Treating Heparin Resistance With Antithrombin or Fresh Frozen Plasma

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Heparin resistance occurs in up to 22% of patients undergoing cardiac surgery requiring cardiopulmonary bypass and it is associated with decreased levels of antithrombin. Treatment options for heparin resistance include administration of antithrombin or fresh frozen plasma. A systematic review revealed no clinical trials directly comparing antithrombin with fresh frozen plasma as heparin resistance treatment during cardiopulmonary bypass. Thus, the aim of this review is to discuss the limited number of published reports assessing antithrombin or fresh frozen plasma in managing heparin resistance and to present emerging data regarding fresh frozen plasma safety issues and practical considerations for antithrombin treatment in patients with heparin resistance undergoing cardiopulmonary bypass.

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Cardiac surgery requiring cardiopulmonary bypass (CPB) is associated with substantial activation of the hemostatic system. This is caused not only by the interface between blood and the large, nonendothelial extracorporeal circuitry, but also by the re-transfusion of pericardial blood exposed to air and thrombogenic surfaces, the effects of microemboli on endothelial cells, and potentially the decrease in circulating protein buffers [1, 2]. Elevated hemostatic activity associated with CPB may induce a systemic inflammatory reaction and lead to clinical complications such as hemorrhage, postoperative thrombosis, and organ dysfunction [3].

Adequate anticoagulation is a critical component of successful management of hemostatic and inflammatory responses associated with CPB. Heparin is commonly administered during CPB to achieve systemic anticoagulation. Heparin alone has no direct anticoagulant effect, but it potentiates the activity of antithrombin (AT, formerly AT-III), an endogenous serine protease inhibitor that irreversibly binds various coagulant enzymes, such as thrombin and factor Xa. Heparin enhances AT-mediated inhibition of coagulant enzymes more than 1,000-fold by reducing the half-life of the enzymes and by promoting their binding with AT through induction of a conformational change in AT [4, 5].

An inadequate response to heparin, known as heparin resistance (HR), has been reported in up to 22% of patients undergoing CPB [6–10]. Among risk factors for developing HR during CPB, decreased AT levels present the greatest risk (Table 1) [11]. During CPB, AT activity decreases dramatically, falling 40% to 50% below preoperative baseline levels [12]. Preoperative heparin treatment may deplete levels of endogenous AT and further worsen acquired AT deficiency associated with CPB [9, 13–15]. Failure to correct AT deficiency during CPB may result in a poor surgical outcome. Low AT activity levels after CPB are significantly associated ($p \leq 0.04$) with a prolonged stay in the intensive care unit, higher frequency of surgical re-exploration, and thromboembolic events [16]. Therefore, maintaining appropriate levels of AT during CPB is a major goal to avoid HR.

In a prospective study of 500 consecutive patients scheduled for coronary artery bypass grafting, HR occurred in 104 patients (21%) and was associated with AT deficiency in the majority of cases (n = 68 [65%]) [8]. However, a substantial subset of patients with HR (n = 36 [35%]) had normal AT levels, suggesting that the development of HR in some patients is not associated with AT deficiency. Mechanisms involved in AT-independent HR are likely to entail activation of various factors that neutralize heparin, including platelet-derived factors and plasma proteins. Thus, proper management of HR during CPB should take into consideration the underlying mechanism of HR (eg, substrate deficiency, hyperactivity of coagulation factors, or natural heparin inhibitors).

Historically, treatment of HR has included administration of additional heparin or fresh frozen plasma (FFP) [17]. Administration of an AT concentrate has re-emerged as an alternative treatment of HR [4]. In addition, a recombinant form of human AT (rhAT) (produced in and purified from the milk of transgenic goats carrying a human AT gene [18, 19]) has been studied in clinical trials including patients with HR [6, 7]. The aim of this comprehensive review is to discuss published clinical studies reporting the effectiveness of FFP (Table 2) [17, 20–23], AT, and rhAT (Table 3) [6, 7, 10, 24–31] in managing HR in patients undergoing cardiac surgery

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Table 1. Risk Factors for Heparin Resistance[a] During CPB[b]

Factor	Likelihood of HR (%)
AT ≤ 60%	57
Preoperative heparin, subcutaneous	37
Preoperative heparin, intravenous	32
Platelets ≥ 300,000 cells/mm^3	31
Age ≥ 65 years	20

[a] Defined as ≥ 1 ACT value < 400 seconds after heparinization or need for AT administration. [b] Data are from Ranucci and colleagues [11].

ACT = activated clotting time; AT = antithrombin; CPB = cardiopulmonary bypass; HR = heparin resistance.

requiring CPB. In addition, safety issues and practical considerations associated with these products are discussed.

Methods

An extensive English language literature search was performed using the MEDLINE and PubMed databases between 1975 and 2006. Keywords used for the search included heparin resistance, antithrombin, recombinant human antithrombin, and fresh frozen plasma. Additional studies were identified from references cited in publications found using the search terms and also in published review articles.

