



The
Heart Surgery Forum[®]

CARDIAC AND VASCULAR SURGERY:
IMPACT OF INFLAMMATION,
TRANSFUSION AND
MICROVASCULAR PERFUSION
ON CEREBRAL PROTECTIVE STRATEGIES

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Target Audience: This activity has been designed to meet the educational needs of cardiothoracic surgeons, cardiac anesthesiologists, blood bank directors, and hematology-oncology consultants.

Needs Statement: This activity will provide a forum for discussion of ways to optimize clinical outcome through understanding the impact of inflammation, transfusion, and microvascular perfusion on cerebral protective strategies.

Learning Objectives:

Upon completion of this activity, the participant should be able to:

- Identify links between coagulation and inflammation in cardiac surgery.
- Discuss ways to stabilize the hemostatic response through the use of antifibrinolytic agents.
- Demonstrate an understanding of ways to control anticoagulation during cardiopulmonary bypass.
- Evaluate the safety and efficacy of antifibrinolytic therapy on cardiac surgery patients.

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Leukocyte Trafficking and Antiinflammatory Strategies in On-Pump CABG Surgery

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Cardiothoracic surgery with cardiopulmonary bypass (CPB) exposes patients to broad disturbances in the coagulation, fibrinolytic, complement, and inflammatory pathways. These disturbances lead to systemic complications, particularly hemostatic insufficiency leading to excessive bleeding, and localized complication from organ injury due to infiltration of cytotoxic leukocytes and ischemia/reperfusion injury, especially in the heart, brain, lungs, and kidneys. Modification of the extracorporeal circuit to limit the extent of contact activation has been generally disappointing. Coating strategies have been empirical and provided few notable clinical benefits. A more successful strategy has been the use of antifibrinolytic agents such as tranexamic acid, ϵ -amino caproic acid, and aprotinin to stabilize the hemostatic response and decrease surgical bleeding. The sparing of inflammatory organ injury has been noted only with the broad-acting serine protease inhibitor aprotinin, a multitarget drug with clinical antifibrinolytic, antithrombotic, and antiinflammatory properties. Other monotargeting drugs have failed to provide the anticipated clinical benefits, and there is a need to consider using such drugs in combination. Future antiinflammatory strategies should target the pool of cytotoxic organ-infiltrating leukocytes that cause end-organ injury.

A More Holistic Approach to the Systemic Inflammatory Response

Improved cardiothoracic surgery strategies are needed to protect patients from the systemic inflammatory response to CPB. The use of antifibrinolytic agents largely controls bleeding, but organ protection remains an area of concern, especially in the heart, brain, lungs, and kidneys. By defining the problem narrowly as one of “inflammation,” we may miss the multisystem origin of the response. In addition to causing exuberant inflammation, on-pump coronary artery bypass graft (CABG) surgery elicits major disturbances to the coagulation, complement, and fibrinolytic pathways.

Excessive bleeding leading to transfusion is independently linked to adverse outcomes in cardiothoracic surgery, and surgical teams are rightly concerned with limiting perioperative bleeding [Michalopoulos 1999, Leal-Noval 2001, Spiess 2004, Koch 2006]. The use of antifibrinolytic agents is widespread, with the lysine analogues (tranexamic acid and ϵ -aminocaproic acid) and the serine protease inhibitor aprotinin all effective at curbing blood loss. The clinical consensus is that aprotinin should be used in higher risk patients and the lysine analogues in lower risk patients. Limiting fibrinolysis only partly addresses the bleeding issue, however, because thrombin generated in the bypass circuit (despite adequate heparinization)

activates platelets and renders them dysfunctional [Boisclair 1993, Brister 1993, Ferraris 1998]. Aprotinin preserves platelets by blocking the high-affinity thrombin receptor PAR1 [Poullis 2000, Day 2004], thus exerting protective effects beyond those of the lysine analogues. This antithrombotic property allied to its antifibrinolytic blockade of plasmin makes aprotinin very beneficial for use in surgical procedures in which thrombosis and fibrinolysis are major concerns [Landis 2001].

Thrombin production is also linked to proinflammatory activation of leukocytes and endothelial cells bearing the thrombin receptor PAR1 [Kaplanski 1997, Kaplanski 1998]. In vivo, PAR1-specific antagonists promise antithrombotic and antiinflammatory protection via blockade of PAR1 without increasing the risk of bleeding (because the procoagulant pathways of thrombin remain intact), as has been demonstrated by the recently concluded phase II TRA-PCI trial of the oral antithrombin antagonist SCH 530348, in which patients showed a 46% reduction in adverse cardiovascular events [Moliterno 2007] and no increased risk of bleeding when SCH 530348 was added to standard antiplatelet therapies (aspirin and clopidogrel) in percutaneous interventional surgery patients. This class of agent may not prove effective in on-pump CABG surgery, however, because this procedure is further complicated by contact activation of humoral and cellular targets by passage of blood through the bypass circuit. Aprotinin is already licensed for use in cardiothoracic surgery, has anti-PAR1 properties, and has demonstrated clinical effects via blockade of PAR1 during on-pump surgery [Day 2004]. To what extent PAR1 targeting may explain the antiinflammatory effects of aprotinin in this group of patients is not certain, because aprotinin blocks a number of other inflammatory pathways, including plasma kallikrein, bradykinin, and leukocyte activation and extravascular migration.

Coating Strategies: Need for Improvement

The contact pathway of activation activates humoral and cellular components during passage of blood through the bypass circuit. The complement system is activated via classical activation of C3, secondary to immunoglobulin M (IgM) and IgG antibody deposition onto the extracorporeal circuit. Coagulation is triggered by absorption of factor XII onto the extracorporeal circuit and activation of the intrinsic pathway, culminating in thrombin generation, and thrombin is produced in direct relation to the amount of time the patient spends on bypass. All of these events occur despite adequate heparinization [Boisclair 1993, Brister 1993]; thus it is reasonable to explore ways to minimize the bioincompatibility of the circuit to curb the extent of contact activation.

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Approaches to curb contact activation include minimization of the circuit surface, use of closed systems, and coating with heparin or biocompatible polymers. Small benefits but no major clinical improvements have been reported in curbing complement and inflammatory cytokine generation [McCarthy 1999, Ask 2006, Bical 2006, Eisses 2007]. Coating strategies have been employed on a somewhat empirical basis (why coat with heparin?), and ample scope remains for exploration of alternative coating strategies aimed at targets nearer the top of the coagulation cascade. Another area needing investigation is examining ways to limit adhesion of platelets and leukocytes to the plastic surfaces of the bypass circuit, which occurs via specialized adhesion receptors and causes cellular activation.

Recently published evidence-based guidelines on the practice of CPB assigned a class IIa, level B recommendation for circuit modification as a way to curb the inflammatory response [Shann 2006]. Data derived from single or nonrandomized studies suggest usefulness/efficacy of this method, and great deal of further work must be done to improve circuit modification so that it acquires a level of recommendation at which the surgical team can be confident of its clinical benefit.

Multitarget Drugs for a Multipathway Problem

A fundamental principle of pharmacointervention to counteract the multisystem imbalances elicited by CPB should be to use multitargeting drugs such as aprotinin or combinations of monotargeting drugs. Multiple pathways feed into the systemic inflammatory response (Figure 1), so any antiinflammatory strategies to improve clinical outcomes must hit multiple targets.

