The Course of D-Dimers as Fibrinolytic Products Generated During Cardiopulmonary Bypass

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Abstract

D-Dimers are the expressed degradation products of the lysis of fibrin. Fibrin monomers may normally occur during routine cardiopulmonary bypass (CPB); therefore, fibrinolysis could play a protective role. Serum D-dimer levels were observed at six events associated with routine CPB. An expected patient D-dimer level while heparinized would be <0.5 mcg/ml showing that fibrin is not being formed.

The majority of elevated D-dimer levels came at the termination of CPB when only one of twenty patients investigated showed a minimal D-dimer level of <0.5. The other patients ranged from 0.5 to >8.0 ug/ml at termination of CPB.

Table A: Event samples with respective ACT and D-Dimer

<table>
<thead>
<tr>
<th>Event</th>
<th>ACT</th>
<th>DD Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>123 ± 15</td>
<td>1.0 ± 1.1</td>
</tr>
<tr>
<td>Post Sternotomy</td>
<td>1.6 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>5 min. on CPB</td>
<td>497 ± 84</td>
<td>1.6 ± 2.3</td>
</tr>
<tr>
<td>Terminate CPB</td>
<td>432 ± 84</td>
<td>5.1 ± 2.8</td>
</tr>
<tr>
<td>Post Protamine</td>
<td>116 ± 11</td>
<td>5.1 ± 2.8</td>
</tr>
<tr>
<td>1 hr. Post Op</td>
<td>4.9 ± 3.0</td>
<td></td>
</tr>
</tbody>
</table>

ACT = mean activated clotting time ± ISD

The last three event D-dimer levels were significantly greater than the D-dimer from the first three events (p<0.01) demonstrating that fibrinolysis may be a normal occurrence during CPB. The weak correlation in the rise in D-dimers during CPB versus the minimal CPB ACT data (n=20, r=-0.114) although not statistically significant, suggests that ACTs should be maintained above 480 seconds throughout CPB to minimize fibrin formation and therefore minimize fibrinolysis.

Introduction

The activated clotting time (ACT) is always a concern to the perfusionist. If too low, there could be clotting taking place within the cardiopulmonary bypass (CPB) circuit which could be lethal to the patient. Jobes (1) stated one way of checking for fibrin formation is by measuring for fibrinopeptide A, a precursor to clot formation. Another method is to measure fibrin degradation products (FDP) after plasmin digestion of fibrin monomer. D-dimers are the expressed degradation products of fibrinolysis (2,3,4,5). By measuring for D-dimers in the blood during CPB, one can evaluate if clotting (crosslinked fibrin), and ultimately fibrinolysis, has occurred (2,3,4). This information is important in the management of anticoagulation and the prevention of fibrin formation.

The immunological measurement of fibrin degradation products, referred to as FDP assays, has been the most common method of evaluation of an active fibrinolytic system (6). Most FDP assays utilize relatively non-specific polyclonal antibodies to evaluate the fibrinolytic system, resulting in products of plasmin digestion: 1) fibrinogen (fibrinogenolysis), 2) non-crosslinked fibrin, and 3) crosslinked fibrin (fibrinolysis), yet not defining which of these digestion processes are actually occurring (2,5,6). Only the digestion of crosslinked fibrin monomers provides evidence of clotting therefore rendering these FDP assays inconclusive (5).

In this study, the clinical course of D-dimer formation was
observed from insertion of the radial arterial sample line to the patient's entry into cardiothoracic ICU. Patients were heparinized and ACTs were performed routinely and concurrently with D-dimer blood samples. D-dimers were measured from arterial blood samples at six different times throughout the surgical procedure. Elevated D-dimer levels existed in 90% (18) of patients at termination of CPB demonstrating that clotting appears to occur routinely resulting in fibrinolysis during CPB.

Materials and Methods

Twenty patients consented and were studied for D-dimer trends throughout the surgical procedure. Criteria for patient selection included both male and female patients greater than 18 years of age scheduled for elective cardiothoracic surgery with CPB. Patients specifically excluded were those with coagulopathies, redo sternotomies, and non-elective surgery.

The CPB circuit consisted of either of two closed system membrane oxygenators (a,b), a custom tubing pack (c), and a rollerhead pump (b). Prise consisted of lactated ringers, hetastarch, and packed red blood cells if hematocrit <20 was anticipated. Patient's heparin loading dose was 300 units/kg by hospital protocol. Activated clotting times (ACTs) were measured and recorded routinely and concurrent with D-dimer samples except in the cardiothoracic ICU using the Hemochron 800 (d). The perfusionist attempted to maintain the ACT >400 seconds by heparin (bovine) dosages according to the individual patient's heparin dose response curve.

