Inflammation: An Old Problem with New Solutions

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Inflammation is a localized protective reaction of tissue to irritation, injury, or infection that serves as a protective response to provide host surveillance and destroy or quarantine both harmful agents and damaged tissue (1–4). We survive as a species because of our ability to generate inflammatory responses. Inflammation represents complex humoral and cellular interactions that generate or express thrombin, complement, cytokines, neutrophils, adhesion molecules, and multiple inflammatory mediators (5,6). However, inflammatory responses can be exaggerated out of proportion to the original insult and produce injury in the host including bleeding, respiratory failure, myocardial dysfunction, renal insufficiency, and neurocognitive defects (7). Besides multiorgan system dysfunction, inflammatory responses also accompany the development of pain, and inflammatory mediators may also play an important role in the treatment of pain (8). In cardiac surgery, inflammatory responses have been referred to as a systemic inflammatory response syndrome (SIRS) similar to sepsis, and the rationale for off-pump coronary artery bypass grafting (OPCAB) is to avoid the inflammatory effects of cardiopulmonary bypass (CPB) (9,10). This review will focus on understanding the clinical relevance of inflammation, reviewing mechanisms involved in inducing responses, and the protein and cellular mediators involved. Novel aspects of inflammation and potential therapeutic approaches to prevention in surgical patients will be reviewed.

Hemostasis and Inflammation

Hemostasis and inflammation are closely linked via a network of both humoral and cellular components including proteases of the clotting and fibrinolytic cascades (especially tissue factor) (4,11–12). Various clinical conditions may cause systemic activation of coagulation, the most severe of which is disseminated intravascular coagulation (DIC). DIC is a widespread systemic activation of coagulation, resulting in diffuse fibrin deposition in small and midsize vessels, producing microvascular dysfunction and contributing to organ failure. In DIC, platelets and coagulation factors are depleted. Conditions that may lead to DIC perioperatively include sepsis, eclampsia, trauma, and CPB. Hemostatic activation by thrombin generation contributes to inflammatory processes because of cross-talk between inflammation and coagulation, during which thrombin and other peptides activate the coagulation system and inflammation.

Inflammation-induced hemostatic activation can occur by means of tissue factor (TF) because TF is expressed on cytokine-activated mononuclear cells, and also after vascular injury (13,14). Coagulation components and their products, including thrombin and factor Xa, have proinflammatory effects. Thrombin also has direct chemoattractant activity for neutrophils, monocytes, and is a potent activator of mast cells (15–17). Vascular endothelial cells perform a pivotal role in mediating responses to systemic inflammation and the cross-talk between coagulation and inflammation (18,19). Endothelial cells respond to the cytokines expressed and released by activated leukocytes but can also release cytokines themselves (20–22). Neutrophils and inflammatory mediators are also important in pain and analgesia (22).

Thrombin can induce various cellular responses involved in inflammation and is also a potent activator of endothelial cells, causing neutrophil adherence, activation, and subsequent (neutrophil-mediated) damage to the endothelium (21–23). Thrombin receptor activation on leukocytes increases the release of chemotactic and inflammatory cytokines (21–25). Thrombin also directly activates protease-activated receptors (PARs). PARs are G-protein-coupled receptors that use a novel mechanism of extracellular proteolytic cleavage that is translated into a transmembrane signal. Thus, thrombin activation by tissue injury in surgical patients can alter the local balance between activation and inhibition of the coagulation cascade and promote thrombin generation at sites of injury (26–32).