One monotargeting drug that has completed phase III trials for use in CABG surgery is pexelizumab, an anti-C5 complement antibody. Although the drug did not achieve a significant reduction in its primary endpoint in CABG (death/myocardial infarction at 30 days), there was a strong trend toward protection, and other secondary endpoints were achieved [Mathew 2004, Verrier 2004, Haverich, 2006]. It might be interesting to combine such anticomplement medication with drugs targeting the leukocyte-endothelial cell interaction. Many of the leukocyte adhesion receptors that mediate sticking to and activation by the extracorporeal circuit have been validated as targets in inflammatory diseases [Kaneider 2006]. Leukocyte chemokine receptors involved in sepsis might also be reasonably targeted as a way to blunt the inflammatory response to CPB [Kaneider 2005], and it would be interesting to evaluate these new categories of drugs in combination with anticomplement medication to achieve improved outcomes.

Aprotinin is possibly unique in its multifaceted mechanism of action. It is antifibrinolytic by virtue of its blockade of plasmin [Kang 2005]; it is antithrombotic by virtue of inhibiting the high affinity thrombin receptor, PAR1, on platelets and endothelial cells [Poullis 2000, Day 2004, Day 2006]; it is platelet protective, most probably via a combination of platelet sparing mechanisms targeting thrombin and plasmin [Shigeta 1997, Day 2004]; and it is antiinflammatory by a multipronged mechanism, including targeting of kallikrein and bradykinin [Kamiya 1993, Wachtfogel 1993], endothelial PAR1 [Day 2006], leukocyte activation [Hill 1995],

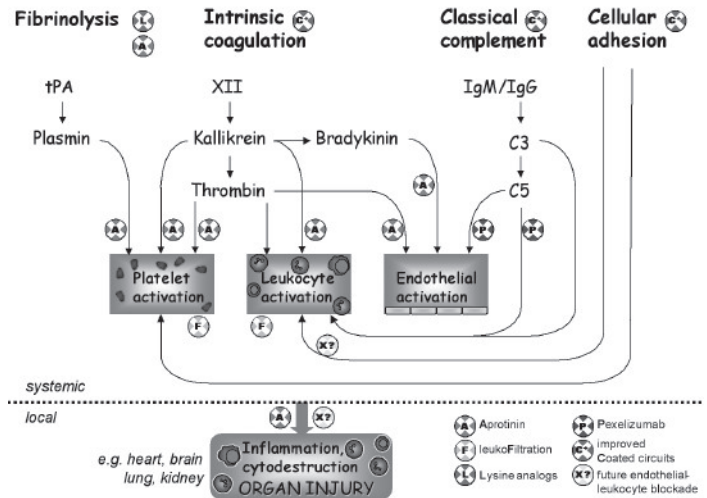


Figure 1. The systemic inflammatory response is composed of multiple insults to the fibrinolytic, coagulation, complement, and cellular adhesion pathways. End-organ injury occurs when activated leukocytes infiltrate susceptible organs and release cytodestructive mediators. This event may combine with ischemia-reperfusion injury to produce organ dysfunction—typically in the heart, lung, brain, and kidney. Realistically, pharmacointervention can be expected to curb the systemic inflammatory response only by use of a multitargeting drug, such as aprotinin, or combinations of monotargeting drugs and/or antiinflammatory strategies. It would be interesting in the future to try combining improved coated strategies and/or pexelizumab with compounds under development that target the leukocyte-endothelial cell interaction. Leuko-filtration, although it does little to curb cellular activation, is a useful adjunctive therapy to prevent activated leukocytes and platelets from re-entering the patient circulation. tPA indicates tissue Plasminogen Activator.

and leukocyte diapedesis [Hill 1996, Asimakopoulos 2000, Pruefer 2003, Anttila 2006, Evans 2007]. Hitting such multiple targets is most probably a requirement for successful pharmacointervention in a complex procedure such as on-pump CABG surgery that elicits broad disturbances to the body's major defense systems. These multiple effects also explain why aprotinin is the most successful state-of-the-art antiinflammatory intervention and has been shown to reduce the length of hospital stay and cost, especially in high-risk patients [Gott 1998, Smith 2004].

Last year, several observational studies raised potential safety concerns regarding the association of aprotinin use with increased risk of renal dysfunction [Karkouti 2006, Mangano 2006, Mangano 2007]. These retrospective studies did not assign patients randomly to aprotinin or control groups, and so, by definition, they could not demonstrate cause and effect. Because aprotinin was used more commonly in higher risk patients, statistical corrections were necessary to take this fact into consideration. Nonetheless, based on the new safety information contained in these studies, the US Food and Drug Administration (FDA) issued a US label modification for aprotinin (Trasylol injection), recommending that aprotinin should be limited to "patients who are at increased risk of blood loss and blood transfusion." The new FDA guidelines have, in effect, reinforced the clinical trend toward reserving aprotinin use for higher risk patients, such as those on antiplatelet medications [van der Linden 2005]. The greatest benefits for aprotinin have always been noted in higher risk patients, and the new FDA guidelines thus make good sense [Gott 1998, Frumento 2003].

Targeting the Extravascular Leukocyte Pool

Contact activation of leukocytes plays a central role in organ damage secondary to bypass. The key point of concern with activated white cells in surgery is not so much systemic inflammation per se but local infiltration of cytodestructive leukocytes into organs. A causal relationship between leukocyte infiltration and central nervous system injury has been demonstrated in animals, and there is increasing evidence that post-surgical neurocognitive deficits are linked to the inflammatory response [Clark 1991, Mori 1992, Kalman 2006, Ramlawi 2006]. Leukocyte diapedesis therefore represents a key target for future antiinflammatory strategies. In the current armamentarium, only aprotinin blocks leukocyte diapedesis, as demonstrated in vitro in animals and clinically [Hill 1996, Asimakopoulos 2000, Pruefer 2003, Anttila 2006, Evans 2007]. The mechanism by which aprotinin blocks leukocyte diapedesis may best explain the stroke-protective properties of aprotinin, as noted in metaanalyses of placebo controlled randomized trials [Sedrakyan 2004].

Conclusion

The systemic inflammatory response to CPB should be thought of in more holistic terms. Rather than being merely a disorder of inflammation, this response comprises major disturbances to the complement, coagulation, and fibrinolytic systems in addition to the inflammatory system. Only a multitargeting drug or combinations of monotargeting drugs are likely to block sufficient arms of the systemic inflammatory response to offer improved clinical outcomes. Future research should be directed toward more upstream interdiction of the contact activation pathways in the extracorporeal circuit and better protection from infiltrating leukocytes, which in combination with ischemia-reperfusion injury mediate the majority of end-organ injury.

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Links between Coagulation and Inflammation: Opportunities for Intervention

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Introduction

Coagulation has been described as proceeding by 2 partially independent pathways, the intrinsic pathway and the extrinsic pathway (see, for example, [Nossel 1967]). The components of the intrinsic pathway are tested for in the activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. A negatively charged surface such as diatomaceous earth is added to plasma (aPTT) or blood (ACT) and the time to clot formation is observed. Heparin will prolong both assays, and so the ACT can be used to assess the degree of anticoagula-

tion in a patient. Deficiencies of high molecular weight kininogen (HK), prekallikrein (PK), or factors XII, XI, IX, VIII, X, V, and prothrombin will also prolong the aPTT or ACT. Patients with deficiencies of HK, PK, and factor XII, however, have no bleeding diathesis, suggesting that physiologically these proteins do not play a significant role in hemostasis.

By contrast, the components of the extrinsic pathway are tested for in the prothrombin time (PT) assay. This assay depends on addition of a membrane-associated protein, tissue factor (also called tissue thromboplastin), which was thought to be found only extrinsic to the

blood. This idea of blood coagulation being initiated when a break in a blood vessel brings the extrinsic component in contact with the components in the blood provided a powerful concept for how blood coagulation could be regulated. PT is not affected by deficiencies of factors IX or VIII, however, even though deficiency of either factor is clearly a cause of bleeding in patients.