Treatment for HR During CPB

Outcome Measures

The activated clotting time (ACT) is commonly measured during CPB to monitor and maintain adequate anticoagulation levels achieved with heparin [32]. The ACT is measured in samples of fresh whole blood in the presence of a coagulation activator, commonly clay (kaolin) or diatomaceous earth (celite). Although ACT values measured in the pre-CPB period correlate well with heparin levels, ACT measurements during CPB may be affected by CPB-related variables, such as hemodilution or hypothermia. Nonetheless, heparin therapy during CPB is generally guided by monitoring ACT values. Heparin resistance is generally defined as the failure to achieve an ACT of 450 to 480 seconds or greater after administration of 300 to 500 IU/kg heparin, although a consensus definition is lacking. In addition to ACT values, common outcome measures of adequate anticoagulation in the setting of cardiac surgery include thrombin generation (eg, measurement of prothrombin fragment 1 + 2), bleeding, and transfusion requirements.

Studies With FFP

PROSPECTIVE CLINICAL TRIALS. No prospective clinical trials to date have evaluated the use of FFP in treating heparin-resistant patients.

RETROSPECTIVE STUDIES. Sabbagh and colleagues [17] retrospectively evaluated 44 patients who underwent CPB and received an initial heparin dose of 300 IU/kg. A second dose of heparin was administered to prolong the ACT to 480 seconds before initiating CPB. Twenty-four patients achieved an ACT of ≥ 300 seconds after the initial heparin dose, which composed the control group. A second group of patients (n = 11) with ACT values of < 300 seconds after the initial dose of heparin received additional heparin. A third group of patients (n = 9) who also failed to achieve ACT values of ≥ 300 seconds received 2 units of FFP at the start of CPB, along with additional heparin, if needed. The total mean amount of heparin required by the patients who received FFP (440 IU/kg) was comparable with requirements of the control group (430 IU/kg), but was significantly lower than requirements of the patients who received additional heparin only (640 IU/kg; $p < 0.001$). Moreover, FFP administration significantly prolonged the ACT from 417 seconds before FFP treatment to 644 seconds after treatment ($p < 0.0001$).

CASE REPORTS. Leong and Ong [21] reported a case of HR in a 75-year-old man who underwent 5 days of preoperative heparin treatment that was discontinued on the morning of surgery requiring CPB. Because the patient received aprotinin prior to surgery, the surgical team deemed an ACT of ≥750 seconds necessary to safely institute bypass. The baseline ACT was 132 seconds, and administration of 1,200 IU/kg heparin (80,000 IU) increased the ACT to 428 seconds. Thus, 500 mL FFP was administered, along with additional heparin (450 IU/kg). A satisfactory ACT of 784 seconds was achieved, and CPB was instituted. During

Table 2. Summary of Studies Evaluating FFP Treatment for HR During CPB

Reference	Study Design	Treatment Regimen	Study Outcome
Barnette and colleagues [20]	In vitro study	0.2 mL FFP added to each of six blood samples	Satisfactory ACT prolongation in three of six samples
Leong and Ong [21]	Case report	500 mL FFP plus additional heparin	Target ACT achieved; additional heparin required during CPB to maintain target ACT
Despotis and colleagues [22]	Case report	2 IU FFP	Transient reduction in heparin requirements
Soloway and Christiansen [23]	Case report	3 IU FFP plus additional heparin	Target ACT achieved; surgical re-exploration required because of bleeding
Sabbagh and colleagues [17]	Retrospective study	2 IU FFP (n = 9)	Significant ACT prolongation after FFP administration

ACT = activated clotting time; CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; HR = heparin resistance.

Table 3. Summary of Studies Evaluating AT as Treatment for HR During CPB

Reference	Study Design	Treatment Regimen	Study Outcome
Levy and colleagues [24]	In vitro study	0.2 mL AT added to blood samples (n = 22)	Successful prolongation of ACT values
Van Norman and colleagues [25]	Case report	2,500 IU AT	Satisfactory increase in ACT value and AT activity
Kanbak [26]	Case reports	1,000 IU AT (n = 3)	Successful prolongation of ACT values
Brown and colleagues [27]	Retrospective study	500 IU AT (n = 44)	Significant ACT prolongation and reduction in heparin requirements
Irani [28]	Retrospective study	1,080 to 3,408 IU AT (n = 12)	Successful prolongation of ACT values
Conley and Plunkett [29]	Retrospective study	AT (n = 101) or additional heparin (n = 110)	Similar surgical outcomes between groups (length of intensive care unit stay, chest tube drainage)
Williams and colleagues [10]	Prospective, crossover RCT	1,000 IU AT (n = 44) or additional heparin (n = 41)	Significantly higher success rate with AT in achieving target ACT values
Lemmer and Despotis [30]	Prospective study	500 IU (n = 45) or 1,000 IU AT (n = 8)	All but 1 patient achieved target ACT value
Koster and colleagues [31]	Prospective RCT	Additional heparin (n = 20) or heparin plus 50 IU/kg AT (n = 20)	Decreased fibrin generation in patients supplemented with AT
Avidan and colleagues [6]	Prospective RCT, DBL, PC	75 IU/kg rhAT (n = 27) or placebo (n = 27)	Significant increases in ACT values and AT levels and decreases in requirement for additional heparin or FFP
Avidan and colleagues [7]	Prospective RCT, DBL, PC	75 IU/kg rhAT (n = 28) or placebo (n = 24)	Significant increase in ACT values and decrease in requirement for FFP

ACT = activated clotting time; AT = antithrombin; CPB = cardiopulmonary bypass; DBL = double blind; FFP = fresh frozen plasma; HR = heparin resistance; ICU = intensive care unit; PC = placebo controlled; RCT = randomized clinical trial; rhAT = recombinant human AT.

