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Aprotinin Dosing: How Much Is Enough?

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Abstract: Coagulopathy and postoperative bleeding continue to be a major concern for patients undergoing cardiac surgery with cardiopulmonary bypass. Pharmacologic attenuation of this morbidity has been one area that clinicians have held in high interest. Aprotinin, a serine protease inhibitor, has been shown to be effective in reducing bleeding as well as the need for blood component transfusions. Although effective, aprotinin is an expensive drug and this, in conjunction with a cost-conscious community, has led clinicians to determine what is the lowest effective dose of aprotinin. From these studies, various aprotinin dosing regimens have been studied with differing results. The purpose of this work is to review the effectiveness of the various dosing strategies and to examine potential benefits of a dosing regimen based on a patient's weight, which may allow clinicians to achieve the maximal benefits from aprotinin without overdosing patients. **Keywords:** aprotinin, plasma concentrations, weight-base dosing. *JECT. 2004;36:384–390*

Cardiac surgery using cardiopulmonary bypass (CBP) results in the activation of various humoral systems in patients. The initiation of these mechanisms results in multiple pathophysiologic consequences, including an increase in vascular permeability, leukocytosis, acute respiratory distress syndrome, multiorgan failure, neurological changes, and bleeding diatheses. One of the key culprits of these morbidities is contact activation. The exposure of blood to foreign surfaces, including the extracorporeal circuit, pleura, and pericardial surfaces results, in the activation of the inflammatory response, the coagulation, and the fibrinolytic systems (1–5).

Contact Activation

When blood is exposed to nonendothelialized surfaces factor XII (Hageman factor) is transformed into its active form XIIa. This active conformation converts prekallikrein to kallikrein, which is integral in converting factor XII to XIIa. This creates a feedback mechanism, causing a cascading increase in both kallikrein and factor XIIa concentrations. Kallikrein plays a vital role in contact activation because it helps to propagate many of the pathways that result in fibrinolysis and inflammation. Kallikrein initiates the inflammatory system by cleaving high molecular weight kininogen to bradykinin, as well as converting complement fragment $C_1$to C_{1a}. This release of C_{1a} initiates the complement cascade resulting in a profound activation of inflammatory response. Kallikrein also plays a role in the conversion of plasminogen to plasmin, which stimulates the fibrinolytic system. The intrinsic coagulation system is stimulated by factor XIIa, which converts factor XI to XIa (Figure 1) (2,3,5,6).

The simultaneous activation of the coagulation and fibrinolytic systems can result in a consumption of coagulation proteins and platelets, resulting in significant postoperative bleeding requiring the transfusion of various blood products (6–8). There have been reports of excessive postoperative bleeding occurring in 5–25% of all cardiac patients who are placed on CPB (8). One of the major concerns about transfusions is the risk of viral transmission. The risk of developing hepatitis after a transfusion is somewhere between 1:30,000 and 1:250,000. The risk of transmitting HIV by blood transfusion is between 1:600,000 and 1:2,000,000 (9). Although these risks seem remote, Handa and colleagues describe a newly discovered viral agent termed transfusion transmitted virus, which is found in 50% of all blood units harvested in the United States. They also report that cytomegalovirus is ubiquitous in the current blood supply (10). Other complications associated with transfusions include graft vs. host disease, transfusion-induced acute lung injury, hypotension, and ABO-Rh incompatibility (11). Given the risk and costs associated with the transfusion of blood products, clinicians have focused their attention on strategies to reduce bleeding and the necessity for transfusions. One main focus has been on pharmacologic agents that attenuate fibrinolysis and preserve platelet function (6,7,12).

Aprotinin is a naturally occurring polypeptide derived from bovine lung. It has a molecular weight of approxi-