A Model for Cell-Mediated Hemostasis

We and others have suggested that a different model of hemostasis, cell-mediated hemostasis, might prove useful. This model takes as its starting point the protein interactions that are the key components of the intrinsic and extrinsic pathways. Our point of divergence from the existing models comes from a focus on the surface on which these reactions occur rather than the reactions themselves [Monroe 2002]. The cell-mediated hemostasis model envisions coagulation proceeding in 3 overlapping phases: initiation, amplification, and propagation [Roberts 1998]. In initiation (Figure 1), hemostasis begins after a disruption or break in the vasculature that brings coagulation proteins in contact with extravascular proteins and, more importantly, brings platelets in contact with the extracellular matrix. Platelets adhere through a number of mechanisms involving both von Willebrand factor and integrins, and these mechanisms activate platelets to a limited extent. However, this adhesion and limited aggregation is not sufficient to provide for a stable plug. Tissue factor-mediated factor X activation leads to limited thrombin generation with factor Va probably provided by activated platelets. This thrombin generation can be detected as fibrin deposition at the margins of a wound, even in the case of hemophilia, where the wound is not otherwise consolidated [Wester 1979, Sixma 1984].

The amplification phase proceeds as the thrombin generated on the tissue-factor-bearing cells further activates platelets, activating factor XI and factor VIII, which is brought to the platelet surface by von Willebrand factor interactions with glycoprotein Ib, and further activates the partially activated platelet factor V, which is released from platelet alpha granules. The activated platelets with activated cofactors are now primed for the propagation phase.

In the propagation phase (Figure 2), factor IXa, activated by factor VIIa/tissue factor, with factor VIIIa on the platelet surface, activates factor X. This activated factor, Xa, can move directly into a protected complex with factor Va, leading to a burst of thrombin generation. Factor XIa on the platelet surface can enhance factor IX activation, leading to additional thrombin generation. The burst of thrombin is important because the ultimate structure of the fibrin clot appears to depend on the rate at which thrombin is produced during the burst phase. Even minute amounts of thrombin are enough to generate some fibrin, but a large burst of thrombin remodels the clot into a fibrinolysis-resistant structure [Wolberg 2007], activates factor XIII, generates activated thrombin-activatable fibrinolysis inhibitor [Bajzar 1995], and cleaves PAR4 on platelets, leading to clot retraction and stabilization.

In this model, hemostasis is not so much terminated as it is confined to the platelet/fibrin mass. Active thrombin remaining in the fibrin mass is useful for repairing small disruptions in the clot.

Hemostasis is further confined by healthy endothelium surrounding the disruption. Thrombin that moves to endothelium binds to thrombomodulin, where it participates in a negative feedback loop by activating-protein C, which then inactivates factors Va and VIIIa, preventing further thrombin generation. Flow and access to circulating anticoagulants further confine thrombus growth to the area of the platelet plug.

One interpretation of this model is that neither the intrinsic nor the extrinsic pathway in and of itself is sufficient for hemostasis, but together they form a single functioning pathway that requires at least 2 different cell surfaces. This separation of the procoagulant cells, platelets, from the activating extravasculature is more efficient than a separation of the protein components, because significant amounts of most of the coagulation proteins are found in the extravasculature [Miller 2000].

Hemostasis in the Surgical Setting

The surgical setting, especially with cardiopulmonary bypass, presents a number of challenges to the hemostatic process (for a review see [Edmunds 2006]). Coagulation is activated in this setting and without anticoagulants clots will rapidly form in the bypass circuit. Heparin effectively blocks this fibrin deposition and targets multiple points on the coagulation cascade by accelerating antithrombin inhibition of not only thrombin but also factors XIa, IXa, and Xa. A further benefit is gained from use of aprotinin [Day 2006, Levy 2006], a potent inhibitor of both plasmin and kallikrein that also weakly inhibits other coagulation proteins, including activated protein C and thrombin. Even in the presence of sufficient heparin to block immediate clotting, however, coagulation is activated, creating disseminated intravascular coagulation in which platelets are activated and cleared or made refractory, coagulation proteases are activated and cleared, and fibrinogen levels are reduced. The result is that the patient is at risk for bleeding.

Activation of coagulation in the bypass setting probably does not proceed by the hemostatic mechanisms described above but rather acts as if the extrinsic and intrinsic components were distinct mechanisms. The extrinsic components may be brought into play through tissue disruption leading to circulating tissue factor on procoagulant microparticles [Nieuwland 1997,

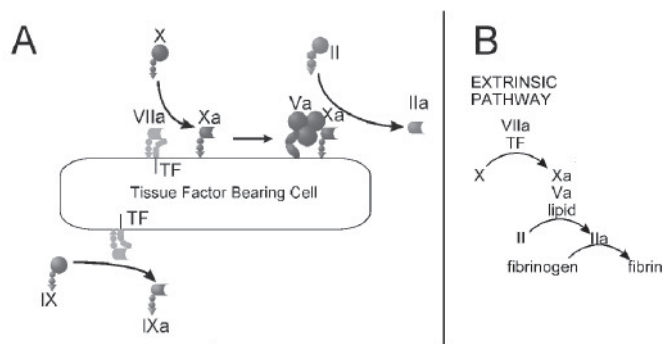


Figure 1. Initiation phase of the cell-mediated hemostasis model. A, Initiation phase on a tissue factor bearing cell. Both factors IX and X are activated but play different roles in the hemostatic process. Factor Xa with factor Va, probably derived from adherent platelets, converts a small amount of prothrombin to thrombin. This thrombin activates platelets and factors XI, VIII, and V. B, The classic extrinsic pathway with the factors tested for in the prothrombin time.

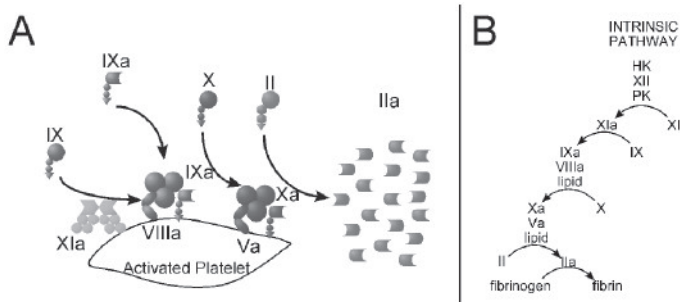


Figure 2. Propagation phase of the cell-mediated hemostasis model. A, Propagation phase on the activated platelet. Factor IXa, activated by factor VIIa/tissue factor, activates factor X on the platelet surface. This protected factor Xa moves directly into a complex with factor Va and provides a burst of thrombin. Prekallikrein, kininogen, and factor XII do not play a major role in the propagation phase. Factor XI acts to provide additional factor IXa above that produced by tissue factor. B, The classic intrinsic pathway with the factors tested for in the activated partial thromboplastin time.

De Somer 2002]. These microparticles promoted thrombus formation in vivo in a rat stasis model [Biró 2003]. This thrombin generation on tissue-factor-bearing and other microparticles may dominate the consumptive coagulopathy in cardiac surgery patients; if so, this process presents an opportunity for targeting strong blocking agents that would not disrupt hemostasis. Tissue factor around vessels appears to be associated with factor VIIa [Hoffman 2007], so that strong anti-tissue-factor agents could potentially be used without disrupting the initiation of hemostasis. One potent agent is active-site-inhibited factor VIIa, which binds to tissue factor with a higher affinity than active-factor VII and blocks tissue factor function. One study looking at a mechanical injury to rat carotid artery showed that active-site-inhibited factor VIIa had an antithrombotic effect equivalent to heparin but with half as much bleeding [Söderström 2001].