CPB, the ACT value fell to 466 seconds, and additional heparin (10,000 IU) was administered.

Another case report of HR resolved by FFP administration involved a 44-year-old man with end-stage ischemic cardiomyopathy [22]. The patient experienced multiple thrombotic episodes in ventricular-assist devices used as a bridge to cardiac transplantation. Heparin requirements were persistently high (4,000 IU/h), and administration of 2 units of FFP on day 43 of hospitalization resulted in a transient 50% reduction in heparin requirements. The patient underwent cardiac transplantation on day 48, had an uneventful postoperative period, and was discharged. Of note in this case, no investigation of heparin-PF-4 antibodies was carried out.

Soloway and Christiansen [23] reported a case of HR in a 68-year-old man with AT deficiency. Prior to surgery, large amounts of heparin were administered (total, 10 mg/kg; roughly equivalent to 1,000 IU/kg), but the target ACT of 480 seconds was not achieved. The patient was suspected to be AT deficient, and 3 units of FFP were obtained for administration. During the wait time required to thaw the FFP, an additional 3.8 mg/kg heparin (equivalent to approximately 380 IU/kg) was administered, the ACT value was increased to 545 seconds, and CPB was initiated. Approximately 30 minutes later, 3 units of FFP were administered, and the ACT value further increased to 830 seconds. Postoperative bleeding necessitated administration of 4 units of whole blood and 2 units of FFP, and surgical re-exploration was also required.

IN VITRO STUDIES. Barnette and colleagues [20] collected blood samples from 18 patients who underwent coronary artery bypass graft surgery. Heparin resistance was defined as an ACT of <400 seconds after administration of 350 IU/kg porcine heparin and this was observed in 6 patients (33%). The mean postheparin ACT in the six samples from patients with HR was 346 seconds; by comparison, the mean postheparin ACT observed in the samples from patients without HR was 470 seconds. Adding FFP (0.2 mL) to heparinized blood samples resulted in ACT values ≥ 400 seconds in 3 of 6 patients with HR (mean ACT, 496 seconds). However, FFP administration failed to resolve HR in the remaining three samples that achieved a mean ACT of only 371 seconds. Thus, in this small in vitro study, the response to FFP treatment was unsatisfactory in half of the cases of HR.

Studies With AT

PROSPECTIVE CLINICAL TRIALS. In a prospective crossover trial, Williams and colleagues [10] defined HR as a failure to achieve a therapeutic ACT (≥ 480 seconds in patients who did not receive aprotinin and ≥ 600 seconds in those who received aprotinin) after administration of 450 IU/kg heparin. Patients with HR were randomized to receive 1,000 IU AT (n = 44) or additional heparin (up to a total heparin dose of 800 IU/kg; n = 41). Patients who failed to achieve a therapeutic ACT in their assigned treatment group were crossed into the opposite treatment group. Therapeutic ACT values were achieved in 42 patients (95%) treated with AT, but in only 28 patients (68%) treated with additional heparin, representing a significantly higher failure rate in the heparin group ($p = 0.001$). Moreover, treatment with AT was successful for all 13

patients who did not respond to additional heparin therapy.

In another prospective study, Lemmer and Despotis [30] evaluated the effect of AT treatment in 53 aprotinin-treated patients with HR, defined as an inability to achieve an ACT of > 600 seconds after administration of more than 600 IU/kg heparin. Administration of AT (500 IU in 45 patients and 1,000 IU in 8 patients) increased mean ACT values from 492 to 789 seconds without additional heparin. In addition, the mean heparin-dose response increased significantly from 37 seconds·IU^{-1}·mL^{-1} before AT treatment to 69 seconds·IU^{-1}·mL^{-1} after AT treatment ($p < 0.0001$). Only 1 patient did not achieve the target ACT.

In a prospective clinical trial, Koster and colleagues [31] identified patients with HR as those needing ≥ 500 IU/kg heparin to achieve a target ACT of 480 seconds, and these patients were randomized to receive additional heparin (n = 20) or heparin supplemented with 50 IU/kg AT (n = 20), a direct thrombin inhibitor (n = 20), or a platelet glycoprotein antagonist (n = 20) for management of HR. Fibrin generation was significantly reduced in the latter three groups compared with the group who received heparin alone. Thus, supplementing heparin treatment with AT in patients with HR was more effective than additional heparin alone for maintaining adequate anticoagulation.