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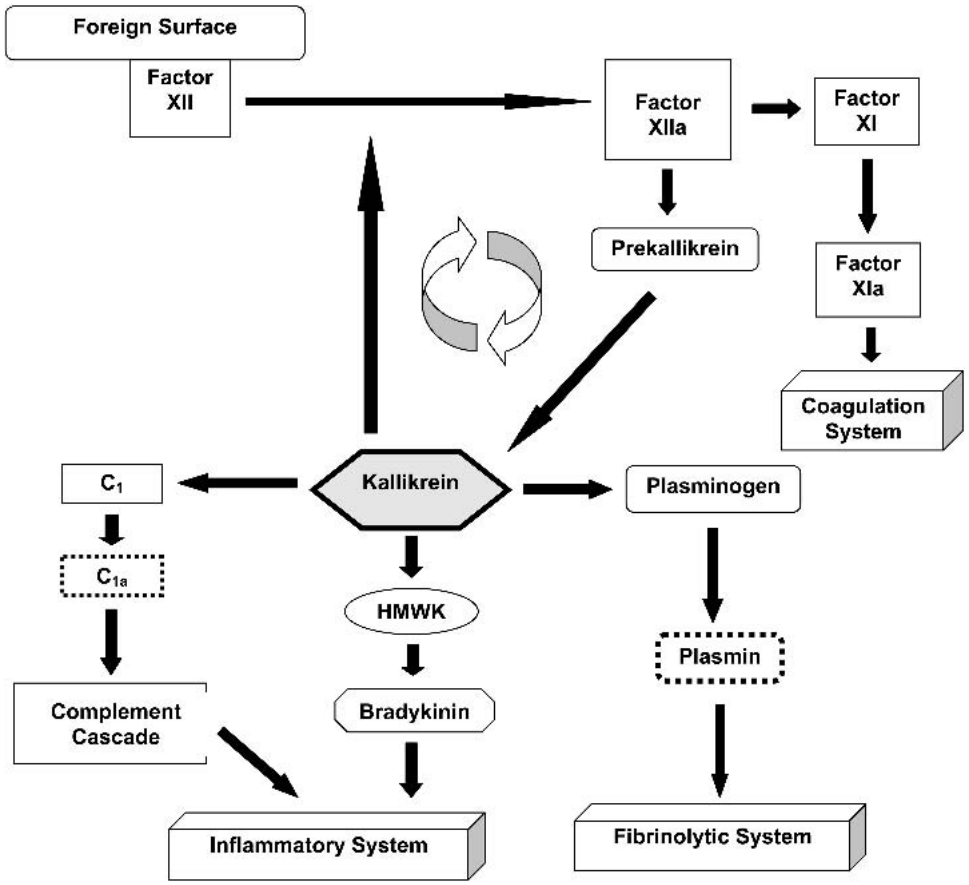

Figure 1. The mechanism of foreign surface blood activation resulting of the coagulation, inflammatory, and fibrinolytic systems, showing the key role that kallikrein plays.

mately 6512 Daltons and consists of 58 amino acid residues that are cross-linked by three disulfide bonds (Figure 2). Aprotinin reversibly binds to serine sites of numerous proteases and has inhibitory properties on trypsin, plasmin, elastase, and both plasma and tissue kallikrein (7,12). The activity of aprotinin is measured in kallikrein inhibitor units (KIU). One KIU is defined as the amount of aprotinin necessary to decrease by 50% the activity of two biological kallikrein units (13,14). Aprotinin demonstrates two distinct half-lives, which are reported as 0.7 hours initially and a terminal half-life of 7 hours (6,13,14).

Three meta-analyses concerning pharmacologic strategies on reducing blood loss have discussed aprotinin usage. Fremes and colleagues (15) performed the first analysis in 1994. They found a 53% reduction in milliliters of allogenic red blood cells (RBCs) transfused between the aprotinin-treated group and the placebo group ($p < .001$) (15). Laupacis et al. (16) found a reduction of 1.43 allogeneic RBC units in the aprotinin group when compared to the control group ($p = .001$). The most recent meta-analysis was preformed by Munoz and associates (17). They were able to compile 52 trials with 2605 patients receiving high-dose aprotinin. They calculated that 45.5% of patients in the high-dose group received RBCs compared to the 70.1% in the placebo group who received RBCs ($p < .001$).

Although there is not much debate on whether aprotinin is effective, there is ongoing controversy as to how much aprotinin should be given to patients. This controversy has lead clinicians to examine various dosing strategies and which patient populations benefit from the various regimens. Two large multicenter, double-blind, placebo-controlled studies have been performed comparing the three most common dosing strategies: high-dose; low-dose; and pump-prime only (18,19). These studies both showed a significant reduction in the transfusion of various blood products in all dosing regimens with the exception of cryoprecipitate in patients having primary cardiac surgery who received low-dose aprotinin (18). The units of various blood products from these two studies are summarized in Table 1.