There is considerable evidence that contact-factor pathway proteins are activated during bypass (reviewed in [Levy 2003]) which supports a rationale for targeting the intrinsic pathway. One study showed that contact factors were activated, but did not show a correlation between thrombin-antithrombin III complex (TAT) levels and factor XIIa levels; however it did show a correlation with factor IX activation and TAT levels [Boisclair 1993]. Another study suggested that the primary effect of heparin on the aPTT was through blocking factor IXa activation of factor X [McNeely 1985]. When active-site-inhibited factor IXa was compared to heparin in bypass, there was no fibrin deposition in the circuit and diminished intraoperative blood loss.

PK, HK, and factor XII do not appear to play major roles in hemostasis. Although kallikrein has been targeted through addition of aprotinin to heparin, it is not clear that kallikrein is the best target. Studies on variant aprotinin molecules with enhanced affinity for kallikrein did not show any change in factor XII activation [Ohri 2001]. It has been shown that factor XII can be activated by an electronegative surface in the absence of kallikrein [Mitropoulos 1999]. This finding suggests that factor XIIa might be an ideal target for inhibition. One ex vivo study (which therefore lacked any microparticle contribution) showed that heparinized blood passed over the extracorporeal mem-

brane surface gave a 40-fold increase in TAT levels relative to the starting blood. Addition of a high concentration of a specific factor XIIa inhibitor blocked 90% of the increase [Hong 2001].

Conclusion

Understanding both the mechanism of normal hemostasis and the mechanisms in play in the consumptive coagulopathy seen in bypass surgery may allow for development of targeted agents to supplement heparin during the surgery. These targeted agents might help significantly reduce thrombin generation during the surgery while interfering minimally with the hemostatic mechanisms necessary for healing of the surgical wounds.

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Targeted Conduit Selection Using Optical Coherence Tomography in Coronary Artery Bypass Grafting

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Introduction

Although the internal thoracic artery (ITA) remains the first-choice conduit in coronary artery bypass grafting (CABG), the saphenous vein (SV) and/or radial artery (RA) are still used frequently. It is possible that the higher rate of early graft occlusion established for these conduits relative to the ITA is related to a greater prevalence of intimal irregularities [Khan 2004, Manchio 2005, Poston 2006]. Therefore the ability to judge intimal integrity in bypass conduits being considered for grafting would provide a great clinical advantage, but methods to perform this assessment are not available. Gross external inspection does not provide an estimate of the degree of endothelial cell disruption, the parameter directly linked to the risk of acute graft failure in previous studies by our group [Manchio 2005].

Catheter-based optical coherence tomography (OCT) is an infrared imaging modality that has been investigated primarily for visualizing intracoronary plaques and thrombi and facilitating intracoronary stenting [Grube 2002, Jang 2002, Bouma 2003, Pinto 2006, Rieber 2006]. Inability to image through blood has been a significant limitation to the clinical value of OCT. The intraoperative imaging of conduits for CABG to characterize the intimal quality is a novel cardiac application of OCT that may overcome this limitation because conduits can be easily flushed of blood prior to imaging. We examined the feasibility of using OCT for judging graft quality in an operative setting.

Methods

Patient Selection

We obtained institutional review board approval (IRB#H25350), and all patients provided informed consent prior to enrollment to this prospective observational study. Between March and December 2006, 27 RA and 33 SV conduits from 35 patients were evaluated.

Surgical Technique

CABG was performed via a median sternotomy, and left ITA was harvested in all patients. RA were procured using either endoscopic (n = 15) or pedicle (n = 12) techniques [Reyes 1995], whereas all SV were harvested endoscopically (VasoView6; Guidant Systems, Inc, Minneapolis, MN). Unfractionated heparin was given intraoperatively to obtain a kaolin-based activated clotting time >300 seconds and heparin level > 2 IU/mL according to protamine titration assay (HMS heparin assay cartridges, Medtronic, Inc, Minneapolis, MN). Aspirin (325 mg daily, administered orally) was given to all patients preoperatively and within 6 hours postoperatively. Procured conduits were flushed with plasmalyte solution containing glyceryl trinitrate and verapamil [He 1993] using controlled distending pressure <100 mmHg.

OCT Analysis

For in situ examinations, a 1.2 F imaging OCT probe (LightLab Imaging, Inc, Westford, MA) was inserted into the vessel. Data were processed using a proprietary OCT imaging system and displayed

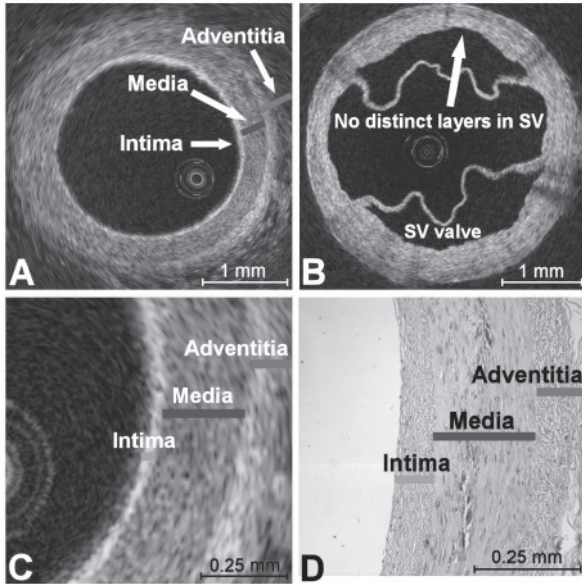


Figure 1. Normal appearance of radial arteries (RA) and saphenous veins (SV). Optical coherence tomography (OCT) imaging of the RA showed 3 distinct layers that correspond to the intima, media, and adventitia (A). However, demarcation of tissue layers was less distinct in SV (B). The clear contrast in imaging characteristics between different layers of RA (C) enabled the assessment of intimal-medial thickness (IMT) ratio that strongly correlated with histological sections (D).

as 2-dimensional tomograms to visualize the optical structure of the conduit. Plaques visualized by cross-sectional imaging were categorized as fibrous, fibrocalcific, or fibroatheromas based on prior criteria [Stary 1995]. Intimal disease was quantified by determining the intimal-medial thickness ratio (IMT) [Kume 2005]. Harvesting injury was categorized as mild when intimal disruption was restricted to the ostium of branch points and severe when the tear affected the luminal surface. Intraluminal thrombus was identified as a lobulated mass with high signal intensity and distal shadowing [Manfrini 2006].

Histological Analyses

At the completion of OCT scans, biopsy specimens for histology were obtained from discarded portions of each conduit and matched with the corresponding OCT images. These image-guided biopsy specimens were stored in solution before being embedded and frozen in cutting compound (Tissue-Tek OCT, Redding, CA). Microscopic sections were stained for elastin (Verhoff van Giesen) to visualize the internal and external elastic lamina for calculation of the IMT ratio. Selected sections were analyzed for macrophages using immunohistochemical techniques with anti-CD68 mAb (Invitrogen, Carlsbad, CA) [Tearney 2003].

Statistics

The degree of agreement of the measured IMT with OCT versus histology was defined using the Pearson correlation coefficient. Reproducibility of intimal injury and plaque characterization were determined by defining the interobserver κ correlation coefficients.