RETROSPECTIVE STUDIES. Brown and colleagues [27] retrospectively evaluated the efficacy of AT treatment in 44 patients with HR. After administration of 500 IU AT (equivalent to 2 units of FFP [30]), mean ACT values increased significantly from 416 seconds to 591 seconds ($p < 0.001$). Treatment with AT also significantly reduced the amount of heparin required to maintain an ACT of 480 seconds (7 IU/kg/min before AT therapy vs 2 IU/kg/min after AT therapy; $p < 0.001$). In addition, a retrospective chart review of 12 patients with HR revealed significant augmentation of mean ACT values from 337 to 844 seconds ($p < 0.0004$) after treatment with AT (1080–3408 IU). Nine (75%) of the 12 patients required no additional heparin administration after treatment with AT [28].

Conley and Plunkett [29] conducted a retrospective analysis of surgical outcomes in 310 patients, 211 of whom had HR, defined by a total heparin requirement of ≥ 5 mg/kg (ie, equivalent to 500 IU/kg heparin). Patients with HR were treated with AT (dosing information not provided; n = 101) or additional heparin (n = 110). Patients without HR (n = 99) were included as a control group. Patients in all three groups experienced similar outcomes in terms of 24-hour chest tube drainage and length of stay in the intensive care unit. However, patients treated with AT before CPB or within 20 minutes of instituting CPB (early AT administration) experienced a significant reduction in 24-hour chest tube drainage compared with patients treated with heparin and with those in the control group ($p = 0.05$). In addition, no patient in the control group, heparin group, or early AT administration group had postoperative coagulopathy develop, and no patient required surgical re-exploration because of bleeding.

CASE REPORTS. Van Norman and colleagues [25] reported a case of HR in a 48-year-old man scheduled for CPB surgery whose low baseline AT activity level (54% of normal) was believed to be caused by preoperative heparin administration. The patient received 2,500 IU AT, which resulted in a prompt increase in AT activity to 120% of normal and an increase in ACT from 347 to 635 seconds. The CPB was initiated, the postoperative course was uneventful, and the patient was discharged from the hospital.

Three cases of management of HR with AT were reported by Kanbak [26]. Therapeutic ACT values (≥ 400 seconds) were not achieved prior to CPB in 1 patient and during surgery in 2 patients, despite administration of up to 2,250 IU/kg heparin. However, after treatment with 1,000 IU AT, the ACT values for each patient remained greater than 400 seconds (range, 407 to 599 seconds) for the duration of surgery, and additional heparin administration was not required.

IN VITRO STUDIES. Levy and colleagues [24] assessed the in vitro ability of AT treatment to prolong ACT values in blood samples from patients who received 1,000 IU/h heparin for ≥ 48 hours before surgery (n = 22) compared with patients who did not receive preoperative heparin (control group, n = 21). Addition of heparin to the blood samples at final concentrations ranging from 4.1 to 6.8 IU/mL (equivalent to 300 and 500 IU/kg heparin, respectively) achieved longer mean ACT values in the control group (range, 568 to 628 seconds) compared with the preoperative heparin group (range, 453 to 496 seconds), indicating that some element of HR developed in patients treated with heparin before surgery. However, ACT values increased when 0.2 IU/mL AT (equivalent to approximately 1,000 IU AT) was added to the anticoagulated blood samples, demonstrating that in vitro administration of AT restored heparin responsiveness.

Recombinant Human AT

PROSPECTIVE CLINICAL TRIALS. Although no placebo-controlled studies to date have evaluated the efficacy of plasma-derived AT in patients with HR undergoing cardiac surgery, two trials have been conducted with rhAT [6, 7]. In a prospective, double-blind, multicenter study, Avidan and colleagues [6] randomized patients with HR (ACT < 480 seconds after 400 IU/kg heparin) to receive 75 IU/kg rhAT (n = 27) or placebo (n = 27). Prior to administration of study medication, patients in both treatment groups had similar ACT values (415 seconds in the placebo group and 424 seconds in the rhAT group). However, patients treated with rhAT versus placebo demonstrated significantly increased ACT values, which were measured 5 minutes after treatment (601 vs 442 seconds; $p < 0.001$) and throughout the perioperative period. In addition, fewer patients in the rhAT group required additional heparin treatment (46% vs 78%; $p = 0.02$) during CPB. Administration of FFP was required in significantly fewer patients in the rhAT group versus the placebo group in the intraoperative period (19% vs 81%;

Table 4. Overview of Clinical Evidence Supporting AT Versus FFP as Treatment of HR During CPB

Factor	AT Advantage
Published clinical reports	11 reports for AT versus only 5 reports for FFP
Risk of viral transmission	AT purification process provides viral inactivation; no cases of transmitted infection related to AT administration
Increased volume load	AT requires administration of 50-fold lower volume versus FFP
TRALI	Underdiagnosed transfusion-related complication, FFP has been associated with 50% of fatal cases reported
Efficiency and cost	AT is more expensive, but requires thaw time for FFP, which may increase cost and procedural risk

AT = antithrombin; CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; HR = heparin resistance; TRALI = transfusion-related acute lung injury.

