Relation Between Activated Clotting Time During Angioplasty and Abrupt Closure

Narins, Craig R. MD; Hliegass, Jr William B. MD, MPH; Nelson, Charlotte L. MS;
Tcheng, James E. MD; Harrington, Robert A. MD; Phillips, Harry R. MD; Stack, Richard S. MD; Califf, Robert M. MD

Author(s):

Issue: Volume 93(4), 15 February 1996, pp 667-671
Publication Type: [Clinical Investigations And Reports]
Publisher: © 1996 American Heart Association, Inc.
Received July 10, 1995; revision received September 28, 1995; accepted October 4, 1995.
Institution(s): From the Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, NC.
Correspondence to Robert M. Califf, MD, Duke University Medical Center, Box 31123, Durham, NC 27710. E-mail callf001@mc.duke.edu.

Abstract
Background: The purpose of this study was to determine whether the degree of heparin anticoagulation during coronary angioplasty, as measured by the activated clotting time, is related to the risk of abrupt vessel closure.

Methods and Results: Sixty-two cases of in- and out-of-laboratory abrupt closure in patients in whom intraprocedure activated clotting times were measured were identified from a population of 1290 consecutive patients who underwent nonemergency coronary angioplasty. This group was compared with a matched control population of 124 patients who did not experience abrupt closure. Relative to the control population, patients who experienced abrupt closure had significantly lower initial (median, 350 seconds [25th to 75th percentile, 309 to 401 seconds]) versus 380 seconds [335 to 423 seconds], P = .004) and minimum (345 seconds [287 to 387 seconds] versus 370 seconds [321 to 417 seconds], P = .014) activated clotting times. Higher activated clotting times were not associated with an increased likelihood of major bleeding complications. Within this population, a strong inverse linear relation existed between the activated clotting time and the probability of abrupt closure.

Conclusions: This study demonstrates a significant inverse relation between the degree of anticoagulation during angioplasty and the risk of abrupt closure. A minimum target activated clotting time could not be identified; rather, the higher the intensity of anticoagulation, the lower the risk of abrupt closure. (Circulation. 1996;93:667-671.)

Key Words: angioplasty, complications, heparin, anticoagulants.

A significant limitation of coronary angioplasty continues to be abrupt closure of the dilated vessel. Abrupt closure occurs in nearly equal 4% to 8% of cases and is associated with significantly increased periprocedural myocardial infarction, emergency coronary artery bypass surgery, and death. [1-4] In conjunction with mechanical processes, such as vessel recoil and intimal flap formation, fibrin-platelet thrombus deposition at the site of arterial injury is postulated to play an important causative role in acute occlusion during and after coronary angioplasty. [5,6] Although heparin is routinely administered to prevent thrombosis, the optimal degree of anticoagulation during angioplasty has not been defined. This study was undertaken to determine whether the degree of anticoagulation during angioplasty, as measured by the activated clotting time, is related to the patient's risk of abrupt closure.

Methods
Study Population
The study population was drawn from 1290 consecutive patients who underwent nonemergency coronary angioplasty at Duke University Medical Center between July 1, 1989, and December 31, 1990. This time period was chosen because it predated our systematic efforts to maintain the activated clotting time above 350 seconds. Patients who had received thrombolytic therapy within 24 hours or who were enrolled in pharmacological trials affecting the hemostatic system were excluded. All patients received aspirin before and after angioplasty and heparin during the procedure. Angioplasty was performed according to standard techniques. [7] After the procedure, most patients were anticoagulated with heparin overnight and...
had their vascular sheaths removed the following morning.

**Abrupt Closure**

In-laboratory (in-lab) abrupt closure was defined as total occlusion (TIMI grade 0 or 1 flow) of the dilated artery occurring at any time during the procedure. Out-of-laboratory (out-of-lab) abrupt closure was defined as repeat catheterization before hospital discharge that showed total occlusion of the previously dilated lesion or subtotal occlusion with ECG evidence of ischemia. In-lab or out-of-lab abrupt closure occurred in 76 (5.9%) of these patients. Activated clotting time data were available in 62.