Results

RA Atherosclerosis

Normal RA showed 3 distinct layers that correspond to the intima, media, and adventitia (Figure 1). The clear contrast between

the layers enabled the measurement of IMT, which showed a strong correlation with histological sections ($R = 0.88$, $P < .001$). The demarcation of the intimal layer by OCT was less distinct in SV, reducing the strength of the correlation to histologic assessments ($R = 0.75$, $P < .01$).

OCT accurately characterized the types of plaques within RA (Figure 2). Homogeneous plaques of signal-rich intensity were classified as fibrous. Fibrocalcific plaques were categorized by areas of intimal calcification of poor intensity with well-demarcated borders. In contrast, areas of signal attenuation (ie, shadowing) and high signal variability were found to be fibroatheroma. Histologic analysis of registered sections confirmed the presence of lipid-laden macrophages within these fibroatheromatous lesions. Characterization of plaques using these criteria was reproducible, as illustrated by strong interobserver κ correlation coefficients (>0.80).

Intimal Trauma and Clots

Minor intimal damage, represented as areas of intimal injury localized to the ostium of branch points, was noted frequently within RA harvested endoscopically, but was not found within SV. On the other hand, a unique feature of endoscopic SV harvest using our current protocol was the near universal finding of residual clot strands which ranged in severity from single minute strand to near-occlusive thrombi (Figure 3). Focal areas of severe dissections were noted with endoscopic harvest SV ($n = 3$) and RA ($n = 2$), each case confirmed with histology. Severe injuries were associated with an increase in local tissue factor activity when compared to adjacent area with intact intima (3.71 versus 0.76 U/cm²).

Discussion

OCT proved to be feasible for intraoperative use with minimal impact on case flow. The high incidence of pathology that is either

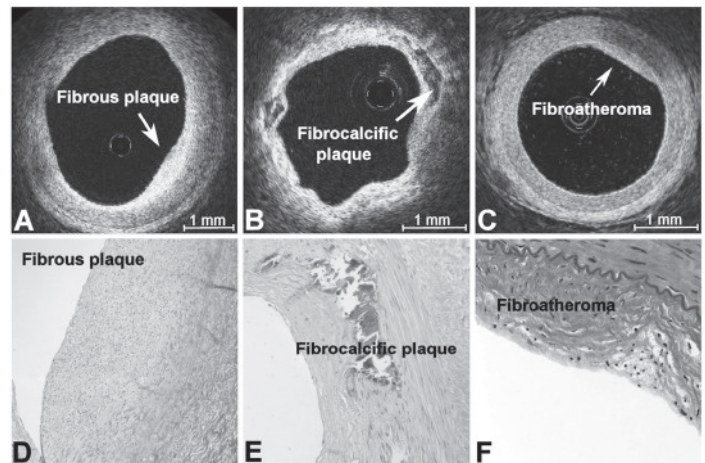


Figure 2. Characterization of plaques within radial arteries (RA). Eccentric areas of intimal thickness (ie, plaques) were characterized into 3 different types using previously established criteria. Fibrous plaque was illustrated by lesions with homogeneous and signal-rich intensity. Areas of poor signal intensity with well-demarcated borders represent intimal calcification (B). Fibroatheromatous lesions appeared on optical coherence tomography (OCT) imaging as a high-intensity layer with strong attenuation of the signal. These criteria were confirmed to correlate with the same diagnosis of plaque type with registered histologic sections taken from the same areas as the OCT image (D-F).

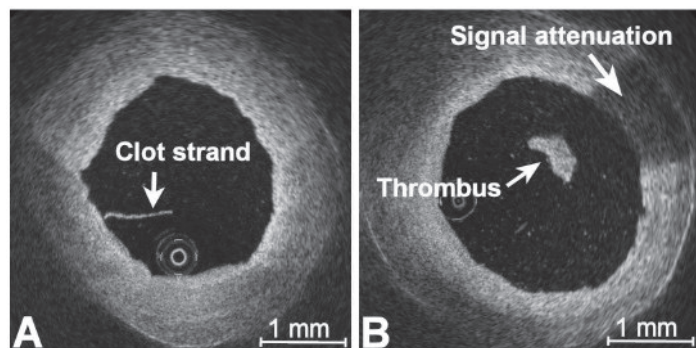


Figure 3. Retained thrombus within saphenous veins (SV). Retained thrombus appeared as an intraluminal lobulated mass with high signal intensity and produced radial signal attenuation because of the presence of entrapped red blood cells. Optical coherence tomography (OCT) readily detected residual clot strands that ranged in size from small (A) to moderate (B) but were a universal finding after endoscopic vein harvest.

preexisting (eg, atherosclerosis) or related to surgical harvesting (eg, intimal injury or clot strands) suggests that OCT evaluation could improve the selection practices for CABG conduits, thereby serving an important clinical need.

Impaired intimal quality and intimal calcification are associated with increased risk of postoperative failure of RA and SV grafts [Ruengsakulrach 2001, Zhang 2005, Kim 2006]. We identified intimal injury and other pathology within conduits using an OCT method that was reproducible and closely correlated with the findings of registered histologic sections. These areas of intimal injury detected by OCT were found to be associated with a focal increase in local tissue factor activity. In light of prior data suggesting that the local activity of tissue factor plays a key role in vascular thrombosis [Muluk 1998], OCT may help identify conduits likely to have abnormal thrombogenicity.

Residual clot strands were a unique finding of ex vivo OCT imaging of endoscopically harvested SV graft. These clots may result from stagnant blood flow within the vein during the endoscopic procedure [Burriss 2006]. If so, these clot strands would likely be preventable with heparinization given prior to the initiation of endoscopic vein harvest. OCT provides an important quality assurance tool to enable objective documentation of the success of this and/or other potential approaches to preventing clot strands.

Because of the exploratory nature of our investigation, we did not alter surgical management during the course of this study. Because conduits are often harvested in greater amounts than required for grafting, identification of abnormalities using OCT could potentially alter the portion of conduit that is selected for grafting. Additionally, in situ OCT imaging could be used to reject poor quality conduits even prior to harvest. This type of targeted conduit selection strategy could improve the quality of grafted conduits and long-term outcomes after CABG.

Conclusion

OCT is a practical and highly accurate method for detecting abnormalities within bypass conduits in real-time in the operative setting. In this pilot study, we imaged conduits that were later used as

bypass grafts and found atherosclerotic plaques, intimal calcification, clot strands, and minor and severe intimal tears. These abnormalities may indicate a conduit that is more thrombogenic and perhaps prone to early graft failure. Targeted conduit selection using OCT imaging is an area with considerable diagnostic and therapeutic potential.

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Safety and Efficacy of Antifibrinolytic Therapy: Recent Controversies and the BART Trial

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Introduction

Perioperative bleeding after cardiac surgery remains an important clinical problem. Approximately 10% of the total transfused allogeneic red cell units are administered to cardiac surgical patients. The efficacy of antifibrinolytics in decreasing blood loss and transfusion, along with an acceptable safety profile, have been frequently documented. However, the benefit of any therapy must be balanced with the risks of receiving it, and the risks of not receiving it. Morbidity and mortality have been directly related to the amount of allogeneic transfusion administered. Thus, antifibrinolytic therapies have become a standard of care for many cardiac operations, and are considered class I indications in the recently published Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists Blood Conservation Guidelines

[Society of Thoracic Surgeons Blood Conservation Guideline Task Force 2007].

