

Review Articles

Aprotinin and Hemostasis Monitoring Concerns During Cardiac Surgery

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Abstract: Aprotinin (Trasyolol) is a serine protease inhibitor, isolated from bovine lung that initially was marketed for the treatment of pancreatitis. In the mid 1980s, reports of its ability to decrease hemorrhaging after cardiopulmonary bypass surgery introduced the drug to the realm of cardiac surgery. Unfortunately, its introduction into this arena was followed by the publication of multiple studies and case reports that blamed aprotinin for poor outcomes in the form of early graft closure. More than 17 years have passed since the initial article describing the use of aprotinin during cardiopulmonary bypass, and with time there has been a significant increase in scientific knowledge and clinical experience. Interestingly, modern literature does not support the dogma that aprotinin is a procoagulant. Aprotinin increases the activated partial thromboplastin time (aPTT), as well as the kaolin- and celite-activated clotting time (ACT), regardless of heparin. Aprotinin, because of its ability to inhibit kallikrein, has been found to decrease thrombin antithrombin III complexes,

fibrin-split products, fibrinopeptide₁₊₂, prothrombin fragments, and all markers of thrombin formation. Some authors have suggested that it may have a synergistic effect with heparin to ensure graft patency. Anticoagulation monitoring during the use of aprotinin also has been developed based on early studies. Aprotinin administration does influence the results of various ACT tests, and consequently different methods of testing anticoagulation have been developed. Researchers have demonstrated that the celite ACT is not “artificially” prolonged in the presence of heparin and aprotinin, rather the kaolin ACT is “artificially” shortened. This article will review the scientific literature with regard to aprotinin’s anticoagulatory effects and review the current recommendations for hemostasis monitoring during the use of aprotinin. **Keywords:** aprotinin, ACT, celite, kaolin, anticoagulation, heparinization, cardiopulmonary bypass. *JECT. 2004; 36:375–383*

Originally isolated from bovine lung (1), in 1953 aprotinin was marketed as a serine protease inhibitor in the treatment of acute pancreatitis (2). Its ability to inhibit trypsin and other proteolytic enzymes, whose zymogen precursors are formed in the pancreas, made it ideal to decrease the inflammatory response. Since its initial discovery, aprotinin has been found to be an alkalotic molecule with a Pka of 10, to have a molecular weight of 6512 Daltons, and to comprise 58 amino acids that are cross-linked by three disulfide bonds (3,4). Amino acids 15 and 16, lysine and alanine, are responsible for its action (4).

REDUCED BLOOD LOSS DURING CARDIAC SURGERY

In 1987 it was noted that the anti-inflammatory properties of aprotinin also could benefit patients who were undergoing heart surgery. van Oeveren et al. (5) examined, in a double-blind randomized study, 22 patients who underwent elective coronary revascularization who were given either full-dose aprotinin or a placebo. They observed a significant reduction in the mean blood loss in the aprotinin treated population (357 mL) compared with placebo (674 mL).

During that same year, an article by Royston et al. (6) discussed 22 patients who underwent repeat open-heart surgery. Again, a reduction in the overall blood loss with aprotinin treatment was discerned. Patients treated with placebo had an eightfold increase in the amount of blood products used, and 7 of the 11 patients who received aprotinin did not require any blood products. Since the publi-

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cation of these two studies, there have been numerous reports (7–16) describing the reduction in postoperative hemorrhage and allogeneic transfusion requirements with the use of aprotinin.

Numerous authors have investigated the mechanism leading to attenuated hemorrhage. They have elucidated that ability the aprotinin to inhibit both plasmin and kallikrein at high doses (200 KIU/ml) (5,17–20) results in the conservation of blood. As a result of plasmin and kallikrein inhibition, platelet function is preserved, leading to the protection of the GpIb receptor, which is responsible for platelet adhesion (21–23). Furthermore, aprotinin protects the GpIIb/IIIa (24,25) receptor, contributing to the platelet's ability to bind fibrinogen at the site of vessel injury (26,27) resulting in improved hemostasis.