High-Dose Strategy

Royston initially described the cardiac use of aprotinin using a dose that is commonly referred to as the full Hammersmith, or "high dose." The typical high-dose regiment includes a loading dose of 2×10^6 KIU (280 mg) upon skin incision; a continuous infusion of 0.5×10^6 KIU/h (70 mg/h) during the course of cardiopulmonary bypass (CPB); and 2×10^6 KIU (280 mg) added to the CPB prime. Royston and associates were able to show an 81% reduction ($p < .001$) in postoperative blood loss when this regimen was

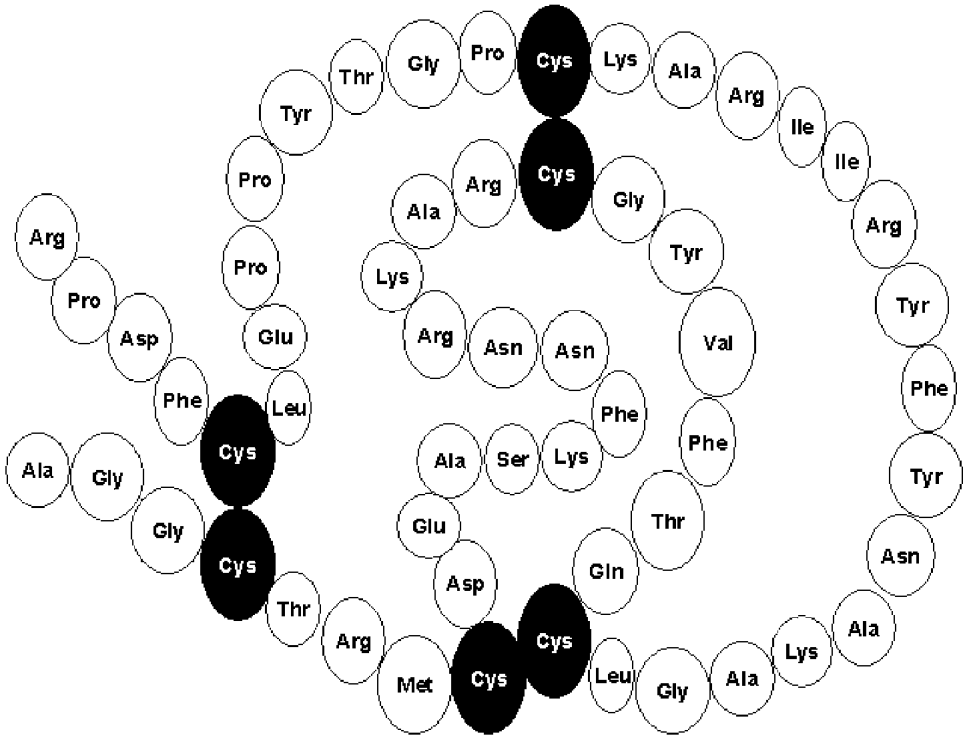

Figure 2. Aprotinin molecule demonstrating the 58 amino acid residues and the three disulfide cross bridges.

used in cardiac reoperations (20). Other studies examining high-dose aprotinin in cardiac reoperations also have found significant reductions in postoperative blood loss; however, not to the extent found by Royston. Cosgrove and associates (21) found a 36% ($p = .001$) reduction in blood loss, and Levy and associates (18) found a 47% reduction in 24-hour postoperative blood loss ($p < .001$).

The efficacy of high-dose aprotinin in primary cardiac surgery has been examined by van Oeveren et al. (22). They showed a 46% ($p < .01$) decrease in postoperative blood loss in the aprotinin-treated group compared with the control group. This significant reduction in blood loss has been supported by other researchers. Lemmer and colleagues (19) compared 173 patients who received high-dose aprotinin during primary coronary artery bypass grafting (CABG) surgery and found a 43% reduction ($p < .001$). Rodrigus and associates (23) were able to demonstrate a 45% decline in 24-hour postoperative blood loss ($p < .001$). Dietrich and associates (24) reviewed 3 years of data and were able to show a 35% reduction in 1784 patients ($p < .05$). Speekenbrink and cohorts (25) found a 52% ($p < .001$) reduction in blood loss. Mongan and associates (26) also found that the percent of patients requiring a transfusion dropped from 66% to 22% when comparing patients not receiving aprotinin to those who were treated with aprotinin ($p < .001$).

Some researchers have suggested that patients who receive high-dose aprotinin may have a lower incidence of stroke after cardiac surgery (27,28). Murkin (27) suggests that high-dose aprotinin can decrease leukocyte activation and transmigration, which may reduce cerebral infarcts and reduce reperfusion injury to cerebral tissue. Frumento and colleagues (28) preformed a retrospective analysis on the ability of aprotinin to attenuate stroke rate. They examined three groups of patients with similar stroke risk

Table 1. Summary of blood products used in the Levy and Lemmer studies.