**Data Collection**

Demographic and procedural data were prospectively collected in the Duke Databank for Cardiovascular Disease and confirmed by retrospective chart review. From the population of 1290 patients, a control group of 124 patients (2 control subjects for every abrupt closure patient) who had procedural activated clotting time data was selected. All patients who matched the case patients on the following previously validated predictors of abrupt closure were identified, then two matching control subjects were randomly chosen for each case: (1) preprocedural total vessel occlusion, [9, 10] (2) unstable angina, [11, 12] and (3) lesion location. [9] The final case and control populations were also well matched for several other potential clinical and preprocedural angiographic predictors of abrupt closure (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Abrupt Closure</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=62)</td>
<td>(n=124)</td>
<td></td>
</tr>
<tr>
<td>Age, y, median (25%, 75%)</td>
<td>60 (50, 67)</td>
<td>58 (52, 65)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>19 (31)</td>
<td>34 (27)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>57 (92)</td>
<td>115 (93)</td>
</tr>
<tr>
<td>Target vessel, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>21 (34)</td>
<td>42 (34)</td>
</tr>
<tr>
<td>LAD</td>
<td>27 (43)</td>
<td>54 (43)</td>
</tr>
<tr>
<td>LCx</td>
<td>14 (23)</td>
<td>28 (23)</td>
</tr>
<tr>
<td>Pre-PTCA total occlusion, n (%)</td>
<td>8 (13)</td>
<td>16 (13)</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>13 (21)</td>
<td>26 (21)</td>
</tr>
<tr>
<td>Vessels diseased (&gt;70%), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>39 (63)</td>
<td>80 (65)</td>
</tr>
<tr>
<td>2</td>
<td>13 (21)</td>
<td>29 (23)</td>
</tr>
<tr>
<td>3</td>
<td>10 (16)</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (11)</td>
<td>25 (20)*</td>
</tr>
<tr>
<td>Pre-lab heparin, n (%)</td>
<td>40 (65)</td>
<td>57 (40)†</td>
</tr>
<tr>
<td>Initial % stenosis, mean±SD</td>
<td>91±8.9</td>
<td>92±8.2</td>
</tr>
<tr>
<td>Initial TIMI flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>9 (15)</td>
<td>22 (18)</td>
</tr>
<tr>
<td>3</td>
<td>53 (85)</td>
<td>102 (82)</td>
</tr>
</tbody>
</table>

RCA indicates right coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; PTCA, percutaneous transluminal coronary angioplasty; Pre-lab, prelaboratory; and TIMI, Thrombolysis in Myocardial Infarction.

*P=.19.
†P<.05.

Table 1. Baseline Patient Characteristics

Adverse postprocedural events consisted of myocardial infarction, need for emergency coronary artery bypass surgery, need for emergency repeat angioplasty after the patient had left the angioplasty suite, and death. Myocardial infarction was defined as any of the following: (1) development of new Q waves (greater or equal to 0.04 ms wide) in two or more contiguous leads, (2) rise in total serum creatine phosphokinase to greater than twice the upper limit of normal with MB fraction > 5%, or (3) total creatine kinase-MB fraction > 20 IU/L (twice the upper limit of normal) with new ischemic
ECG changes. Major bleeding was defined as blood loss or a bleeding complication requiring blood transfusion after angioplasty but before hospital discharge. Unstable angina was defined as new-onset, crescendo, exertional, or postinfarction angina.

Activated Clotting Times

Activated clotting times were determined in the angioplasty laboratory by use of the Hemochron device (International Technidyne Corp.).[13-15] The control activated clotting time for the Hemochron is 126 plus/minus 13 seconds.[15] After vascular access was achieved, a heparin bolus was administered (usually 10,000 U), and the activated clotting time was obtained 5 to 10 minutes later. In a minority of patients, a supplemental heparin bolus was given and another activated clotting time was determined before the first balloon inflation. The activated clotting time after the final preprocedural heparin bolus was referred to as the "initial" activated clotting time. This initial activated clotting time, therefore, represented the patient's state of anticoagulation at the time of first balloon inflation. The timing and number of subsequent activated clotting time determinations and heparin boluses were at the discretion of the operator. Continuous heparin infusions were not used during the procedure. The minimum and maximum activated clotting times were recorded. The relation between maximum in-lab clotting time and transfusion risk was also evaluated.