EFFECT ON ACTIVATED CLOTTING TIME (ACT) DATA

As aprotinin began to find its way into the common practice of cardiopulmonary bypass (CPB), many clinicians began to notice that the use of it often coincided with a reduced heparin requirement for the patient. In 1990, de Smet et al. (8) published an article in which they reported that aprotinin reduced the amount of heparin given to a patient on CPB by an average of 63 mg. Therefore, they suggested that aprotinin was a heparin sparing agent that would be useful for those patients who exhibited resistance to heparin.

In 1992, Wang et al. (28) also reported on this phenomenon. In their study, results from kaolin and celite-activated ACT tests were evaluated using heparinized and unheparinized blood samples containing 0, 80, 120, and 180 KIU/mL of aprotinin. In the absence of heparin, the ACT results were not significantly changed at any aprotinin concentration with either celite or kaolin tests. However, after the addition of heparin, there were significant discrepancies. The celite-activated ACT was elevated by 47–71% when both heparin and aprotinin were included in the sample compared with samples containing heparin alone (28). Because the tests in this study did not respond to aprotinin in the absence of heparin, and results of the kaolin tests were unaffected by aprotinin under all conditions, three conclusions were given. First, aprotinin did not have any inherent anticoagulation properties. Second, celite ACT tests were less reliable than kaolin tests when aprotinin is used suggesting that values greater than 400 seconds on celite-activated tests are not accurate and should be viewed with skepticism. Therefore, their final conclusion was that kaolin-activated tests should be used to accurately assess the “anticoagulation” status of patients during CPB (28). Now, more than a decade later, it may be time to reevaluate these long-held conclusions.

APROTININ AND GRAFT CLOSURE

Cosgrove et al. (29), also in 1992, reported a clinical study promulgating the potential adverse effects of aprotinin in conjunction with celite-activated ACT tests. They documented that the incidence of Q-wave myocardial infarction in patients who underwent coronary artery bypass grafting and received a high dose aprotinin was increased compared with those who received a placebo (17.5% to 8.9%). Furthermore, postmortem examination of vein grafts revealed 6 of 12 in the aprotinin group had thrombosed whereas none of the placebo group had any evidence of thrombosis.

In response to the report by Cosgrove, it was established that the celite ACT was an inferior way to monitor “anticoagulation” in concordance with aprotinin. In response to the Cosgrove data, Bidstrup suggested that aprotinin is not a heparin-sparing agent and that values of 750 seconds should be maintained during CPB when aprotinin is used (17). He later explained that he believed the nonlinear relationship between ACT values and heparin concentration to be exacerbated by aprotinin and that this led to chronic under “anticoagulation” of CBP patients when aprotinin is used (17). It was therefore suggested that a target celite ACT of 750 seconds should be used in presence of aprotinin, during CPB (30). Following this, there were a number of reports which stated that the kaolin ACT was a superior method for monitoring anticoagulation during CPB because it was unaffected by the presence of aprotinin (31,32) Salmenpera et al. (32) stated “the prolongation of the ACT with aprotinin should not be considered a heparin-sparing effect, since it is probably only an *in vitro* effect; a normal anticoagulation dose and concentration of heparin should be used to prevent coagulation *in vivo*.”

These reports influenced the evolving clinical practice causing clinicians to require kaolin-activated ACT test to be greater than 480 seconds and celite-activated test values to be greater than 750 seconds when using aprotinin during CPB. It is important to note that the ACT guidelines were established to adequately measure “heparinization” not “anticoagulation.” Although these authors concluded that a celite ACT value of 750 seconds was appropriate, this conclusion was reached despite the absence of empirical data.

APROTININ AS AN ANTICOAGULANT

Although many researchers have labeled aprotinin as a procoagulant, others are still investigating its anticoagulant properties, which are a direct and indirect result of its ability to inhibit kallikrein (33). As described in Figure 1, the initiation of contact activation converts prekallikrein to kallikrein, which then converts Factor XII to factor