	High Dose	Low Dose	Pump-Prime	Placebo
Levy (1995)				
Percent of patients requiring any blood product	54% $p < .001$	53% $p < .001$	74% $p = .293$	85%
Red blood cell units per patient	2.2 $p < .001$	3.4 $p < .001$	5.1 $p = .001$	10.3
Platelet units per patient	0.5 $p < .001$	1.2 $p < .001$	2.1 $p < .001$	4.8
Fresh-frozen plasma units per patient	0.1 $p < .001$	0.3 $p < .001$	0.5 $p < .001$	1.6
Cryopercipitate units per patient	0 $p = .031$	0.3 $p = .391$	0 $p = .037$	0.5
Lemmer (1996)				
Percent of patients requiring any blood product	34% $p = .000$	37% $p = .000$	35% $p = .000$	55%
Red blood cell units per patient	0.8 $p = .000$	0.9 $p = .000$	0.9 $p = .000$	1.8
Platelet units per patient	0.4 $p = .001$	0.3 $p = .000$	0.5 $p = .001$	1.2
Fresh-frozen plasma units per patient	0.2 $p = .000$	0.2 $p = .000$	0.2 $p = .000$	0.7
Cryopercipitate units per patient	0 $p = .003$	0.1 $p = .011$	0 $p = .003$	0.4

indexes. The first group was composed of patients who received full-dose aprotinin and the stroke rate was 0% (0/26), the second group received low-dose aprotinin and had a stroke rate of 22% (15/67), and the third group received no aprotinin and had a stroke rate of 16% (9/56) ($p < .05$). From these findings Frumento and colleagues suggest that full-dose aprotinin should be given to patients at high risk for stroke.

Low-Dose Strategy

Aprotinin is a very expensive drug; Bennett-Guerrero and associates quote a cost of $900-$1200 per patient who receives full Hammersmith (29). As a cost-saving measure, clinicians have studied the effects of giving a half Hammersmith dose; this regimen also is called "low dose." This dosing strategy is 1×10^6 KIU (140 mg) upon skin incision; 25×10^4 KIU/h (35 mg/h) infusion on initiation of CPB; and 1×10^6 KIU (140 mg) added to the CPB prime. Levy and associates (18) demonstrated that patients presenting for repeat CABG who received low-dose aprotinin had a 39% ($p = .001$) reduction in total thoracic drainage volume. Cosgrove and associates found a 23% ($p = .001$) reduction in chest drainage when a low-dose aprotinin regimen was compared to placebo in CABG reoperations (21). Lemmer and associates (19) examined the use of low-dose aprotinin in primary CABG surgery and found a 36% ($p < .001$) decrease in postoperative bleeding.

Pump Prime

In an ever cost-conscious environment, clinicians have examined the efficacy of reducing the amount of aprotinin given to patients, which has resulted in the origin of a third dosing regimen. This ultra-low dose is often referred to as pump-prime-only aprotinin dosing. In this strategy, no aprotinin is given by the anesthesiologist, with the exception of a test dose; instead, aprotinin is only added to the pump prime. This regimen most often described as 2×10^6 KIU (280 mg) added to the CPB prime (25,30–34) This dosing strategy has been described in some literature as low-dose aprotinin; however, it is more accurately described as pump-prime-only rather than confusing it with the half-Hammersmith treatment. To add to this confusion, some studies have examined the usage of 1×10^6 KIU (140 mg) to the pump prime (35,36).

The efficacy of pump-prime-only dosing in patients having cardiac reoperations has resulted in some conflicting results. Levy and associates found no significant differences in blood loss when pump prime dosing was compared to placebo in patients undergoing cardiac reoperations (18). However, Kirzner and associates (31) found a 38% ($p = .03$) reduction in post-operative bleeding in heart valve reoperations.

There has been more extensive research into the efficacy of the pump prime regimen in patients undergoing primary cardiac surgery. Lemmer and associates found a 30% reduction in post-operative blood loss ($p < .001$) when comparing patients who received a pump prime regimen to patients in the placebo group (19). These results are supported by other studies, which also have found a significant decrease in post-operative bleeding. Speekenbrink and colleagues (25) found a 38% decrease ($p < .001$), Santamaria et al. (32) found an 11% reduction ($p < .005$), and Ashraf and associates (34) found a reduction of 49% ($p < .001$).