$p < 0.001$) and throughout hospitalization (48% vs 85%; $p = 0.009$). Moreover, in 20 patients in the placebo group, the mean ACT value increased from 415 seconds before FFP treatment to only 424 seconds 5 minutes after FFP treatment, suggesting a minimal effect of 2 units of FFP in achieving therapeutic ACT values. A similar study [7] reported comparatively favorable results in patients who received rhAT (n = 28) versus placebo (n = 24) for the management of HR during cardiac surgery requiring CPB.

Summary and Critical Appraisal of Published Studies

A review of the literature regarding treatment options for HR offers several valuable insights, despite the current lack of a published clinical trial directly comparing FFP and AT administration. First, despite its widespread use, there is a surprising paucity of evidence-based support for the clinical use of FFP in managing HR during CPB (Table 2). Compared with 11 published reports assessing AT as a treatment option for HR during cardiac surgery (Table 3), only 5 reports have evaluated FFP. Moreover, recent systematic reviews, including as many as 57 clinical trials, found no evidence of reduced blood loss or transfusion requirements with prophylactic administration of FFP during cardiac surgery in general (HR not considered) [33, 34]. Thus, FFP administration during cardiac surgery is not only poorly studied but also demonstrated limited efficacy in reported studies.

Studies evaluating AT administration in patients with HR generally reported successful prolongation of the ACT value to initiate CPB (Table 3). As noted, ACT measurements during CPB can be highly variable and limited in terms of correlation with heparin levels [32]. Several heparin concentration assays have been developed and may be more effective than ACT monitoring for guiding heparin dosing during CPB. In addition, future studies of anticoagulant therapy during CPB need to include broader outcome measures to assess the clinical benefit of treatment. Although some clinical trials of AT treatment in patients with HR have assessed outcomes such as transfusion requirements [6, 7], additional endpoints such as blood loss and surgical re-exploration should be considered. In one controlled trial of rhAT treatment in patients with HR, 85% of patients in the placebo group required FFP administration during hospitalization [6]. Although rhAT treatment significantly reduced transfusion requirements, almost half of the patients in the rhAT group received FFP. The lack of a greater effect of rhAT in reducing transfusion requirements could be attributed to AT-independent HR in a subset of patients. Patients who develop HR in the absence of AT deficiency are unlikely to benefit from AT treatment [8], and alternative anticoagulants such as direct thrombin inhibitors should be considered [8, 35]. Clinical trials that directly compare anticoagulant strategies in patients with HR during CPB are lacking, as are appropriately designed studies (eg, a "heparin-alone" control group may be an inappropriate comparator for AT treatment in patients with HR caused by AT deficiency because heparin requires AT to exert its anticoagulant effect).

FFP Versus AT: Issues for Consideration

Safety

VIRAL TRANSMISSION AND ADVERSE EVENTS. In addition to the lack of demonstrated efficacy, safety issues associated with FFP administration may limit its potential as a candidate therapy for resolving HR (Table 4). For example, transmission of viral infections, such as human immunodeficiency virus (HIV), hepatitis B, and hepatitis C, is a small but measurable risk associated with transfusion of homologous blood products such as FFP (ie, 1 in 10 million donations for human immunodeficiency virus [HIV]; 1 in 1.2 million donations for hepatitis B, and 1 in 50 million donations for hepatitis C) [33]. Other viral risks, including emerging viruses, may be related to transfusion of blood products. For example, prions that cause variant Creutzfeld-Jacob disease are carried in the plasma, but the risk of transfusion-related transmission is uncertain [33]. The recent epidemic of West Nile virus is also notable; prevalence of the virus among blood donors in the United States ranged from approximately 1 in 1,000 in 2002 to 1 in 23,000 in 2004 [36].

The rigorous heat treatment and purification process implemented in manufacturing AT has been shown to effectively achieve viral inactivation [37, 38]. Thus, AT is potentially safer than FFP with respect to infectious disease transmission. No cases of viral transmission have been reported in patients who have received AT and were not transfused with other blood products [4, 39–41];

two cases of hepatitis B seroconversion in patients who received AT were considered to be related to multiple transfusions with other blood products [40]. Similarly, no case of viral transmission related to AT administration has been reported in patients who underwent cardiac surgery [41]. During clinical trials, adverse reactions were reported in 13 of 452 infusions of AT (3%) that included chest tightness, dizziness, hives, light-headedness, abdominal cramps, fever, shortness of breath, and foul taste in the mouth [39]. Thus, AT administration is associated with a low incidence of adverse events, including a low risk of allergic reactions.