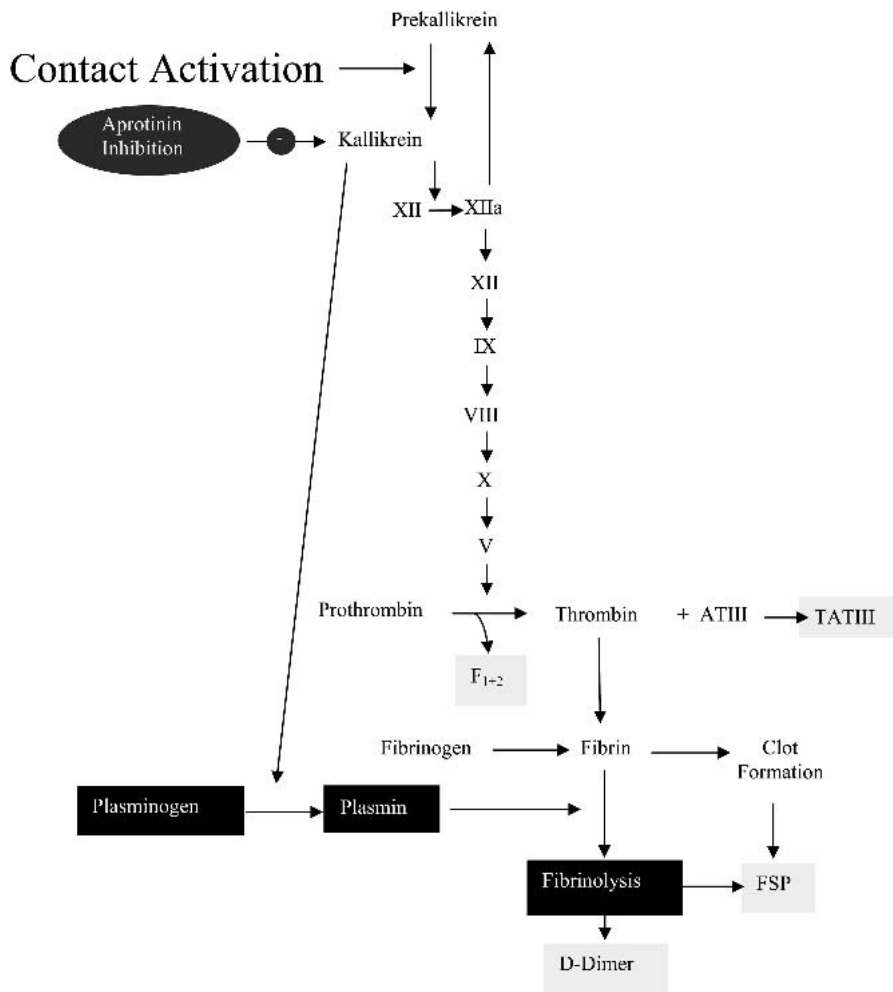


Figure 1. The intrinsic coagulation cascade is initiated by contact activation, which converts prekallikrein to kallikrein. The subsequent clotting cascade is displayed in black text and results in clot formation. Coincidentally, fibrinolysis begins with kallikrein as well. The abbreviated fibrinolysis cascade is displayed in white text. Subclinical coagulation can be monitored by chemical markers of coagulation. Several of these markers are displayed in gray boxes. As described in the text, Aprotinin inhibits kallikrein and therefore reduces both contact phase coagulation and fibrinolysis. The anticoagulatory effect of aprotinin has been shown to reduce markers of subclinical coagulation.

XIIa. Factor XIIa serves a dual function to convert Factor XI to XIa while additionally facilitating a reciprocal activation cascade, which increases conversion of prekallikrein to kallikrein. The anticoagulatory effects of aprotinin result from its primary inhibition of the initial activation of XII by kallikrein and the subsequent secondary inhibition of the downstream acceleration of prekallikrein conversion.

Prentice first reported this in 1970. He noted that aprotinin had inhibited contact phase activation, (intrinsic cascade) (35). Although he recognized that this inhibition involved Hageman factor, he could not determine whether this was a direct inhibition of Hageman factor, or merely a prevention of the reaction between Hageman factor and factor XI (35).

Both Hunt and Najman demonstrated that the aPTT of CPB patients is elevated by aprotinin in a dose dependant manner. Additionally, heparin interacts synergistically with aprotinin in these patients (30,18). Furthermore, Despotis and Najman concur that after protamine administration in patients undergoing CPB, aprotinin's anticoagulatory effects can be detected (36,18).

