Relation Between Procedural Activated Coagulation Time and Outcome After Percutaneous Transluminal Coronary Angioplasty

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Objective. The purpose of this study was to determine whether a low procedural activated coagulation time is associated with a high rate of in-hospital complications and to identify whether there is an activated coagulation time range that may be associated with a low rate of complications.

Background. In recent years the activated coagulation time has come into widespread use for monitoring anticoagulation in the catheterization laboratory. However, considerable controversy exists as to the standards by which to judge “adequate” anticoagulation for interventional procedures.

Methods. From a total of 1,469 consecutive patients with percutaneous transluminal coronary angioplasty, we retrospectively identified 103 (Group I, 7% of the overall population) with major complications of death or emergency or urgent coronary artery bypass graft surgery and compared them with 460 patients without complications (Group II). Group I patients had more high risk clinical characteristics, such as type B and C lesions, class III and IV angina, recent myocardial infarction and recent thrombolytic treatment. Activated coagulation times were compared between Groups I and II at baseline, after administration of 10,000 U of heparin and at the end of the procedure.

Results. There were no differences in baseline activated coagulation times between Groups I and II. Group I had significantly lower activated coagulation times after heparin therapy and at the end of the procedure: 61% <250 s, 20% between 250 and 275 s, 11% between 275 and 300 s and 8% >300 s; 27% <250 s, 33% between 250 and 275 s, 17% between 275 and 300 s, and 21% >300 s (p < 0.0001).

Complications occurred in all patients with final activated coagulation times <250 s but in only 0.3% of patients with final activated coagulation times >300 s.

Conclusions. A diminished activated coagulation time response to an initial bolus of heparin is associated with major in-hospital complications after coronary angioplasty, although patients with complications did have a higher risk before the procedure. It remains to be determined whether there is an ideal “target” activated coagulation time for interventional procedures.

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performed at St. Luke's Episcopal Hospital. We retrospec-
tively identified all 103 patients (7%) in this group with major
in-hospital complications of death (11 patients) and emer-
gency (75 patients) and urgent (same day) (17 patients)
coronary artery bypass surgery. The patients with major
complications (Group I) were compared with 400 patients
with successful coronary angioplasty from the same time
period (Group II). Group II patients comprised the first 400
patients in our patient data base of the original cohort of
1,469 patients with no procedural complications who had
activated coagulation times measured at baseline, after heparin
therapy and at the end of the procedure.

As part of the normal routine in the catheterization
laboratory, activated coagulation times were measured in all
patients at baseline, before any heparin was administered.
Patients then routinely received an intravenous bolus of
10,000 U of heparin, and activated coagulation time was
again measured at least 5 min after the heparin bolus. All
blood samples were drawn through the arterial sheath. All
activated coagulation time measurements were performed
with use of a HemoTec coagulation timer and high range
cartridges with kaolin activator. These cartridges are
designed to give a response of ~100 s for every 1 U/ml of
heparin. Duplicate samples were run, and the results of the
two samples were averaged to provide a final value.

During the course of the subsequent coronary angioplasty
procedure, additional heparin was administered, and addi-
tional procedural activated coagulation times were checked
At the discretion of the operator. A final activated coagula-
tion time was measured at the end of the procedure, just
before the patient left the catheterization laboratory.

The following activated coagulation times were measured
or calculated in each patient: baseline, after heparin therapy,
at the end of the procedure (final activated coagulation time)
and activated coagulation time heparin response (defined as
the activated coagulation time after heparin therapy minus
the baseline activated coagulation time). Measurements
were compared between Groups I and II by a two-sample t
and by chi-square analysis. Measurements were com-
pared between patients with and without complications at
different activated coagulation time levels by chi-square
analysis, and p < 0.05 was considered significant.

Table 1. Patient Characteristics for Groups I and II

<table>
<thead>
<tr>
<th>Group</th>
<th>Total No.</th>
<th>Men</th>
<th>Women</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent CABG</td>
<td>17</td>
<td>15</td>
<td>2</td>
<td>68 ± 10</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>75</td>
<td>55</td>
<td>20</td>
<td>59 ± 7</td>
</tr>
<tr>
<td>Death</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td>61 ± 13</td>
</tr>
<tr>
<td>Total</td>
<td>103</td>
<td>79</td>
<td>24</td>
<td>59 ± 10</td>
</tr>
<tr>
<td>Group II</td>
<td>400</td>
<td>308</td>
<td>92</td>
<td>57 ± 11</td>
</tr>
</tbody>
</table>

Values presented are mean value ± SD or number of patients. CABG = coronary artery bypass graft surgery.