As stated previously, some researchers have used a pump prime dose of 1×10^6 KIU. Hayashida and associates (35) used this reduced pump prime dose and found no significant differences between this strategy and placebo for post-operative blood loss. Another study that used this lower dose of aprotinin was preformed by Bailey and Wielogorski (36), who found 49% reduction ($p < .001$) when compared with a control group.

Plasma Concentrations

Fritz and Wunderer (14) report that a 50% inhibition of plasmin occurs with levels as low as 50 KIU/mL and that 90% inhibition occurs at plasma levels of 125 KIU/mL. They go on to report that the in vitro threshold for kallikrein inhibition is 200 KIU/mL. However, aprotinin plasma concentrations as high as 500 KIU/mL may be necessary during surgery to inhibit 90% of kallikrein activity. This has been attributed to the greater activation and release of kallikrein caused by surgical trauma and contact activation that occurs with CPB and cardiac surgery (20). The reporting of aprotinin plasma concentrations has confounded the fact that concentrations have been reported in various units of measure, including KIU/L, mmol/L, and mg/L. Another confusing factor that has plagued clinicians when comparing studies is that results can be significantly different depending on which type of assays are used to measure aprotinin plasma concentrations. The two most commonly used assays are an aprotinin functional assay and an enzyme-linked immunosorbent assay. It has been reported that aprotinin levels measured by the functional assay is significantly higher than when the enzyme-linked immunosorbent assay is used to measure the same sample. This difference has been attributed to the potency of the standards that come with the different tests. Cardigan and associates state that due to the lack of an international standard for aprotinin measurement they were not able to determine which standard potency is correct, only that results will significant vary between the two assays (37).

Dietrich and associates (33) measured plasma concentrations of aprotinin when a high-dose regimen was used. They found aprotinin plasma concentrations of 152 ± 61 KIU/mL after the loading dose from anesthesia. This level

rose with initiation of CPB to a plasma concentration of 335 ± 106 KIU/ mL. They found that levels decreased continuously throughout CPB to a level of 191 ± 62 KIU/ mL. Two hours postoperative aprotinin levels were measured at 74 ± 31 KIU/ mL (33). Bennett-Guerrero and colleagues (29) also measured aprotinin plasma concentrations using high-dose aprotinin they found plasma concentrations pre-CPB of 234 ± 30 KIU/mL. Thirty minutes after CPB was initiated the levels were 229 ± 35 KIU/ mL. Aprotinin plasma concentrations decreased to 184 ± 27 KIU/mL after 60 minutes on CPB and reached a level of 179 ± 22 by termination of CPB (29). Beath and associates (37) found high-dose aprotinin plasma concentrations peaked at 401 ± 92 KIU/mL after 5 minutes of CPB. Levels decreased to 236 ± 81 KIU/mL after an hour on CPB. The aprotinin infusion was stopped 2 hours after the patient arrived in the intensive care unit (ICU), and the measured aprotinin plasma concentration was 122 ± 75 KIU/mL (38).

A group from the Netherlands measured plasma concentrations of aprotinin using a modified high dose strategy. They found that prior to CPB the plasma aprotinin levels were 185 ± 19 KIU/mL. With the commencement of CPB the plasma levels dropped to 150 ± 20 KIU/mL. This finding is in contrast to previous studies in which plasma concentrations increased with the initiation of CPB. This finding can be attributed to the fact that this group added 1×10^6 KIU rather then the typical 2×10^6 KIUs. This reduced pump prime dose as well as the fact that the priming volume of the extracorporeal circuit was just more than 2 liters may explain the reduction in plasma aprotinin levels when the patient was placed on CPB. When the aortic cross clamp was removed, aprotinin levels dropped to 80 KIU/mL (no standard deviation was reported) (22).

Beath and colleagues (37) measured aprotinin plasma concentrations during CPB when a low-dose regimen was used. They found that levels decreased from 226 ± 56 KIU/mL measured five minutes after CPB was initiated to 160 ± 63 KIU/mL after being on CPB for 60 minutes. Two hours after the patient arrived in ICU, the aprotinin plasma concentration was 74 ± 72 KIU/mL (38).