The 3 main safety issues related to antifibrinolytic drugs are hypersensitivity reactions, effects on organ function, and risk for thrombotic events. Aprotinin is a heterologous protein and therefore has antigenic properties and histamine-releasing potential. Hypersensitivity reactions including anaphylaxis have occurred in aprotinin-treated patients. Adverse reactions to aprotinin occur in <1% of patients on first exposure and 2.7% on reexposure; 5% if reexposure occurs within less than 6 months and 0.9% if greater than 6 months [Dietrich 1997, 2001]. All patients treated with aprotinin should first receive an initial (test) dose to help assess the potential for allergic reactions. Prophylactic treatment with H₁/H₂ blockade and/or reexposure to aprotinin at the time

Table 1. Clinical Safety Outcomes of Antifibrinolytic Use*

Treatment versus Control	†Nonfatal MI	†CVA	†Thrombosis	†Renal Dysfunction	Mortality
Aprotinin‡	.97 (.69-1.36)	.43 (.16-1.19)	.64 (.31-1.31)	1.19 (.79-1.79)	.87 (.63-1.19)
Tranexamic acid‡	.69 (.21-2.29)	2.27 (.65-7.99)	.98 (.49-1.94)	.87 (.08-9.78)	.43 (.15-1.18)
ε-Aminocaproic acid	.90 (.30-2.76)	.26 (.03-2.36)	.20 (.01-4.14)	Not reported	1.66 (.46-6.01)

*Data from [Henry 2006]. MI indicates myocardial infarction; CVA, cerebrovascular accident.

†Data are relative risk (95% confidence interval).

‡Data include cardiac and noncardiac clinical trials.

of initiation of cardiopulmonary bypass (CPB) may alleviate the adverse effects of a hypersensitivity reaction. Administration of Trasyolol to patients with a known or suspected aprotinin exposure during the last 12 months is contraindicated; the drug is indicated for patients who are at increased risk for blood loss and transfusion. See Trasyolol (aprotinin injection) prescribing information for warnings and precautions.

All of the currently used antifibrinolytic agents are excreted by the kidney. The elimination pattern of aprotinin is biphasic, with an initial half-life of 0.7 hours and a terminal half-life of 7 hours. In patients with renal dysfunction the clearance of aprotinin is reduced and the half-life prolonged ε-Aminocaproic acid (EACA) is excreted unchanged in the urine and has an elimination half-life of 1 to 5 hours [Butterworth 1999]. Tranexamic acid is eliminated by glomerular filtration and has an elimination half-life of 2 hours. Thirty percent of the initially administered dose is recovered in the urine after 1 hour and 90% after 24 hours [Dowd 2002].

Conflicting data exist regarding the effect of aprotinin on renal function. Results of some early studies suggested potential benefit in terms of increased clearance of creatinine, sodium, and free water, whereas others found transient increases in postoperative creatinine levels. Other study results suggested that aprotinin and EACA are associated with increased renal excretion of proteins indicative of tubular injury. Concerns have been expressed about the possible prothrombotic potential of these agents to produce catheter thrombosis, vascular occlusion and myocardial infarction (MI). In the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial [Alderman 1998], the overall graft

patency differences in the aprotinin group have been attributed to practice differences at 2 of the 13 sites. Most randomized clinical studies with high-dose aprotinin have not found an increase in graft occlusion or MI compared to placebo. Similarly, Karski et al [2005] found no difference in graft patency rates using magnetic resonance imaging (MRI) in a randomized trial of 312 patients who received tranexamic acid or placebo. An association of aprotinin with a reduction in incidence of stroke has also been identified.

Data from Metaanalyses

Several metaanalyses or systematic reviews of antifibrinolytic agents have been done. The Cochrane Review revision by Henry et al [2006] found no statistically significant difference between antifibrinolytic therapies or a control in the relative risk of clinical safety outcomes (Tables 1 and 2).

Recent Observational Studies

The debate about the safety of antifibrinolytic agents in cardiac surgery has recently intensified. Mangano et al [2006] used propensity-adjusted multivariable logistic regression from observational data on 4374 patients and reported an association between use of aprotinin and adverse renal, cardiac, neurologic, and long-term outcomes. Compared to placebo, all 3 agents reduced bleeding. Karkouti et al [2005] propensity-matched 449 aprotinin-treated patients with 449 tranexamic acid-treated patients from a single center database.

Table 2. Safety Data from Reported Trials of Aprotinin (Full Dose) versus Placebo

Treatment versus Control	*CVA	*MI or CVA	*Renal Dysfunction or Event	*Renal Failure	Mortality
Sedrakyan 2004†	.53 (.31-.90)	.85 (.63-1.14)	-	1.01 (.55-1.83)	.87 (.63-1.19)
Levi 1999†	2.15 (1.12-4.11)	-	-	.55 (.34-0.90)	
Karkouti 2006 1.15 (versus tranexamic acid)	(.54-2.45)	1.20 (.51-2.81)	1.43 (1.03-1.98)	-	.91 (.54-1.52)
Mangano 2006a (primary study)	2.15 (1.14-4.06)	1.42 (1.09-1.86)	2.34 (1.27-4.31)	-	1.59 (0.76-3.34)
Mangano 2006b (complex study)	1.29 (0.71-2.35)	1.08 (.75-1.57)	2.59 (1.36-4.95)	-	.86 (0.44-1.70)

*Data are relative risk or odds ratio (95% confidence interval).

†Metaanalysis.

Table 3. Preliminary Outcomes of the BART Trial

Outcome	N (%)
Bleeding from chest tubes	93 (7.7)
Massive transfusion	30 (2.5)
Death due to hemorrhage	9 (0.7)
Reoperation for massive post-op bleeding	87 (7.2)
Any massive bleeding event	135 (11.2)

They found no difference in transfusion rates and as association of aprotinin use with renal dysfunction. These 2 studies have generated many questions and much discussion in the medical and nonmedical literature. Another recent report by Dietrich et al [2006] suggested that aprotinin doses based on higher weight were not associated with increased risk of renal dysfunction.

The BART Trial

The BART trial (Blood conservation using Antifibrinolytics: Randomized Trial in high-risk cardiac surgery) should provide more definitive data on safety of antifibrinolytic drugs. This Canadian study is the largest blinded randomized controlled trial of antifibrinolytic drugs. It is designed to determine whether aprotinin is superior to EACA and tranexamic acid in decreasing massive postoperative bleeding in high-risk cardiac surgery (ie, redo coronary artery bypass graft [CABG], redo aortic or mitral valve replacement [MVR], initial MVR, and combined cardiac or ascending aortic procedures). Patients are randomized to receive either aprotinin, EACA, or tranexamic acid. The prespecified primary outcomes are (1) massive bleeding, defined as bleeding from chest tubes exceeding 1.5 L over an 8-hour period; (2) massive transfusion (replacement of blood exceeding 10 red blood cell units over 24 hours); (3) death due to hemorrhage (evidence of bleeding for at least 2 hours prior to death or confirmed as a cause on autopsy); or (4) reoperation for massive postoperative bleeding (bleeding in excess of 200 mL/h for more than 2 hours and/or tamponade). Secondary outcomes include allogeneic transfusions, renal dysfunction/failure, stroke, and cardiovascular events. More than 2000 patients have already been enrolled in 18 Canadian centers. The first blinded interim analysis included 1210 patients, 64% of whom underwent combined procedures, and 13% of whom had redo CABG. The incidence of massive bleeding as defined by any of the 4 outcomes above was 11.2%. Fatal/life-threatening adverse events (excluding troponin MI) occurred in 12.2%, and serious events occurred in 36.0% of patients. The incidence of renal dysfunction was 17%, and dialysis was done on 3% of patients. The overall mortality was 5.0%. Other outcomes are shown in Table 3.

After this interim analysis, the Data Safety Monitoring Board and Safety Board (DSMB) urged continuation of the trial with no change. A second interim analysis was recently completed, after which the DSMB unanimously recommended completion of the study as planned. The BART trial and other future publications should help

to resolve some of the controversies about the safety and efficacy of antifibrinolytic drugs.