VOLUME LOAD. In addition to reducing the risk of viral transmission, AT treatment requires administration of a small volume of fluid compared with a substantial volume load associated with FFP administration [10]. The initial loading dose of AT should be calculated to elevate the plasma AT level to 120%, based on an expected 1.4% increase above baseline activity level per IU/kg of AT administered [39]. One IU of AT corresponds to the activity of AT in 1 mL of normal human plasma. Because 1 vial of AT containing approximately 500 IU AT is reconstituted with water to 10 mL of solution, administration of a minimal volume of medication achieves a dramatic increase in AT concentration [10, 30, 42]. In contrast, FFP contains approximately 1 IU of AT per mL of plasma; thus, 2 units of FFP (roughly 500 mL) are required to achieve a dose of 500 IU AT [4, 25, 30]. The increased volume load associated with FFP administration is a safety concern for at-risk patient populations, including those with congestive heart failure [10]. In addition to potentially causing volume overload, administration of FFP results in hemodilution [25]. In turn, low platelet counts are associated with transfusion of additional units of FFP [43], which may further exacerbate hemodilution and prompt transfusion of platelets or red blood cells. Thus, patients receiving FFP may be predisposed to a higher likelihood of transfusion of other blood products to maintain adequate platelet concentrations during surgery [25, 43].

TRANSFUSION-RELATED COMPLICATIONS. An emerging safety concern with FFP administration is the risk of transfusion-related acute lung injury (TRALI). Characterized by acute respiratory distress and noncardiogenic pulmonary edema typically developing within 6 hours of transfusion of blood products [44–49], TRALI is currently the leading cause of transfusion-related mortality [48]. A retrospective review of 58 TRALI fatality cases reported to the United States Food and Drug Administration during a 5-year period (1997 to 2002) implicated FFP administration in 50% of the fatalities, followed by red blood cells (31%), platelets (17%), and cryoprecipitate-reduced plasma (2%) [46]. Moreover, experts agree that TRALI remains an underdiagnosed and underreported complication of transfusion therapy [48]. In a case-control study nested within a retrospective cohort of critically ill patients (n = 1,351) who underwent a transfusion and did not require respiratory support at the time of transfusion, Rana and colleagues [49] identified 24 cases of suspected or possible TRALI. Among 8,902 units transfused (5,044 units red blood cells, 2,745 units FFP, 885 units platelets, and 228 units cryoprecipitate), the incidence of suspected TRALI was 1 per 1,271 units transfused (or 1 per 193 recipients), and the incidence of possible TRALI was 1 per 534 units transfused (or 1 per 79 recipients). Suspected or possible cases of TRALI were associated with a mortality rate of 47%. Importantly, none of the cases detected during the retrospective review had been reported to the blood bank, emphasizing the underdiagnosis of the syndrome. In addition, development of suspected or possible TRALI was associated with infusion of FFP, as well as infusion of plasma from female donors; prospective studies are warranted to determine whether these potential risk factors play a causative role in TRALI. Thus, although questions regarding the exact incidence and cause of TRALI currently remain unanswered, the syndrome clearly represents a potentially serious complication of FFP administration [44–49].

In addition to the risk of developing TRALI, patients with diminished cardiac reserve are susceptible to transfusion-associated cardiac overload. In the work by Rana and colleagues [49], incidence of transfusion-associated cardiac overload was 1 per 356 units transfused (or 1 per 54 recipients) among patients in the intensive care unit, and mortality associated with the syndrome was 20%. Thus, along with less frequent, widely recognized adverse outcomes, such as viral transmission, pulmonary edema is emerging as an important safety consideration associated with the transfusion of blood products.

Efficiency and Cost

The expense associated with AT versus FFP administration is also an important issue for practical consideration. Although the 2006 Red Book price for AT is $2.07 per IU [50], most institutions acquire AT for approximately $1.68 per IU. Thus, a standard 500-mL dose of AT is associated with a cost of approximately $840. Currently, FFP costs approximately $35 to $55 per unit, resulting in a lower acquisition cost (approximately $70 to $110 for 500 mL) compared with AT. Although AT is a more expensive treatment compared with FFP in terms of acquisition, overall cost assessment should take into account the expense associated with thawing FFP and transporting units to the operating room. Antithrombin can be reconstituted and available for administration in a matter of minutes [27], thus eliminating waiting time, which may increase costs for the hospital staff and confer additional risk for the patient in terms of development of adverse events [10, 25].

Comment

In conclusion, heparin resistance is common in patients undergoing cardiovascular surgery requiring CPB and may be caused by decreased levels of AT. Failure to correct AT deficiency associated with CPB may result in inadequate coagulation and increase the risk of thromboembolic events, surgical re-exploration, and other adverse events. Treatment options for HR include AT and

FFP. Published clinical reports are limited but generally favor AT as a safe, effective, and efficient choice for clinical management of HR. Administration of FFP may resolve HR in some cases. However, it is important to take into account emerging safety issues, such as increased risk of transfusion-related complications, as well as practical considerations related to FFP administration, including costs associated with acquisition, overhead, and adverse events. Thus, FFP in reality may be costlier than AT, and health economic studies are warranted to further elucidate the potential overall cost and patient benefits associated with AT treatment in patients with HR. Heparin resistance may well be the downstream manifestation of the population response to heparin administration. Multiple randomized trials are needed to investigate AT administration in cardiac surgery as a repletion technique to resolve the loss of AT. Given that AT mediates a number of inflammatory and coagulation reactions and also protects endothelial cells, consumption of AT by preoperative heparin administration or during routine CPB may present multiple levels of risk for patients undergoing cardiac surgery. Quite simply, we need to know a great deal more about AT in human biology with respect to CPB.