Dietrich and associates (33) measured aprotinin plasma concentrations with a pump-prime-only regimen. They found that aprotinin levels reached 118 ± 30 KIU/mL five minutes after CPB was started. These levels continuously decreased throughout CPB and were measured at 42 ± 21 KIU/mL. Speekenbrink et al. (25) found that aprotinin plasma concentrations reached 250 ± 65 KIU/mL when a pump-prime-only strategy was used and dropped to 72 ± 26 KIU/mL after protamine administration.

The results from these studies demonstrate that with the exception of the pump-prime regimen performed by Dietrich and associates (33), all of the aprotinin dosing regimens result in plasma concentrations maintained above the plasmin inhibition threshold (>50 KIU/mL). However, the aprotinin plasma concentration dropped below the quoted threshold for kallikrein inhibition (<200 KIU/mL) either during CPB or prior to protamine administration in every regimen. The only exception was the high-dose regimen performed by Beath and colleagues. However, they did not measure aprotinin concentrations from the time period between 60 minutes on CPB and two hours after the patient arrived in the ICU (38).

Weight-Based Dose

Royston and peers (39) compared aprotinin plasma concentrations between a weight-based and fixed-dose strategy. The fixed-dose strategy used for the study was a high-dose regimen. The weight-based strategy involved giving two doses of 4×10^4 KIU/kg (5.6 mg/kg) given as two separate aliquots given over a ten minute span. As would be expected, the study found that plasma aprotinin levels were more consistent when a weight-based dosing regimen was used. This finding has been supported by another weight-based study by Nuttall and associates who also found plasma concentrations to be more stable when a weight-based dosing strategy was compared to a fixed dose regimen (40). When examining full-dose aprotinin, Royston et al. (39) stated that there is an apparent relative overdose in 40% of the fixed-dose group as measured by plasma concentrations during the operative procedure. They continues to remark that by using a weight-based strategy less aprotinin may need to be given, to achieve the desired plasma concentration (39). Nuttall and associates (40) present dosing strategies to maintain concentrations of 100 KIU/mL, 150 KIU/mL, 200 KIU/mL, and 250 KIU/mL. The total aprotinin dose for the two lower concentrations was lower than if the patient had received full-dose aprotinin, however the total amount of aprotinin given to patients in the higher two concentration groups exceeded that had they received full-dose aprotinin (40). It is interesting to note that in the three high-dose studies presented that measured aprotinin plasma concentrations when CPB was discontinued, all found that aprotinin levels had decreased to less then 200 KIU/mL. From this, it can be theorized that only a weight-based dosing regimen would allow a clinician to maintain plasma concentrations, which have been reported as the threshold for kallikrein inhibition throughout the duration of CPB.

Many researchers have reported on the hemostatic affects of aprotinin with cardiac surgery. A MEDLINE search on the key words “aprotinin” and “cardiac surgery” resulted in 236 articles published from 1966 through December of 2003. Despite being one of the most studied drugs, many questions still remain about aprotinin. One issue that makes it difficult to compare results of aprotinin studies is differences found between patient body weights among the various studies. It can be easily theorized that should a large patient receive a full-dose strategy, that

patient may have a plasma concentration that is lower than a small patient who receives a half-dose of aprotinin. The mean patient weight varied from 55.33 ± 10.27 kg (31) to 86.2 ± 15.3 kg (26) in the cited works of this article.

Another variable that has not been examined thoroughly is the prime volume of the CPB circuit. The original reasoning for the dose of aprotinin added to the pump prime was to eliminate the hemodilutional effects of the large prime volume (20). However, as technology has advanced through the years, blood–gas-exchange devices have been developed which require less prime volume. Another manner in which prime volumes have been reduced is the utilization of techniques of autologous priming (RAP). At one institution alone, the usage of RAP has resulted in a 50% reduction in prime volume that a patient is exposed to when CPB is initiated. The use of prime reducing methods such as RAP or the use of low prime circuits raises the question of whether the amount of aprotinin added to the extracorporeal circuit prime should be decreased to compensate for this reduction in prime volume.

Current publications have shown that adjusting the dose aprotinin by the patients' weight or circulating blood volume results in more stable plasma aprotinin concentrations and these concentrations are more reliable then when a fix-dose strategy is used. The current health care environment places increasing pressure on clinicians to prove the efficacy of expensive drugs such as aprotinin. By changing to a weight-based dosing strategy, clinicians would be able to reduce the relative "over-dosing" that occurs in smaller patients. In larger patients a weight-based dosing strategy would allow a clinician to maintain plasma concentrations suitable to inhibit both plasmin and kallikrein activation so that the protective nature of aprotinin would be fully used.

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