To eliminate the possibility that the specific activator in the aPTT tests influenced these findings, Francis and Howard (37) investigated the effect of aprotinin on aPTT using 25 different activators. Using aprotinin concentrations from 0 to 400 KIU/mL and heparin concentrations from 0 to 1.00 IU/mL, Francis concluded that all 25 tests were prolonged by aprotinin alone in a dose-dependent manner and further prolonged by the combination of heparin and aprotinin (37). However, it was observed that the magnitude of this effect, on the aPTT, was not consistent between all 25 reagents. The authors hypothesized that this was a result of the phospholipid composition of each reagent. This is known to cause changes in the heparin sensitivity, and was resulting in altered aPTT values when heparin and aprotinin were administered in combination (37). However, upon classifying the reagents the etiology of the inconsistencies could not be discerned.

As a result of the data published in the mid-1990s, which strongly suggested that aprotinin was an anticoagulant, Despotis et al. (38) examined the anticoagulant nature of heparin and aprotinin, looking for equivalency. After studying the whole blood clotting times after aprotinin or

heparin anticoagulation, they constructed linear regression models and evaluated the relationship between heparin and aprotinin. They determined that 200 KIU/mL of aprotinin prolonged the whole blood clotting time to an equal extent as 0.69 ± 0.28 IU/mL of heparin (38) and concluded that the anticoagulant nature of aprotinin leads to a prolongation of the celite ACT.

Further assessment of the anticoagulant properties of aprotinin was performed using thromboelastography (TEG). Mortier et al. (39) examined TEG upon unheparinized samples treated with NaCl, 50, 100, and 200 KIU/mL of aprotinin. They observed a dose-dependent increase in the time required for initial fibrin formation in samples treated with aprotinin. The mean reaction times for placebo, and aprotinin at 50, 100, and 200 KIU/mL were 8.02, 11.42, 13.07, and 14.08 minutes, respectively (39). This dose-dependent elevation of the TEG reaction time caused by aprotinin has been confirmed by numerous authors (40–42).

APROTININ REDUCES SUBCLINICAL COAGULATION DURING CPB

Heparin administered to a patient potentiates the actions of anti-thrombin III (ATIII), which leads to the inhibition of all factors in the coagulation cascade with the exception of factor VIIa (19). Through this mechanism, heparin inhibits thrombin formation. However, the heparin/ATIII inhibition of coagulation is not absolute. Consequently, factor consumption and fibrin formation do occur in the presence of heparin at an attenuated rate. This subclinical coagulation can be monitored by the formation of markers of coagulation. These markers include fibrin split products (FSP), fibrinopeptide₁₊₂ (F₁₊₂) prothrombin fragments, and thrombin anti-thrombin III (TAT-III) complexes.

Fibrin split products (FSPs) are an indication that either coagulation or fibrinolysis is occurring. Dietrich et al. (20) observed a decrease in the number of FSP after patients were treated with high-dose aprotinin. They noted that, after patients were weaned off bypass, there was a mean of 2510 ± 3932 ng/mL of FSP with the aprotinin-treated population. However, patients treated with heparin alone had an average of $10,824 \pm 7,261$ ng/mL of FSP (20). Although the reduction of FSP certainly is a result of the antifibrinolytic effects of aprotinin, which will reduce the break down of fibrin (10), its anticoagulatory effects have may also contributed significantly by reducing the production of fibrin. Although it is difficult to ascertain how much of the anticoagulant properties of aprotinin influenced the amount of FSP production, there are further markers of subclinical coagulation that identify the anticoagulant effects of aprotinin.

One of these markers is the F₁₊₂ prothrombin fragment,

which correlates with thrombin generation, and has been observed to be decreased in patients who are given high-dose aprotinin. In a prospective, double-blind, randomized study, Dietrich et al. (9) observed that 60 minutes after CPB the average number of F₁₊₂ fragments were decreased in the aprotinin-treated population compared with control (9.7 ng/mL vs. 7.5 ng/mL). Therefore, this indicates the reduction in thrombin formation that is characteristic of an anticoagulant.