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References

1. Despotis GJ, Avidan MS, Hogue CW Jr. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. Ann Thorac Surg 2001;72:S1821–31.
2. Paparella D, Brister SJ, Buchanan MR. Coagulation disorders of cardiopulmonary bypass: a review. Intensive Care Med 2004;30:1873–81.
3. Rinder C. Cellular inflammatory response and clinical outcome in cardiac surgery. Curr Opin Anaesthesiol 2006;19:65–8.
4. Bharadwaj J, Jayaraman C, Shrivastava R. Heparin resistance. Lab Hematol 2003;9:125–31.
5. Edmunds LH Jr, Colman RW. Thrombin during cardiopulmonary bypass. Ann Thorac Surg 2006;82:2315–22.
6. Avidan MS, Levy JH, Scholz J, et al. A phase III, double-blind, placebo-controlled, multicenter study on the efficacy of recombinant human antithrombin in heparin-resistant patients scheduled to undergo cardiac surgery necessitating cardiopulmonary bypass. Anesthesiology 2005;102:276–84.
7. Avidan MS, Levy JH, van Aken H, et al. Recombinant human antithrombin III restores heparin responsiveness and decreases activation of coagulation in heparin-resistant patients during cardiopulmonary bypass. J Thorac Cardiovasc Surg 2005;130:107–13.
8. Ranucci M, Isgrò G, Cazzaniga A, et al. Different patterns of heparin resistance: therapeutic implications. Perfusion 2002;17:199–204.
9. Staples MH, Dunton RF, Karlson KJ, Leonardi HK, Berger RL. Heparin resistance after preoperative heparin therapy or intraaortic balloon pumping. Ann Thorac Surg 1994;57:1211–6.
10. Williams MR, D'Ambra AB, Beck JR, et al. A randomized trial of antithrombin concentrate for treatment of heparin resistance. Ann Thorac Surg 2000;70:873–7.
11. Ranucci M, Isgrò G, Cazzaniga A, Soro G, Menicanti L, Frigiola A. Predictors for heparin resistance in patients undergoing coronary artery bypass grafting. Perfusion 1999;14:437–42.
12. Hashimoto K, Yamagishi M, Sasaki T, Nakano M, Kurosawa H. Heparin and antithrombin III levels during cardiopulmonary bypass: correlation with subclinical plasma coagulation. Ann Thorac Surg 1994;58:799–804.
13. Cloyd GM, D'Ambra MN, Akins CW. Diminished anticoagulant response to heparin in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 1987;94:535–8.
14. Dietrich W, Spannagl M, Schramm W, Vogt W, Barankay A, Richter JA. The influence of preoperative anticoagulation on heparin response during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1991;102:505–14.
15. Esposito RA, Culliford AT, Colvin SB, Thomas SJ, Lackner H, Spencer FC. Heparin resistance during cardiopulmonary bypass. The role of heparin pretreatment. J Thorac Cardiovasc Surg 1983;85:346–53.
16. Ranucci M, Frigiola A, Menicanti L, Ditta A, Boncilli A, Brozzi S. Postoperative antithrombin levels and outcome in cardiac operations. Crit Care Med 2005;33:355–60.
17. Sabbagh AH, Chung GK, Shuttleworth P, Applegate BJ, Gabrhel W. Fresh frozen plasma: a solution to heparin resistance during cardiopulmonary bypass. Ann Thorac Surg 1984;37:466–8.
18. Edmunds T, Van Patten SM, Pollock J, et al. Transgenically produced human antithrombin: structural and functional comparison to human plasma-derived antithrombin. Blood 1998;91:4561–71.
19. Levy JH, Weisinger A, Ziomek CA, Echelard Y. Recombinant antithrombin: production and role in cardiovascular disorder. Semin Thromb Hemost 2001;27:405–16.
20. Barnette RE, Shupak RC, Pontius J, Rao AK. In vitro effect of fresh frozen plasma on the activated coagulation time in patients undergoing cardiopulmonary bypass. Anesth Analg 1988;67:57–60.
21. Leong CK, Ong BC. A case report of heparin resistance due to acquired antithrombin III deficiency. Ann Acad Med Singapore 1998;27:877–9.
22. Despotis GJ, Levine V, Alsoufiev A, Joist H, Goodnough LT, Pasque M. Recurrent thrombosis of biventricular-support devices associated with accelerated intravascular coagulation and increased heparin requirements. J Thorac Cardiovasc Surg 1996;112:538–40.
23. Soloway HB, Christiansen TW. Heparin anticoagulation during cardiopulmonary bypass in an antithrombin-III deficient patient. Implications relative to the etiology of heparin rebound. Am J Clin Pathol 1980;73:723–5.
24. Levy JH, Montes F, Szlam F, Hillyer CD. The in vitro effects of antithrombin III on the activated coagulation time in patients on heparin therapy. Anesth Analg 2000;90:1076–9.
25. Van Norman GA, Gernsheimer T, Chandler WL, Cochran RP, Spiess BD. Indicators of fibrinolysis during cardiopulmonary bypass after exogenous antithrombin-III administration for acquired antithrombin III deficiency. J Cardiothorac Vasc Anesth 1997;11:760–3.
26. Kanbak M. The treatment of heparin resistance with antithrombin III in cardiac surgery. Can J Anaesth 1999;46:581–5.
27. Brown ME, Gallagher JM, Armitage JM. The use of antithrombin III concentrate for treatment of heparin resistance during cardiopulmonary bypass. J Extra Corpor Technol 2000;32:75–8.
28. Irani MS. Antithrombin concentrates in heparin-resistant cardiopulmonary bypass patients. Clin Appl Thromb Hemost 1996;2:103–6.
29. Conley JC, Plunkett PF. Antithrombin III in cardiac surgery: an outcome study. J Extra Corpor Technol 1998;30:178–83.