Special arrangements were made with the hospital coagulation laboratory; as study patients were selected, lab technicians were notified to stand by for periodic D-dimer measurements. A total of six samples were drawn during the surgical procedure, inserted into blue-stoppered tubes (4.5 cc each tube), labeled appropriately, and sent to the coagulation lab for D-dimer analysis. Sample I was drawn at radial arterial sample line insertion; sample II, 5-10 minutes post sternum split; sample III, 5-10 minutes post CPB initiation; sample IV, within five minutes of CPB termination; sample V, 20 minutes post protamine administration; and sample VI, within one hour after admission to cardiothoracic ICU. D-dimers were measured from each sample and recorded. The lowest ACT during each CPB case was recorded and compared to the sample IV D-dimer (Table 2).

Results

Table 1 shows the number of patients in each D-dimer range for each blood sample drawn. D-dimer levels were significantly higher in blood samples IV-VI than in blood samples I-III (p < 0.01).

Among 20 patients, the mean lowest ACT was 392 seconds with a SD = 53 seconds. Table 2 lists each patient's lowest CPB ACT with their respective CPB termination D-dimer range. Correlation between the rise in D-dimers at CPB termination and the lowest CPB ACT (n = 20, r = .114) was weak and not statistically significant (See Graph 1). Table 3 lists each D-dimer value range found at CPB termination among the 20 patients, number of patients in each D-dimer range at CPB termination, and the mean lowest CPB ACT within each range. Table 3 is graphically represented in Graph 2.

Mean ACT values in sample II were not measured but assumed to be unchanged from sample I since no heparin had yet been given.

Discussion

The D-dimer assay is based on a highly specific monoclonal antibody directed against a unique neoantigen on the covalently crosslinked D fragments which result from fibrinolysis (2,3,6). If plasmin degrades either non-crosslinked fibrin or fibrinogen, then X, Y, D and E fragments result (2,4,5). Fragments of non-crosslinked fibrin degradation differ from fragments of fibrinogen degradation only in the loss of fibrinopeptides A and B from the E domain of non-crosslinked fibrin (2,5) (See Figure 1). If the fibrin has been crosslinked forming a clot, its degradation products would include covalently crosslinked D-D fragments (D-dimers) as well as other crosslinked FDPs (2) (see Figure 1). D-dimers are measured in ranges as follows: < 0.5 ug/ml, 0.5-1.0 ug/ml, 1.0-2.0 ug/ml, 2.0-4.0 ug/ml, 4.0-8.0 ug/ml and > 8.0 ug/ml. The clinical value of this D-dimer assay is its ability to specify a FDP subset allowing the assay to differentiate between fibrinolysis and fibrinogenolysis, an impossible distinction using the polyclonal FDP assay (2,4).

Elevated D-dimer levels suggest that crosslinked fibrin has
formed followed by activation of the fibrinolytic system to lyse
the apparently formed clots (2,4). The elevated D-dimer levels
at CPB termination in this study suggest there was clot
formation, followed by fibrinolysis at some time during the
CPB procedure. Elevated D-dimer levels do not necessarily
mean that ACTs were managed inadequately (10). By most
standards, ACT >600 seconds would be considered more than
adequate to prevent clotting. In patient #6 data, (see Table 2),
ACTs remained >600 (no additional heparin given after loading
dose and prime) throughout CPB, yet D-dimers were elevated at
CPB termination to 1.0-2.0 ug/ml.

If D-dimers are not elevated at CPB termination (<0.5
ug/ml), then very little if any fibrinolysis should have taken
place during CPB as shown by patient #1 (see Table 2). Minimum
CPB ACT for patient #1 was 400 seconds, well below
the generally accepted 480 seconds, yet contrary to what one
might predict, measurable D-dimers were not formed. It is
possible this patient’s coagulation cascade did not activate
forming fibrin monomer and eventually elevated D-dimers (10).

Two extreme examples have been presented that were
inconsistent with the D-dimer/ACT hypothesis of high ACT-
low D-dimer, low ACT-high D-dimer. The other 18 study
patients fell somewhere between these extremes with the
correlation between the lowest CPB ACTs and CPB termination
elevated D-dimers being weak which could be due to a pre-
operative abnormality with patient’s coagulation and fibrinolytic
systems. Perhaps more consistent results could have been
obtained if narrower limits on preoperative fibrinogen levels
and other pro-coagulants would have been set. Even though the
low ACT/high D-dimer correlation was weak, a trend was
observed indicating elevated D-dimers (>0.5 ug/ml) corresponding to low ACTs (<450 seconds)(see Graphs 1, 2).