Another marker of subclinical coagulation is thrombin anti-thrombin III (TAT-III) complexes, which are formed as the result of thrombin binding to anti-thrombin III. Aprotinin's inhibition of kallikrein contact activation results in decreasing thrombin formation and an overall decline in the TAT III complexes. This was elucidated by Dietrich et al. (9), who measured the TAT III complexes after 30 minutes of CPB, as well as at its cessation with administration of either full dose aprotinin or a control. After 30 minutes of CPB the control had an average of 48 ± 21 ng/mL of TAT III complexes, whereas the aprotinin-treated patients had a mean of 24 ± 11 ng/mL of TAT III complexes (20). At the cessation of CPB, the ratio of TAT III complexes when comparing the control to aprotinin was approximately 2:1 (82 ± 42 ng/mL vs. 47 ± 14 ng/mL). Similar experiments recorded nearly identical results, noticing a marked reduction in the amount of TAT III complexes upon administration of aprotinin (43,44). Therefore, if TAT complexes are a result of thrombin and AT III combination, the coagulation cascade must have progressed converting prothrombin to thrombin, and if aprotinin reduces the formation of TAT III complexes that are an example of subclinical coagulation, then aprotinin is inhibiting coagulation. The reduction in these subclinical coagulation markers further proves the ability of the aprotinin to reduce thrombin formation (9,20). Interestingly, it could be stated that the ideal method of anticoagulation in patients on CPB would be obtained by using heparin and aprotinin in conjunction, as they can prevent the formation of thrombin via two separate pathways (9,20,21,45).

APROTININ AND GRAFT CLOSURE

After Cosgrove's report in 1992, which observed a high number of graft failures associated with aprotinin, concern was raised about aprotinin and graft patency (29). In 1998 the IMAGE trial was published which reported the graft closure rate with the use of aprotinin. This was a multicenter trial involving a total of 13 U.S. and foreign hospitals. In a randomized, double-blind, placebo-driven study, patients undergoing myocardial revascularization were given either a full dose of aprotinin or a control. Initially, it was reported that the aprotinin-treated population had a vein graft thrombosis rate of 15.4% compared with 10.9% for the control population (46). However, further

evaluation revealed that a large number of graft failures came from one foreign institution, where the surgeon was grafting targets less than 1 mm. The graft failure rate for all U.S. centers was 9.4% with aprotinin compared to 9.5% with placebo (46). Furthermore, the difference between the two groups for myocardial infarction was insignificant as was the rate of mortality. This was the first large study completed which showed that aprotinin did not affect graft patency. Although an earlier investigation had similar results (47), this was the first multi-center trial to refute earlier patency outcomes. Later studies confirmed that there was no difference in both graft patency (48), and myocardial injury (14) after aprotinin administration.

A study published by Quereshi et al. (45) titled "Aprotinin: the ideal anticoagulant?" indicates that aprotinin may be used for anticoagulation. This study reported on the patency of a 1.0 mm polytetrafluoroethylene infrarenal aortic graft placed in rats after the administration of a control, full-dose aprotinin, full-dose heparin, or full-dose aprotinin with full-dose heparin. Coagulation tests were also performed after the anastomosis, including the aPTT and the bleeding time. The control had a mean graft occlusion time of 20.2 ± 1.8 minutes; aprotinin alone had a graft closure time of 71.7 ± 20.4 minutes, which was significantly higher than the control. The heparin-treated population had a mean graft failure at 118.3 ± 26.4 minutes and the aprotinin heparin combination had a mean graft closure at 109 ± 15.2 minutes (45). The aPTT also was elevated in the aprotinin alone treated population when compared to the control (40.7 vs. 21.9 seconds). In the heparin and heparin/aprotinin group, the aPTT was greater than 300 seconds. The bleeding times in the aprotinin and control groups were nearly identical (2.9 vs. 3.0 minutes). However, the bleeding time for the heparin and heparin/aprotinin were significantly higher (22.5 ± 2.3 vs. 18.9 ± 4.1 minutes) (45). These data showcases the potent anticoagulatory effects of aprotinin combined with its beneficial platelet preservation effect, which are both desirable characteristics of the ideal anticoagulant.