30. Lemmer JH Jr, Despotis GJ. Antithrombin III concentrate to treat heparin resistance in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg 2002;123:213–7.
31. Koster A, Fischer T, Gruendel M, et al. Management of heparin resistance during cardiopulmonary bypass: the effect of five different anticoagulation strategies on hemostatic activation. J Cardiothorac Vasc Anesth 2003;17:171–5.
32. Despotis GJ, Gravlee G, Filos K, Levy J. Anticoagulation monitoring during cardiac surgery: a review of current and emerging techniques. Anesthesiology 1999;91:1122–51.
33. Casbard AC, Williamson LM, Murphy MF, Rege K, Johnson T. The role of prophylactic fresh frozen plasma in decreasing blood loss and correcting coagulopathy in cardiac surgery. A systematic review. Anaesthesia 2004;59:550–8.
34. Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. Br J Haematol 2004;126:139–52.
35. Warkentin TE. Anticoagulation for cardiopulmonary bypass: is a replacement for heparin on the horizon? J Thorac Cardiovasc Surg 2006;131:515–6.
36. Stramer SL, Fang CT, Foster GA, Wagner AG, Brodsky JP, Dodd RY. West Nile virus among blood donors in the United States, 2003 and 2004. N Engl J Med 2005;353:451–9.
37. Hoffman DL. Purification and large-scale preparation of antithrombin III. Am J Med 1989;87(Suppl 3B):23S–6S.
38. Morrica A, Nardini C, Falbo A, Bailey AC, Bucci E. Manufacturing process of anti-thrombin III concentrate: viral safety validation studies and effect of column re-use on viral clearance. Biologicals 2003;31:165–73.
39. Schwartz RS, Bauer KA, Rosenberg RD, Kavanaugh EJ, Davies DC, Bogdanoff DA, and The Antithrombin III Study Group. Clinical experience with antithrombin III concentrate in treatment of congenital and acquired deficiency of antithrombin. Am J Med 1989;87(Suppl 3B):53S–60S.
40. Menache D, O'Malley JP, Schorr JB; and the Cooperative Study Group, et al. Evaluation of the safety, recovery, half-life, and clinical efficacy of antithrombin III (human) in patients with hereditary antithrombin III deficiency. Blood 1990;75:33–9.
41. Preiss DU, Abdullah D, Eberspächer B, Wilhelm K. Safety of virus inactivated antithrombin III concentrate antithrombin III immuno (AT III). Thromb Res 1992;65:677–86.
42. Bucur SZ, Levy JH, Despotis GJ, Spiess BD, Hillyer CD. Uses of antithrombin III concentrate in congenital and acquired deficiency states. Transfusion 1998;38:481–98.
43. Covin R, O'Brien M, Grunwald G, et al. Factors affecting transfusion of fresh frozen plasma, platelets, and red blood cells during elective coronary artery bypass graft surgery. Arch Pathol Lab Med 2003;127:415–23.
44. Bux J. Transfusion-related acute lung injury (TRALI): a serious adverse event of blood transfusion. Vox Sang 2005; 89:1–10.
45. Gajic O, Moore SB. Transfusion-related acute lung injury. Mayo Clin Proc 2005;80:766–70.
46. Holness L, Knippen MA, Simmons L, Lachenbruch PA. Fatalities caused by TRALI. Transfus Med Rev 2004;18: 184–8.
47. Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: a review. Chest 2004;126:249–58.
48. Toy P, Popovsky MA, Abraham E, et al. Transfusion-related acute lung injury: definition and review. Crit Care Med 2005;33:721–6.
49. Rana R, Fernández-Pérez ER, Khan SA, et al. Transfusion-related acute lung injury and pulmonary edema in critically ill patients: a retrospective study. Transfusion 2006;46:1478–83.
50. Red Book, 2006 ed. Montvale, NJ: Thomson PDR, 2006: 678.