Statistical Methods

Baseline characteristics were described in terms of the median and 25th and 75th percentiles or mean plus/minus SD for continuous variables and by percentages for discrete variables. Chi² analysis was used to assess significant differences in discrete variables. The relation between activated clotting time and abrupt closure was evaluated with a multivariable binary logistic regression model.[16] Although the control population was matched on several known predictors of abrupt closure (i.e., preprocedure total occlusion, unstable angina, and lesion location), the relation of activated clotting time and abrupt closure was evaluated multivariably to correct for other potentially significant baseline differences (i.e., prelaboratory intravenous heparin use). The relation between activated clotting time and abrupt closure could be tested for linearity by fitting a restricted cubic spline function[17] and testing the need for the nonlinear terms in the model using the Wald chi² statistic.

The logistic model quantifies the effect of the predictor, activated clotting time, on the outcome, abrupt closure, in terms of a logarithm of the odds or odds ratio. However, many prefer to interpret a model in terms of predicted probabilities rather than odds. To convert odds to a predicted probability scale, the model was adjusted for the oversampling of cases (in our case-control population) by assuming the known population risk of abrupt closure of 5.9% present in our overall population of 1290 consecutive patients (from which the case-control population was derived).

Results

Baseline Clinical Data

Of the 1290 patients who underwent nonemergency coronary angioplasty during the study period, 76 (5.9%) experienced abrupt closure. Activated clotting time data were available for review in 129 (82%). Of these, 34 patients had out-of-lab abrupt closure, 26 had in-lab abrupt closure, and 2 experienced abrupt closure both during and after angioplasty. The matched control group comprised 124 patients derived in the manner described above.

Preprocedural demographic, clinical, and lesion characteristics were similar among the 62 abrupt closure and the 124 control patients (Table 1). The groups differed only with respect to intravenous heparin use before angioplasty, which was more common in the abrupt closure group. Details concerning heparin dosing and activated clotting time monitoring during angioplasty are shown in Table 2. Although the case and control groups received similar amounts of heparin in the laboratory before the initial balloon inflation, the abrupt closure group received significantly more total in-lab heparin, reflecting the operators' response to the untoward event (Table 2).
Table 2. Procedural Description

Sequela of Abrupt Closure

Of the 62 patients who experienced abrupt closure, 21 (33.9%) suffered acute myocardial infarction, 23 (37.7%) required emergency coronary artery bypass surgery, and 2 (3.3%) died. All the patients who developed abrupt closure after leaving the angioplasty suite returned for repeat coronary angiography. Repeat angioplasty was attempted in 31 (86.1%), and 11 (30.6%) ultimately required emergency bypass graft surgery.

Activated Clotting Time Values

In our study population, the activated clotting time at the time of initial balloon inflation ranged from 236 to 672 seconds (median, 371 seconds; 25th to 75th percentile, 324 to 413 seconds). Two or more activated clotting times were checked in 30.6% of the patients (Table 2). The minimum in-lab activated clotting time ranged from 236 to 659 seconds (median, 361 seconds; 25th to 75th percentile, 312 to 411 seconds). The maximum in-lab activated clotting time ranged from 236 to 672 seconds (median, 380 seconds; 25th to 75th percentile, 332 to 417 seconds). The cumulative distributions of initial in-lab activated clotting time values in both the case and control populations are depicted in Figure 1.
Compared with the control population, patients who suffered abrupt closure had significantly lower activated clotting times at the time of initial balloon inflation (median, 350 versus 380 seconds, \( P = .004 \)) and lower minimum in-lab activated clotting times (median, 345 versus 370 seconds, \( P = .014 \)) (Table 3). Patients who suffered in-lab abrupt closure tended to have lower minimum in-lab activated clotting times than patients who had out-of-lab abrupt closure (median, 323 seconds [25th to 75th percentile, 271 to 367 seconds] versus 355 seconds [25th to 75th percentile, 324 to 404 seconds], \( P = .04 \)), but there was no significant difference in initial activated clotting times between the in-lab and out-of-lab abrupt closure groups. Lower initial and minimum in-lab activated clotting times were likewise significantly related to the need for repeat emergency angioplasty (\( P = .005 \)) or emergency coronary artery bypass surgery (\( P = .017 \)) before hospital discharge.