APROTININ's EFFECT ON ACT TESTS

Many researchers have demonstrated variable results with aprotinin and ACT tests, especially when using celite as an activator. Dietrich et al. analyzed the notion that aprotinin leads to an artificial or exaggerated prolongation of the celite ACT in 1990. Previously, it had been well documented that the celite ACT in the presence of heparin and aprotinin caused prolongation (17,28). However, Dietrich et al. further observed that the baseline celite ACT, prior to bypass and heparinization, in the aprotinin treated group was higher than placebo. The aprotinin treated population had a celite ACT of 141 ± 13 seconds whereas the placebo group had a baseline celite ACT of 122 ± 25 seconds (20). This study correlated with the previous study by Najman et al. (18), who reported that the baseline ACT did not normalize after the administration of protamine. Despotis et al. observed that aprotinin alone increased the nonactivated clotting time (non-ACT). In their study, Despotis et al. took blood samples from 56 patients undergoing heart surgery. They compared blood samples using the celite and kaolin activators as well as nonactivated whole blood clotting time tests and concluded patients treated with aprotinin alone increased the nonactivated whole blood clotting time and further "po-

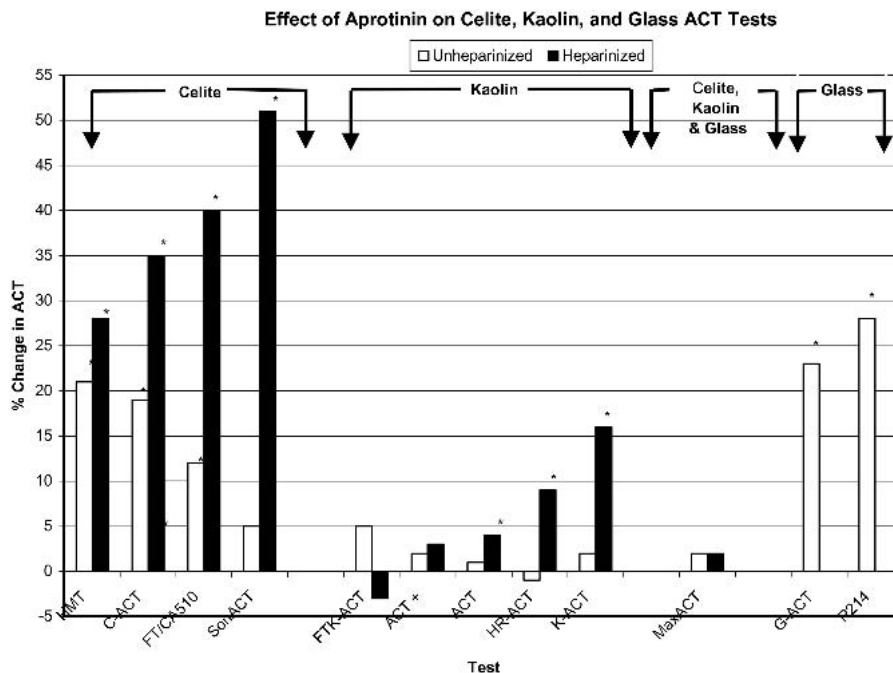
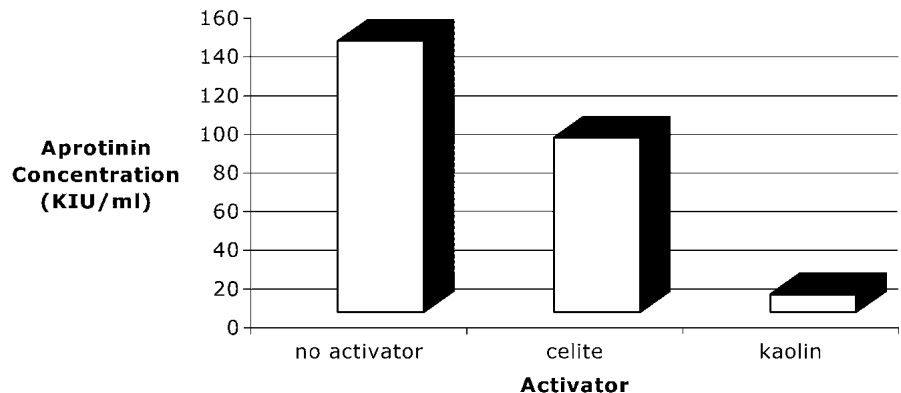


Figure 2. The effect of aprotinin on a variety of different ACT tests is shown. Results show that each test responds uniquely to the presence of aprotinin and supports the suggestion that classification of ACT tests by activator alone is too simplistic a notion. When determining an anticoagulation monitoring regimen, the influence of aprotinin on the particular test that will be used in your clinical practice should be considered. (Reprinted with permission from Jones et al. JECT, 2004;36:51-57.)