Table 2. Clinical Characteristics of Patients in Groups I and II

<table>
<thead>
<tr>
<th></th>
<th>Group I (complications)</th>
<th>Group II (no complications)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 103)</td>
<td>(n = 400)</td>
</tr>
<tr>
<td>Lesion type*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>3 (5.9%)</td>
<td>10 (2.5%)</td>
</tr>
<tr>
<td>B</td>
<td>50 (48.5%)</td>
<td>274 (68.5%)</td>
</tr>
<tr>
<td>C</td>
<td>49 (47.6%)</td>
<td>84 (21.0%)</td>
</tr>
<tr>
<td>NYHA functional class*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0%)</td>
<td>4 (1.0%)</td>
</tr>
<tr>
<td>II</td>
<td>2 (2%)</td>
<td>42 (10.5%)</td>
</tr>
<tr>
<td>III</td>
<td>30 (29.1%)</td>
<td>124 (31.5%)</td>
</tr>
<tr>
<td>IV</td>
<td>71 (69%)</td>
<td>220 (55%)</td>
</tr>
<tr>
<td>Recent MI (&lt;30 days)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 (20.4%)</td>
<td>26 (6.5%)</td>
</tr>
<tr>
<td>Recent thrombolysis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (14.6%)</td>
<td>17 (4.25%)</td>
</tr>
<tr>
<td>Total procedural heparin dose (1,000 U)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.7 ± 4.0</td>
<td>17.8 ± 1.9</td>
</tr>
<tr>
<td>Heparin drip before PTCA*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 (29%)</td>
<td>75 (18.7%)</td>
</tr>
</tbody>
</table>

* p < 0.0005 Group I versus Group II. * p < 0.05 Group I versus Group II. Values presented are mean value ± SD or number (%) of patients. MI = myocardial infarction; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty.

Results

The demographic characteristics of Groups I (major com-

 complications) and II (no major complications) (Table 1) were
not significantly different between the two groups. However,
there were clinical differences between both groups, as
shown in Table 2. Group II patients had more type A and
fewer type C lesions and were more often in New York
Heart Association functional classes II and III, with fewer
patients in class IV. In Group I there were more patients
with a recent myocardial infarction who had undergone
recent thrombolysis and more patients on a heparin drip
before coronary angioplasty. Group I patients had also
received significantly less procedural heparin than Group II
patients.

Activated coagulation times at baseline, after heparin
therapy, and at the end of the procedure in Groups I and II
are shown in Table 3. There was no significant difference in
baseline activated coagulation times between the two
groups, but activated coagulation times after heparin therapy
and at the end of the procedure were significantly lower in
Group I, as was the activated coagulation time heparin
response. Activated coagulation time values for each of the
three major complications are also listed in Table 3.

Table 4 shows the number of patients in Groups I and II
with and without complications at four different activated
coagulation time levels after heparin therapy. Of 171 patients
in both groups with activated coagulation times <250 s after
heparin therapy, 63 (representing 37% of the 171 patients at
that activated coagulation time level, or 61.2% of all Group
I patients) had major complications, and 108 (representing
65% of the 171 patients at that activated coagulation time
level, or 27% of all Group II patients) did not. Of 243 patients
in both groups with activated coagulation times >275 s after
heparin therapy. 19 (representing 8% of the 243 patients at
that activated coagulation time level, or 18.4% of all Group I
patients) had complications, and 224 (representing 92% of
the 243 patients at that activated coagulation time level, or
56% of all Group II patients) did not. The differences
between groups were significant (p < 0.0001).

Table 5 shows the number of patients in Groups I and II
with and without complications at four different final acti-
vated coagulation time levels. All 87 patients with final
activated coagulation times <250 s had complications. Only
three (0.8%) of 379 patients with final activated coagulation
times ≥275 s had complications, and only one (0.3%) of 317
patients with a final activated coagulation time =300 s had
complications. The differences between groups were signif-
ificant (p < 0.0001).

Table 6 shows the number of patients in Groups I and II
with and without complications at four different heparin
response levels. Of 333 patients in both groups who in-
creased their activated coagulation times by <150 s after a
10,000-U bolus of heparin, 87 (representing 26% of the 333
patients at that activated coagulation time level, or 84.5% of
all Group I patients) had complications. Of 95 patients in
both groups who increased their activated coagulation time
by >175 s after a 10,000-U bolus of heparin, 3 (represen-
ting 3% of the 95 patients at that activated coagulation time level,
or 2.9% of all Group I patients) had complications. The
differences between groups were significant (p < 0.0001).