These observations served as pilot data leaving many
questions unanswered. It is not understood why D-dimers may
form while ACTs are consistently managed at a high value (e.g.
>600 seconds), or inversely, why D-dimers are not formed at
times when the ACT is allowed to drop to lower values
(e.g.<480 seconds). Kongsgaard et al (7) demonstrated that the
injection of heparin would induce a transient activation of the
fibrinolytic system. Still, D-dimers should only appear if
clotting had taken place. It could be that the preexisting level of
patient clotting factors may play a role. Another possibility
could be an underlying pathology with the patient fibrinolytic
system. Careful pre-operative patient screening in future CPB
ACT/D-dimer studies could eliminate these possible sources of
interference.

One must also consider the half-life of D-dimers. Looking
at Table 1, there was almost no change in patient D-dimer levels
between samples IV and V with an average time between
samples of about 30 minutes. There were significantly more
decreases in patient D-dimer levels between samples V and VI
with an average time between samples of about 75 minutes.
From this data, D-dimer half-life may be estimated at
approximately 30-40 minutes. Since lowest CPB ACTs tend
to be toward the end of CPB, sample IV D-dimer levels are
probably a result of low CPB ACT values and not from
fibrinolysis occurring before total body heparinization.

In conclusion, these data suggest that fibrinolysis does
seem to routinely occur during CPB. The occurrence of
fibrinolysis during CPB may be considered good for the patient,
but if excessive, can also be undesirable. Some degree of
fibrinolysis indicates clotting has occurred causing consumption
of clotting factors (8). If excessive, fibrinolysis may lead to clot
instability and poor surgical hemostasis during the post CPB
period (9,10).

Do these data suggest an answer to the controversial
question "What minimum ACT should be maintained on CPB?"
No, but more thorough research into the CPB ACT/D-dimer
relationship is certainly warranted. Controversy continues
concerning the adequate minimum CPB ACTs as was shown
recently by Metz and Keats (10) who concluded the adequate
ACT level is probably <400 seconds while this study, in some
cases, shows the fibrinolysis above an ACT of 400 seconds,
therefore suggesting an adequate ACT level to be some time

Table 2

<table>
<thead>
<tr>
<th>Patient #</th>
<th>(seconds)</th>
<th>Lowest CPB ACT</th>
<th>(ug/ml)</th>
<th>Sample IV D-dimer</th>
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<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>&lt; 0.5</td>
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<tr>
<td>2</td>
<td>335</td>
<td>2.0-4.0</td>
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<td>3</td>
<td>437</td>
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<tr>
<td>4</td>
<td>350</td>
<td>2.0-4.0</td>
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<td></td>
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<tr>
<td>5</td>
<td>363</td>
<td>4.0-8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>&gt; 600</td>
<td>1.0-2.0</td>
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<td></td>
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<tr>
<td>7</td>
<td>432</td>
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<td>8</td>
<td>385</td>
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<td>18</td>
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<tr>
<td>19</td>
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<tr>
<td>20</td>
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</table>
Graph 1

**D-DIMER @ CPB TERMINATION VS MIN CPB ACT**

Graph 2

**CPB D-DIMERS AND FIBRINOLYSIS**

**MEAN LOW ACT VS SAMP IV DD**
Figure 1: The Process of Fibrin Formation and Lysis - the diagram shows the plasmin degradation of fibrinogen, noncrosslinked fibrin, and covalently crosslinked fibrin, as well as the potential degradation products from each process measured by conventional assays (drawing by Edwin G. Bovill, MD).

Table 3

Comparison of observed mean lowest CPB ACT to Sample IV (CPB termination) D-Dimer and # of patients with the measured D-Dimer range.

<table>
<thead>
<tr>
<th>Sample IV D-dimer (mg/ml)</th>
<th>Mean lowest CPB ACT (seconds/SD)</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5</td>
<td>400</td>
<td>1</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>339/43</td>
<td>2</td>
</tr>
<tr>
<td>1.0-2.0</td>
<td>&gt; 600</td>
<td>1</td>
</tr>
<tr>
<td>2.0-4.0</td>
<td>390/55</td>
<td>8</td>
</tr>
<tr>
<td>4.0-8.0</td>
<td>381/56</td>
<td>7</td>
</tr>
<tr>
<td>&gt; 8.0</td>
<td>374</td>
<td>1</td>
</tr>
</tbody>
</table>

period > 400 seconds.

References