Aprotinin binding by different activators

Figure 3. Blood samples from 11 patients receiving aprotinin were subjected to three different activators before their level of aprotinin was determined. The activators in ACT tests bind aprotinin removing its anticoagulatory effects from the blood sample. Kaolin-activated tests remove nearly all of the aprotinin and, therefore, provide artificially shortened coagulation time results. Celite-activated tests remove less aprotinin and, therefore, report coagulation time results that more accurately account for the combined anticoagulatory effects of heparin and aprotinin. (Reprinted from J Thorac Cardiovasc Surg, 109, Dietrich W and Jochum M, Effect of celite and kaolin on activated clotting time is reduced by binding of aprotinin to kaolin, 177–178, copyright 1995 with permission from American Association for Thoracic Society.)



tentiated the prolongation of whole blood clotting time by heparin” (38).

Previously in our laboratory, we have demonstrated the affect that aprotinin has on the ACT test results from different manufactures (Figure 2) (49). These data establish that each manufacturers test responds uniquely to aprotinin and that a simple classification of all tests as either celite- or kaolin-activated oversimplifies the issue.

ETIOLOGY OF INCREASED CELITE ACT VALUES WITH APROTININ

In 1995 Dietrich et al. proposed a mechanism for the observation of increased ACT results with celite-activated tests. In this study, citrated blood samples were placed in ACT tubes that contained celite, kaolin, or no activator as a control. The blood samples interfaced with a mechanical ACT device, which maintained the sample temperature at 37°C and provided standardized mixing of the sample and the activator for 10 minutes. The whole blood samples were then centrifuged, and the plasma was analyzed for aprotinin concentration. Both activators showed a marked decrease in the recoverable plasma aprotinin concentration compared with control samples. However, the celite-activated samples contained 60% of the aprotinin concentration compared with control samples whereas the kaolin-activated samples contained less than 5% (Figure 3). Dietrich et al. concluded, on the basis of these results, that celite-activated ACT tests are not artificially prolonged; rather, kaolin-activated tests are artificially shortened. This is a result of the reaction that occurs between the positively charged aprotinin and the negatively charged surface of kaolin. The negatively charged clay, used in the kaolin tube, has the potential to bind to the positively charged aprotinin molecule. Consequently, there is a decrease in the concentration of aprotinin in the sample,

resulting in a decrease in the ACT (50). The diatomaceous earth used in the celite ACT, although also negative, is less negatively charged than the clay in kaolin, and the degree of binding is decreased. This implies that it is the celite ACT yields the most accurate picture of total anticoagulation during CPB.

Prior to Dietrich et al’s demonstration of aprotinin binding by ACT activators, one author suggested that the explanation for varying results between celite-activated and kaolin-activated tests may have been caused by the ability of aprotinin to inhibit kallikrein and the XIIa-dependent clotting pathway, which is the means by which celite determines anticoagulation, whereas kaolin may examine the intrinsic pathway through means unaffected by kallikrein and, therefore, would not take into account the inhibition of contact activation (51). This suggestion seems less likely in light of Dietrich et al’s data.

DETERMINATION OF HEPARIN ADMINISTRATION

It is not the intention of this review to suggest a radically new or different technique for anticoagulation management when aprotinin is used during cardiac surgery. It is the intention of this review to provide background and understanding to the current techniques that are used so that clinicians can select the anticoagulation management techniques which best suits their needs.

To fully understand strengths and weaknesses of each technique, one must appreciate the difference between “heparinization” and “anticoagulation.” By its very design, the ACT is a whole blood coagulation test. It is designed to measure anticoagulation and should be expected to be effected by any variable that influences coagulation. There are many variables that influence coagulation including but not limited to factor concentration, tempera-

ture, and medications. Of course, heparin is the most prevalent anticoagulation medication in the cardiac surgery arena and is generally the primary variable influencing coagulation during CPB. Because heparin is the primary variable influencing coagulation for the CPB patient, ACTs often are thought of a test of heparinization. Considering the extent to which clinical practice is influenced by variables other than heparin the understanding of ACT tests as heparinization test as opposed to anticoagulation test may seem to be purely academic. The wide spread application of aprotinin, however, forces all clinicians to be aware of the not so subtle difference between anticoagulation and heparinization. With the application of aprotinin for its antifibrinolytic effects, the cardiac surgical team must be additionally aware of its anticoagulatory effects and understand how this effect may influence coagulation monitoring.