Discussion

Present study. We documented that low procedural acti-
vated coagulation times are associated with a higher rate of
in-hospital complications after coronary angioplasty. Our
data suggest that the risk of complications (urgent and emer-
gency surgery, death) are substantially increased in patients
with activated coagulation times <250 s after heparin ther-
apy or at the end of the procedure and in patients with an
activated coagulation time response to 10,000 U of heparin
<150 s. Conversely, patients with activated coagulation
times ≥275 s after heparin therapy or at the end of the
procedure or an activated coagulation time response to
10,000 U of heparin >175 s had very few complications.

All of our measurements were performed with a Hemo-
Tec automated coagulation timer, which uses a totally dif-
ferent measurement technique from the Hemochron system,
the other commercially available automated coagulation
timer. The results of these two different systems are not in
any way comparable, and a target activated coagulation time
of 300 s on one machine is not the same as a target activated
coaulation time of 300 s on the other (15).

Interpretation of results. One factor to consider in inter-
preting our results is that there was individual variation
among physicians in our institution with regard to manage-
ment of patients, aggressiveness with which procedural
anticoagulation was approached and selection of patients for
bypass surgery. The complications in Group I may be solely
attributed to their higher incidence of clinical risk factors,
many of which are associated with new or recent coronary
thrombosis. The diminished activated coagulation time re-
sponse in Group I may be a secondary phenomenon, and, in
the face of lower procedural heparin doses, it cannot be
concluded that the complications were related only to the
lower activated coagulation time. The complications in these
patients may have resulted from their high risk profile and a
low final activated coagulation time as a result of less
procedural heparin.

Table 3. Activated Coagulation Times for Groups I and II

<table>
<thead>
<tr>
<th>ACT After Heparin Therapy (s)</th>
<th>ACT I</th>
</tr>
</thead>
<tbody>
<tr>
<td>227 ± 36</td>
<td>232 ± 37</td>
</tr>
<tr>
<td>227 ± 32</td>
<td>232 ± 27</td>
</tr>
<tr>
<td>284 ± 37</td>
<td>226 ± 32</td>
</tr>
<tr>
<td>259 ± 45</td>
<td>303 ± 25</td>
</tr>
</tbody>
</table>

*p < 0.0001 Group I versus Group II. ACT = activated coagulation time. CABG = coronary artery bypass graft surgery.

Table 4. Activated Coagulation Times After Heparin Therapy

<table>
<thead>
<tr>
<th>ACT After Heparin Therapy (s)</th>
<th>Group I (complications)</th>
<th>Group II (no complications)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;250</td>
<td>68 (12.2%)</td>
<td>68 (17.5%)</td>
<td>136</td>
</tr>
<tr>
<td>250–275</td>
<td>21 (40.4%)</td>
<td>140 (35%)</td>
<td>161</td>
</tr>
<tr>
<td>275–300</td>
<td>11 (10.7%)</td>
<td>4 (1.3%)</td>
<td>15</td>
</tr>
<tr>
<td>&gt;300</td>
<td>8 (7.5%)</td>
<td>4 (1.3%)</td>
<td>12</td>
</tr>
</tbody>
</table>

*p < 0.0001 by chi-square analysis. Percent refers to total number of patients in Group I or Group II. ACT = activated coagulation time.
With the widespread application of activated coagulation times in our catheterization laboratory, there were changes in the practice pattern of physicians performing interventional procedures in our institution as they began to rely more heavily on activated coagulation time measurements for the proper guidance of anticoagulation. The time period of the present study (1988 to 1989) was early in our experience, and we did not rely as heavily on activated coagulation times as we do now.

In interpreting these results it is also important to remember that this is a retrospective study. We compared a group with complications with a randomly selected subgroup of patients from the same time period without complications. Because of this approach, the absolute percent of complications at any given activated coagulation time level or at any given response to an initial dose of heparin may be lower, but the trends exhibited in our data should still be valid. We did not evaluate procedural activated coagulation times after subsequent heparin boluses (other than the final activated coagulation time), so we cannot directly extrapolate our results to the concept of an activated coagulation time “threshold” or “target.”

In addition, the final activated coagulation time measurements may reflect events that transpired in the catheterization laboratory, which, in turn, may have resulted in adverse events as well as in affecting the total dose of heparin administered. We noted a number of circumstances where abrupt vessel closure in the catheterization laboratory is accompanied by a precipitous decrease in activated coagulation time. Low final activated coagulation times may reflect an ongoing thrombotic process (perhaps initiated by in-laboratory complications or inadequate heparinization, or both. The activated coagulation time after heparin therapy and the activated coagulation time response to an initial bolus of heparin are associated with complications after coronary angioplasty. However, a low activated coagulation time after heparin therapy and a diminished heparin response may also reflect antecedent clinical events, and rather than being an independent risk factor, impaired heparin response may be a secondary manifestation of the underlying clinical state.