### Table 3. Activated Clotting Times

<table>
<thead>
<tr>
<th>Abrupt Closure Patients (n=62)</th>
<th>Control Subjects (n=124)</th>
<th>( P )†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial ACT, s*</td>
<td>350 (309, 401)</td>
<td>380 (335, 423)</td>
</tr>
<tr>
<td>Minimum ACT, s†</td>
<td>345 (287, 387)</td>
<td>370 (321, 417)</td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time. Values are median (25th, 75th percentile).

*ACT at the time of initial vessel dilatation.
†Minimum ACT during angioplasty.
‡Logistic model, Wald \( \chi^2 \).

To further characterize the activated clotting time as a predictor of abrupt closure, the relation between the activated clotting time and the probability of subsequent abrupt closure was examined with multivariable binary logistic regression analysis (Figure 2). The relation between the initial activated clotting time and abrupt closure risk was highly significant (\( P = .015 \)). Moving from the 25th percentile of activated clotting time (324 seconds) to the 75th percentile (413 seconds), the probability of abrupt closure declined from 7.9% to 4.5%. Although there was a significant difference in preprocedural intravenous heparin use between the case and control patients, preprocedural heparin use was not a significant independent predictor of abrupt closure in our population (\( P = .095 \)). Likewise, the relation between the initial activated clotting time and abrupt closure remained unchanged after adjustment for this difference in preprocedural heparin use by the multivariable regression model.

![Figure 2. Graph showing probability of abrupt closure with upper and lower 95% confidence limits versus the initial activated clotting time (seconds) measured with the Hemochron device. ACT indicates activated clotting time.](http://ovidsp.tx.ovid.com.monster.cc.columbia.edu:2048/spa/ovidweb.c...
Optimal Activated Clotting Time for Coronary Angioplasty

We attempted to use our population to define a threshold activated clotting time above which abrupt closure becomes less likely and more intense heparin anticoagulation is of no added benefit. As seen in Figure 2, an inverse (statistically linear) relation between the initial activated clotting time and the probability of abrupt closure persists throughout the observed range of activated clotting time values (Wald test for departure from linearity, $P = .88$). Thus, because the probability of abrupt closure continues to decrease progressively with increasing activated clotting times, no minimum "safe threshold" activated clotting time was evident above which a further increase in degree of anticoagulation would not be associated with a further reduction in the probability of abrupt closure.

Bleeding Complications

Twenty-four patients (12.9%) received blood transfusions after angioplasty but before hospital discharge (Table 4). No relation existed between major bleeding, as defined by the need for blood transfusion, and the initial or maximum activated clotting times during angioplasty ($P = .85$). The lack of association between bleeding and activated clotting time persisted even after exclusion of patients who underwent coronary artery bypass surgery.

<table>
<thead>
<tr>
<th>Patients Requiring Transfusion*</th>
<th>Case</th>
<th>Control</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial ACT, s†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;350</td>
<td>5</td>
<td>3</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>350-400</td>
<td>4</td>
<td>3</td>
<td>7 (12.7)</td>
</tr>
<tr>
<td>&gt;400</td>
<td>5</td>
<td>4</td>
<td>9 (14.8)</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>11</td>
<td>24 (12.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maximum ACT, s‡</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;350</td>
<td>4</td>
<td>3</td>
<td>7 (11.5)</td>
</tr>
<tr>
<td>350-400</td>
<td>4</td>
<td>3</td>
<td>7 (12.3)</td>
</tr>
<tr>
<td>&gt;400</td>
<td>5</td>
<td>5</td>
<td>10 (14.7)</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>11</td>
<td>24 (12.9)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft surgery; ACT, activated clotting time. *Number of patients who required red blood cell transfusion(s). †ACT at the time of initial vessel dilatation. ‡Maximum ACT during angioplasty.