Currently, there are four primary techniques for managing anticoagulation of the CPB patient when using aprotinin. All of these techniques focus on maintaining "heparinization." The first technique is fixed heparin dosing. During fixed heparin dosing a standard loading dose of heparin is administered to the patient, as well as a dose circulated throughout the bypass pump. These two doses must total at least 350 IU/kg (52). Once the patient is on bypass additional heparin can be given according to the approximate length of the pump run, as well as the patient's weight. Bayer currently recommends administering one third of the initial heparin dose in IU/kg every 45 minutes. Protamine is then administered according to the amount of heparin given (38). However, the known limitations of this protocol are related to the lack of confirmation that adequate anticoagulation has been obtained. This protocol calls for the periodic administration of additional heparin throughout the CPB procedure regardless of any measure of coagulation monitoring.

The second technique, heparin level maintenance, builds upon the first with the application of tests for monitoring the blood concentration of heparin during the case. Combined with a Heparin Dose Response test, which identifies an individual patient's responsiveness to heparin administration, heparin levels can be maintained throughout the procedure, which are specifically tailored to the individual patient's response to heparin as determined prior to the administration of either heparin or aprotinin. Linear regression models then determine when additional heparin should be administered throughout the case (53,54). It is advised that heparin levels should remain above 2.7 U/mL, 2.0 mg/kg, or the level indicated according to the heparin dose response curve created at the beginning of the case, whichever is higher (52). This additional method of heparin administration does not rely on anticoagulation monitoring which can be influenced by aprotinin. However, heparin levels are limited, as they do

not reflect the biological effect of anticoagulation. Furthermore, when compared to kaolin ACT measurements, Despotis reported that this technique of coagulation management overestimates the heparin requirements of most patients (55).

The final two techniques both use the results of ACT tests to monitor coagulation. Celite-activated ACT tests have long been considered to have a poor correlation with heparin concentration, especially at values longer than 500 seconds (17). Observation contributed to early suspicions that celite ACT tests were unreliable during aprotinin administration. As described at length in this review we now know, however that during aprotinin administration, celite ACT tests are a reasonable measure of total anticoagulation and poor measure of heparinization. Current protocols that require celite ACT values of greater than 750 seconds are designed to correct for aprotinin's influence on coagulation and therefore provide a method of managing heparinization. Considering the sensitivity of celite-activated tests to both heparin and aprotinin, these tests can only be recommended for clinical use during aprotinin administration, if the clinicians are interested in and aware that they are monitoring total anticoagulation. The celite ACT should not be used as a measure of heparinization during aprotinin administration.

Kaolin ACT tests, however, have been shown to correlate well with heparin concentration in individual patient's even at values longer 500 seconds (55). This fact, combined with the knowledge that kaolin removes aprotinin from solution and thereby eliminates its anticoagulatory effect, makes kaolin an ideal test for monitoring heparinization during aprotinin administration. Consequently kaolin act values of longer than 480 seconds are generally considered to represent acceptable levels of anticoagulation during aprotinin administration on CPB. The clinicians should be aware, however, that the patient's true anticoagulation status is not fully recognized by the kaolin ACT test and that the additional anticoagulatory effects of aprotinin are not being monitored. Furthermore, as with celite ACT tests, the varying response of different kaolin act tests should be considered prior to establishing any clinical protocol. Despite having the same activator, different celite and kaolin tests may provide test results that differ by as much as 50% and 20% respectively (29).

SUMMARY

Aprotinin is a useful pharmacologic agent that has been shown to reduce blood loss during cardiac surgery by inhibiting kallikrein. Reports of early graft closure led to suggestions that aprotinin had procoagulant effects. These concerns were compounded by the observation that different ACT tests provided very different results during aprotinin administration. However, more recent data has

emerged which supports the idea that aprotinin has anticoagulant properties. Although it was originally thought that the celite ACT was artificially prolonged in the presence of aprotinin, data has been presented which suggests that celite-activated ACT tests provide a more accurate total anticoagulation measure than kaolin-activated tests. Because kaolin-activated tests bind the majority of the aprotinin in a blood sample, they may be a more accurate measure of heparinization while underestimating the total anticoagulation status of the blood sample.

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