Unanswered questions. We have not answered the question of whether the anticoagulation status, as expressed in the activated coagulation time, is a primary or secondary cause of in-hospital complications. Do patients have complications because their activated coagulation times are low, or are their activated coagulation times low because they have complications? Is there truly an activated coagulation time threshold that signifies “adequate” anticoagulation? Again, the answers to these questions will require prospective studies. In our own laboratory, however, we have adopted a fairly aggressive approach to anticoagulation. Most operators in our laboratories will attempt to achieve a Hemo-Tec activated coagulation time of at least 275 to 300 s. Our data suggest that an association exists between in-hospital complication and a low activated coagulation time after heparin therapy (<250 s), a low heparin response (<150 s) and a low final activated coagulation time (<250 s). Conversely, there appears to be an association between freedom from complications and a high activated coagulation time after heparin therapy (>275 s), a high heparin response (>175 s) and a high final activated coagulation time (>275 s). Whether these associations can be predictive on an individual basis will require further prospective study.

Previous cardiopulmonary bypass data (1,2) cited by other investigators in support of a “target” activated coagulation time range of 300 s were obtained using a manual system for measuring activated coagulation times (16), not with either of the commercial automated systems. Previous studies (12) have also suggested that a 10,000–U bolus dose of heparin provides “adequate” anticoagulation (a target activated coagulation time arbitrarily defined as 300 s using a

Table 5. Final Activated Coagulation Times for Groups I and II*

<table>
<thead>
<tr>
<th>Final ACT (s)</th>
<th>&lt;250</th>
<th>250–275</th>
<th>275–300</th>
<th>&gt;300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (complications)</td>
<td>87 (84.5%)</td>
<td>13 (12.6%)</td>
<td>2 (1.9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Group II (no complications)</td>
<td>0 (0%)</td>
<td>24 (6%)</td>
<td>60 (15%)</td>
<td>316 (79%)</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td>37</td>
<td>62</td>
<td>317</td>
</tr>
</tbody>
</table>

*p < 0.0001 by chi-square analysis. ACT = activated coagulation time.

Table 6. Activated Coagulation Time Heparin Response Values for Groups I and II*

<table>
<thead>
<tr>
<th>ACT Heparin Response (s)</th>
<th>&lt;150</th>
<th>150–175</th>
<th>175–200</th>
<th>&gt;200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (complications)</td>
<td>87 (84.5%)</td>
<td>13 (12.6%)</td>
<td>2 (1.9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Group II (no complications)</td>
<td>246 (61.5%)</td>
<td>62 (15.3%)</td>
<td>40 (10%)</td>
<td>52 (13%)</td>
</tr>
<tr>
<td>Total</td>
<td>333</td>
<td>75</td>
<td>42</td>
<td>53</td>
</tr>
</tbody>
</table>

*p < 0.0001 by chi-square analysis. Percent refers to total number of patients in Group I or Group II. ACT = activated coagulation time.
Hemochron machine) in 89% of patients; 11% of patients will require additional heparin. Previous data (13) using a Hemo-Tec machine instead of a Hemochron machine suggest that the percent of patients achieving “adequate” anticoagulation is much lower. Only 13% of patients had an activated coagulation time >300 s after a 10,000-U bolus of heparin. In the present study, 34% of the total group of patients had an activated coagulation time <250 s; 18% had an activated coagulation time between 250 and 275 s; 30% had an activated coagulation time between 275 and 300 s; and 18% had an activated coagulation time of >300 s. There are currently no real standards to date for determining what is truly “adequate” anticoagulation.

Conclusions. 1) There are no differences in baseline activated coagulation times between patients with and without major in-hospital complications after coronary angioplasty. 2) A diminished activated coagulation time response to heparin is associated with major in-hospital complications after coronary angioplasty, although patients with complications did have higher preprocedure risk. 3) It remains to be determined prospectively whether there is a threshold activated coagulation time level that, if achieved during an interventional procedure, would reduce the risk of major complications.

We acknowledge the invaluable assistance of Angie Espinell and Chris Wildes in the preparation of the manuscript; the enthusiasm of the authorization laboratory technical staff and the cardiology faculty at St. Luke’s Episcopal Hospital and the Texas Heart Institute in the acquisition of data for the study; the statistical support of William K. Vaughan, PhD, and the assistance of James T. Willerson, MD, in reviewing the manuscript.

References