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The Role of PAR Receptors and Serine Protease Inhibitors in Cerebral Microcirculation and Ischemic Brain Injury

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Introduction

Kallikrein is one of the primary enzyme systems involved in regulating inflammatory processes. While being an effective antifibrinolytic, full-dose aprotinin therapy—approximately 6 million kallikrein inactivator units (KIU) for an adult patient—was designed to achieve plasma concentrations of approximately 200 KIU/mL as an anti-inflammatory strategy [Royston 1992]. The plasma levels of aprotinin achieved, 4.3 $\mu\text{mol/L}$, fall within the inhibitory range of kallikrein, trypsin, plasmin, and elastase from leukocytes as well as other inflammatory mediators [Fritz 1983]. This report focuses on the interaction between several serine proteases and various inflammatory processes in ischemic injury.

Kallikrein, Bradykinin, and Cerebral Edema

Kallikrein plays a fundamental role after an ischemic injury by interacting to produce bradykinin, a key enzyme responsible for cerebral edema formation. Kallikrein also incites complement and coagulation cascade activation, increases in vascular permeability, activation of white blood cells (WBC), and chemotaxis [Francel 1992]. Both kallikrein and bradykinin are potent serine protease enzyme, and both aprotinin and soybean trypsin inhibitor attenuated cerebral edema with less lactate and greater postischemia preservation of high-energy phosphates, demonstrating that bradykinin plays a key role in the development of postischemic cerebral edema.

Serine Protease Inhibitors and Cerebral Vasoreactivity

In a neonatal piglet model, Aoki and colleagues [1994] demonstrated that administration of aprotinin decreased cerebral edema formation after 60 minutes of hypothermic circulatory arrest. Magnetic resonance spectroscopy was also used to demonstrate that aprotinin minimized the amount of cerebral edema formation and allowed accelerated recovery of cerebral high-energy phosphates, and aprotinin-treated animals showed greater preservation of in vivo cerebral and systemic acetylcholine-mediated vasodilation. Other serine proteases have similarly demonstrated an influence on cerebral vasoreactivity.

A preventive effect of the serine protease inhibitor FUT-175 (nafamostat mesilate) against cerebral vasospasm was demonstrated in a clinical study of 34 high-risk patients with thick and diffuse subarachnoid hemorrhage (SAH) demonstrated by computed tomography corresponding to Fisher group 3 [Kaminogo 1998]. In this study all patients underwent surgery within 96 hours following SAH and received the thromboxane A₂ synthetase inhibitor, OKY-046, as part of standard care. FUT-175 (40-160 mg/day) was administered dur-

ing the initial 4 days after surgery. A database of 455 patients treated without FUT-175 formed the control group. FUT-175 significantly decreased the incidence of symptomatic vasospasm in patients with severe neurological grade (Hunt and Hess grade 3, $P < .02$; Hunt and Hess grade 4, $P < .02$). The incidence of favorable outcome was 76.5% in the FUT group and 60.4% in the non-FUT group, but this difference was not statistically significant. When patients of Hunt and Hess grade 5 were excluded, however, the FUT group had a significantly improved outcome ($P < .05$). This study suggests that FUT-175 has an additive effect to OKY-046 in preventing vasospasm in high-risk patients with severe SAH.

The results of this study by Kaminogo et al [1998] are consistent with those of a previous, nonrandomized study in patients with acute SAH. That study [Yanamoto 1992] also demonstrated a significantly lower incidence of cerebral vasospasm and improved neurological outcomes with treatment with nafamostat. These clinical results are consistent with laboratory studies. In a rabbit model of cerebral vasospasm induced by injection of polystyrene beads into the cerebrospinal fluid space, nafamostat demonstrated significant attenuation of vasospasm [Yanamoto 1994]. Until recently the mechanism of this preservation of vasoreactivity was not well understood, but recent observations on the interaction between serine protease inhibitors and thrombin receptors may provide some insights.

Thrombin, Protease-Activated Receptors, and Stroke

Although the platelet-preservation effects associated with aprotinin administration during cardiopulmonary bypass (CPB) were initially thought to reflect nonspecific antifibrinolytic inhibition of plasmin activity, more recent studies have identified this effect as very specific to aprotinin, mediated through a dose-related blockade of a novel class of thrombin receptors, protease-activated receptor (PAR) receptors.

Aprotinin has been shown to block the platelet release reaction in a dose-dependent fashion by inhibiting the activation of the PAR-1 receptor by thrombin [Poullis 2000]. This finding helps to explain the previous observations of aprotinin-associated preservation of platelet morphology and functionality [Huang 1993, Lavee 1993]. PAR receptors are also identified on the vascular endothelium and are increasingly recognized as having a fundamental role in the response to ischemic brain injury [Striggo 2001]. Day and colleagues [2006] recently demonstrated that endothelial cell activation by thrombin and downstream inflammatory responses can also be inhibited by aprotinin in vitro through blockade of PAR-1. It is interesting to

speculate that preservation of endothelial PAR receptors may provide a potential mechanism for effects of serine proteases on the vasoreactivity of the cerebral microcirculation and vasospasm observed in the studies cited above.

One serine protease that is associated closely with and produced in response to central nervous system injury is thrombin. Thrombin, via PAR receptor activation, plays a fundamental role in the response to cerebral ischemia [Wang 2003, Xi 2003]. Thrombin enters the injury cascade in the brain via a compromised blood-brain barrier or possibly from endogenous prothrombin. Thrombin mediates its action through the PAR family (PAR-1, -3, and -4). PARs belong to the superfamily of G protein-coupled receptors with a 7-transmembrane domain structure and are activated by proteolytic cleavage of their N-terminus.

Recent studies of platelets from patients presenting with acute cerebral ischemia have provided further indirect clinical evidence for massive thrombin generation in the presence of acute cerebral ischemia [Jurk 2004]. Current investigations have identified a powerful cerebroprotective effect associated with absence of PAR-1 receptor activation. A 3-fold reduction in infarct volume after transient focal cerebral ischemia has been demonstrated using a strain of mice lacking PAR-1, leading these authors to speculate that inhibition of PAR-1 may provide a novel cerebroprotective mechanism for decreasing neuronal damage associated with ischemia [Jurk 2004]. Their findings are consistent with those of studies in ischemic rat brain, demonstrating increased expression of PAR-1 and PAR-3 on microglia only 12 and 48 hours after an ischemic insult, but not on day 7 postischemia [Henrich-Noack 2006]. PAR-4 was expressed exclusively in neuronal cells, a finding that suggests that PAR-1 and PAR-3 may be involved in thrombin-modulated initiation of postischemic inflammation, and PAR-4 may be associated with neuronal degeneration.

Leukocytes and Brain Injury

Another aspect of the whole-body inflammatory response during ischemia is nonspecific activation of white cells and platelets. Activation of WBC has also been implicated in acute cerebral ischemic injury. Normally neutrophils circulate centrally within a vascular blood column. Release of various cytokines, including interleukin-1, interleukin-6, and others from perivascular monocytes and damaged endothelium, induces expression of a class of WBC receptors known as selectins that induce margination of WBC and endothelial rolling, bringing leukocytes into contact with specific endothelial receptors and intercellular adhesion molecules, which ultimately facilitate WBC binding to endothelium and transmigration and release of lytic enzymes into perivascular tissue [Price 2003]. Acute infiltration of WBC in the presence of ischemic stroke has recently been demonstrated clinically using an indium-labeled neutrophil scan in patients with clinical symptoms [Heinel 1994].