Table 4. Major Bleeding Versus Activated Clotting Time

Discussion

This study demonstrates a significant inverse relation between the intensity of anticoagulation during angioplasty, as measured by the activated clotting time, and the risk of abrupt closure. This finding strongly supports the contribution of thrombus formation in the development of acute occlusion from coronary angioplasty. In addition, because the risk of abrupt closure continued to decline without a leveling-off effect as the activated clotting time increased, currently used threshold activated clotting time values for angioplasty may be inadequately low.

Since the inception of the procedure, patients undergoing coronary angioplasty have been routinely premedicated with antiplatelet and antithrombin agents to prevent thrombotic complications. Prospective randomized trials have convincingly demonstrated the role of platelet inhibition in decreasing acute ischemic complications after angioplasty. \[18, 19\] Although it is widely accepted that administering heparin during angioplasty also reduces ischemic complications, formal evidence of this relation is limited. In a series of 189 patients who underwent 201 elective angioplasty procedures, no relation existed between activated clotting time and ischemic postprocedural complications. \[20\] These results, limited by the low number of ischemic events in this series, are contrary to the findings of Ferguson et al. \[21\] who demonstrated in a retrospective analysis of 1469 patients that a very low in-lab activated clotting time (< 250 seconds) was associated with increased major in-hospital complications (death and need for emergency bypass surgery) after coronary angioplasty. Topol et al. \[22\] in a study of escalating doses of the specific thrombin inhibitor hirulog during routine angioplasty, showed a reduction in the incidence of abrupt closure from 11.3% at lower doses to 3.9% at the maximum tested dose, without increased bleeding complications. The lower abrupt closure rates seemed to be closely related to the activated clotting time achieved by a given dose of hirulog. Despite the suggestive findings of these earlier studies, the lack of data demonstrating an independent relation between heparin anticoagulation as measured by the activated clotting time during angioplasty and the risk of abrupt closure formed the basis for this study. The case-control format allowed matching or adjustment for other potential clinical and angiographic predictors of abrupt closure within a large, well-defined population with a known overall rate of abrupt closure. Total occlusion has consistently been shown to be the strongest preprocedural angiographic predictor of abrupt closure and outcome. \[9, 10, 12, 23\] The target artery and the presence of unstable angina have also frequently been identified as predictors of abrupt closure. \[9, 11, 12\] Therefore, patients were matched on these characteristics. The control population was also very similar for several other potentially confounding clinical and angiographic variables (Table 1). A significant difference was found, however, in the frequency of preprocedural heparin therapy between case and control patients, despite matching on angina status. Controlling for this difference with multivariable analysis shows that preprocedural heparin therapy did not significantly affect the observed relation between activated clotting time and abrupt closure risk.

Study Limitations
This analysis is based on the initial activated clotting times, which reflect the patient's state of anticoagulation at the time of initial balloon inflation. Although initial activated clotting times were determined after the heparin bolus and before the first angioplasty balloon inflation in a standardized fashion, there was no standard schedule for checking subsequent activated clotting times during angioplasty. Hence, we cannot comment on the significance of subsequent measurements, because events in the laboratory may have blurred the timing of these measurements. In addition, we used the Hemochron system, which does not yield values identical to those with the HemoTec system. Thus, the absolute values from these data cannot be extrapolated to the HemoTec system. Finally, given the relation between low activated clotting time, abrupt closure, and the need for a subsequent invasive procedure, an association between activated clotting time and bleeding may have been masked due to oversampling of abrupt closures in this case-control study. In addition, the total number of bleeding events, defined as the need for transfusion, was too small to draw definitive conclusions. The relation between intensity of anticoagulation as measured by activated clotting time and clinical bleeding risk requires further investigation in a large, unselected group of patients undergoing angioplasty.

Conclusions

The results of this study demonstrate a significant inverse relation between the degree of anticoagulation during angioplasty, as measured by activated clotting time, and the probability of abrupt closure. Because the probability of abrupt closure continued to decline throughout the range of activated clotting times encountered in our population (nearly equal to 250 to 500 seconds), no "safe threshold" activated clotting time was apparent. Progressively higher procedural activated clotting times were associated with a continuously decreasing probability of abrupt closure at activated clotting times well above the currently used thresholds of 300 or 350 seconds.

Acknowledgments

We are indebted to Pat Williams and Penny Hodgson for their skilled editorial assistance during the preparation of this manuscript.

REFERENCES


