I and Simplate 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 usu-
ally 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 iso-
lated 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 be-
tween any value derived from the bleeding time test and any
index of actual bleeding.

This negative conclusion is in line with a number of previ-
ous 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, postopera-
tive, but not preoperative, bleeding time was related to post-
operative 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 ap-
ppeared 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 re-
cently reemphasized the same finding using the ratio of pre-
operative bleeding time to preoperative packed red blood
cell volume to predict the need of postoperative blood trans-
fusion. 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. How-
ever, 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 preopera-
tive screening of cardiac surgery patients. Our negative con-
clusion 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 undergo-
ning coronary surgery without history of bleeding and of recent
intake of non-steroidal anti-inflammatory drugs.

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