In an ischemia/reperfusion rat model of global forebrain ischemia, leukopenia significantly decreased tissue injury after a transient cerebral ischemic event. In control animals, a given ischemic insult produced 70% hemispheric lesion, and in vinblastine-treated animals

there was a significant reduction of infarcted tissue to 20%, associated with preserved electroencephalographic and somatosensory evoked potential activity [Heinel 1994]. In the presence of clinically relevant concentrations of aprotinin there is a significant reduction in transmigration of WBC into areas of damaged endothelium [Asimakopoulos 2000]. Whether this also occurs in brain is currently unclear.

In a rat cerebral ischemia/reperfusion model, a dose-related decrease in cerebral infarct size associated with a significant decrease in WBC tissue infiltration, was demonstrated in response to urinary trypsin inhibitor, a serine protease inhibitor with a spectrum of action not dissimilar from aprotinin [Yano 2003]. This result provides further evidence in favor of the hypothesis that in the presence of an acute ischemic injury such as may occur during cardiac surgery, administration of a multimodality antiinflammatory agent such as aprotinin can produce a potent cerebroprotective effect [Levy 1995, Smith 1996, Frumento 2003, Sedrakyan 2004].

Summary

Serine protease inhibitors can broadly impact inflammatory responses to ischemia through several mechanisms. These may include an antibradykinin effect, which can reduce cerebral edema formation; suppression of thrombin-mediated PAR-1 receptor activation, which has a significant effect in decreasing nonspecific platelet activation and the modulation of cerebral PAR-mediated pathways; inactivation or suppression of interleukin and tumor necrosis factor; and suppression of WBC activation and inhibition of WBC transmigration into perivascular tissue. When these various antiinflammatory mechanisms are considered in light of the intriguing association with decreased incidence of perioperative stroke, a specific cerebroprotective effect associated with clinical use of serine protease inhibitors appears increasingly plausible [Murkin 1997, 2001].

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Cardiac and Vascular Surgery: Impact of Inflammation, Transfusion and Microvascular Perfusion on Cerebral Protective Strategies

CME Assessment Test

Please write the letter of your answers in the POST-TEST ANSWER on p. 17.

- Which of the following is true regarding the “systemic inflammatory response” to on-pump CABG surgery?
 - It is composed of multiple systemic imbalances to the fibrinolytic, complement, coagulation, and inflammatory pathways.
 - It results in systemic (bleeding) and local (organ injury) complications perioperatively.
 - It causes end-organ injury through a combination of ischemia reperfusion injury and infiltration by cytotoxic leukocytes.
 - All of the above.
- Which of the following statements most accurately characterizes aprotinin?
 - Aprotinin is possibly unique in its multifaceted mechanism of action.
 - Aprotinin is antifibrinolytic but not antithrombotic.
 - Aprotinin has not been shown to have antiinflammatory effects.
 - All of the above.
- Which of the following statements is true regarding the cell-mediated model of normal hemostasis?
 - Protein interactions are the key components of the intrinsic and extrinsic pathways, and the cell-mediated model focuses on the surface on which these reactions occur rather than the reactions themselves.
 - The cell-mediated hemostasis model envisions coagulation proceeding in 4 overlapping phases: initiation, amplification, propagation, and equilibrium.
 - Both A and B.
 - Neither A nor B.
- Which of the following mechanisms affect hemostasis during cardiopulmonary bypass?
 - Coagulation is activated in this setting, and without anticoagulants clots will rapidly form in the bypass circuit.
 - Activation of coagulation in the bypass setting probably does not proceed by normal hemostatic mechanisms but rather acts as if the extrinsic and intrinsic components were distinct mechanisms.
 - Thrombin generation on tissue-factor-bearing and other microparticles has the potential to contribute to the consumptive coagulopathy seen in bypass patients.
 - All of the above.
- Which of the following is/are true regarding findings revealed by use of optical coherence tomography (OCT) for real-time intraoperative evaluation of conduits?
 - Evidence of minor intimal damage was rare after endoscopic but common after open RA harvest.
 - Endoscopic harvest was not associated with severe intimal injury.
 - Residual clot strands were found in endoscopically harvested SV and RA.
 - None of the above.
- Which of the following problems in CABG surgery may be addressed with OCT?
 - Poor circulation in patient extremities.
 - Residual clot strands in harvested SV.
 - Presurgical patient anxiety.
 - All of the above.
- The 3 main safety issues related to antifibrinolytic drugs are:
 - Hypersensitivity reactions, high cost, and increased risk for cerebral edema.
 - Hypersensitivity reactions, effects on organ function, and increased risk for thrombotic events.
 - Drug interactions, effects on organ function, and narrow therapeutic range.
 - None of the above.
- The BART study (Blood conservation using Antifibrinolytics: Randomized Trial in high-risk cardiac surgery) is investigating which of the following?
 - Whether dose modification can reduce the risk of hypersensitivity to aprotinin.
 - Whether aprotinin is more cost-effective than EACA and tranexamic acid.
 - Whether aprotinin is superior to EACA and tranexamic acid in decreasing massive postoperative bleeding in high-risk cardiac surgery.
 - All of the above.
- Which of the following is NOT a mechanism by which Serine protease inhibitors can broadly impact inflammatory responses to ischemia?
 - An antibradykinin effect, which can reduce cerebral edema formation.
 - Stimulation of thrombin-mediated PAR-1 receptor activation, which has a significant effect in increasing nonspecific platelet activation.
 - Inactivation or suppression of interleukin and tumor-necrosis factor.
 - Suppression of WBC activation and inhibition of WBC transmigration into perivascular tissue.
- Which of the following is true regarding kallikrein?
 - Kallikrein is one of the primary enzyme systems involved in regulating inflammatory processes.
 - Kallikrein plays a fundamental role after an ischemic injury by interacting to produce bradykinin, a key enzyme responsible for cerebral edema formation.
 - A and B.
 - Neither A nor B.

Cardiac and Vascular Surgery: Impact of Inflammation, Transfusion and Microvascular Perfusion on Cerebral Protective Strategies

Evaluation Form

Medical Education Resources, Inc., respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment of participation for this activity.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

Extent to Which Program Activities Met the Identified Objectives Upon completion of this activity, the participant should be able to:

Identify links between coagulation and inflammation in cardiac surgery.

5 4 3 2 1

Discuss ways to stabilize the hemostatic response through the use of antifibrinolytic agents.

5 4 3 2 1

Demonstrate an understanding of ways to control anticoagulation during cardiopulmonary bypass.

5 4 3 2 1

Evaluate the safety and efficacy of antifibrinolytic therapy on cardiac surgery patients.

5 4 3 2 1

Overall Effectiveness of the Activity

Was timely and will influence how I practice 5 4 3 2 1

Will assist me in improving patient care 5 4 3 2 1

Fulfilled my educational needs 5 4 3 2 1

Avoided commercial bias or influence 5 4 3 2 1

Impact of the Activity

The information presented: (check all that apply)

- Reinforced my current practice/treatment habits
- Will improve my practice/patient outcomes
- Provided new ideas or information I expect to use
- Enhanced my current knowledge base

Will the information presented cause you to make any changes in your practice?

- Yes No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

Future Activities

Do you feel future activities on this subject matter are necessary and/or important to your practice?

- Yes No

Please list any other topics that would be of interest to you for future educational activities:

Follow-up

As part of our ongoing continuous quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

- Yes, I would be interested in participating in a follow-up survey.
- No, I'm not interested in participating in a follow-up survey.

Additional comments about this activity:

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POST-TEST ANSWERS

1	2	3	4	5	6	7	8	9	10

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