Pain as an Inflammatory Response

When tissue is injured after surgery or trauma or invaded by leukocytes in inflammation, numerous

mediators are delivered into the circulation and/or liberated from local or extravasated inflammatory cells at the site. Proalgesic mediators include proinflammatory cytokines, chemokines, nerve growth factor, and prostaglandins, produced by invading leukocytes or by local cells (22). Analgesic mediators, which counteract pain, are also produced in inflamed tissues (22). These include antiinflammatory cytokines and opioid peptides. Interactions between leukocyte-derived opioid peptides and opioid receptors can lead to potent, clinically relevant inhibition of pain (analgesia) (22). Opioid receptors are present on peripheral endings of sensory neurons. Opioid peptides are synthesized in circulating leukocytes, which migrate to inflamed tissues directed by chemokines and adhesion molecules. Under stressful conditions or in response to releasing agents (e.g., corticotropin-releasing factor, cytokines, norepinephrine), leukocytes can secrete opioids (22). They activate peripheral opioid receptors and produce analgesia by inhibiting the excitability of sensory nerves and/or the release of excitatory neuropeptides (22).

Inflammation Associated with Ischemia Reperfusion Injury

After interruption of blood flow in an organ, ischemia-reperfusion (I/R) injury can occur with manifestations that range from reversible postischemic organ dysfunction to permanent tissue damage including myocyte necrosis (33–35). I/R injury is associated with an acute inflammatory response that is mediated by cytokines, chemokines, and adhesion molecules that recruit neutrophils, monocytes, and other inflammatory cells that lead to damage of ischemic myocardium. TF and thrombin generation activation can occur after I/R injury and may be independent of fibrin deposition (35). Thrombin can contribute to local inflammation and tissue damage by activation of a family of PAR receptors (36,37) that stimulate cells to express cytokines, such as interleukin (IL)-1, and IL-6; chemokines, such as IL-8 and monocyte chemotactic protein-1 (MCP-1); and adhesion molecules (e.g., P-selectin, E-selectin, and ICAM-1) (21–22,36–38).

Inflammatory Cells

Neutrophils represent important inflammatory cells but other cells including mast cells and basophils are also involved in acute inflammation and may also be involved in inflammatory responses in surgical patients. Mast cells are tissue-fixed inflammatory cells that are distributed in the heart, lung, and skin. When activated, mast cells release multiple mediators that affect vascular endothelial cells, inflammatory cells, and vascular smooth muscle (39). Mast cells have been suggested to play important roles in a series of inflammatory disorders, including anaphylaxis. Mast cells therefore may play a pivotal role in linking coagulation and inflammation (10–20). Different agents can degranulate mast cells by multiple complex pathways that may not be different from pathologic activation by immunoglobulin (Ig)E (40–42). Both mast cells and basophils contain stored inflammatory mediators including histamine and other chemical mediators associated in anaphylaxis and other inflammatory processes (1); they also constitutively express plasma membrane receptors that bind with IgE antibodies (43–46).

Disseminated Intravascular Coagulation

Multiple mechanisms can produce DIC, as previously discussed in surgical patients including sepsis, eclampsia, tissue injury, and CPB. Inflammatory changes during CPB are similar to the pathophysiologic changes occurring in sepsis or systemic inflammatory response syndrome (SIRS) (47–48). DIC can also occur after cardiopulmonary bypass. In DIC, overactivation of thrombin and/or clotting leads to bleeding complications resulting from depletion of coagulation proteins, platelets, and endothelial dysfunction to produce microvascular dysfunction and a thrombotic state. DIC is characterized by decreased platelet counts, low fibrinogen, elevated prothrombin time (PT), and partial thromboplastin time (PTT), and elevated D-dimer levels, changes that can also occur in the pharmacologically naïve patient who undergoes CPB (49,50). Acquired antithrombin III (ATIII) deficiency in the perioperative cardiac surgical period may be related to the preoperative use of heparin, the effects of hemodilution, and/or CPB-related consumption. ATIII levels as low as 40%–50% activity, which are similar to levels observed with heterozygous hereditary deficiency, are commonly seen during CPB (51,52). Because the data in DIC suggests ATIII may play a major role in reducing inflammation and/or end-organ dysfunction, we have further expanded this consideration to cardiac surgical patients and are investigating whether ATIII represents an important therapeutic intervention that may alone, or in conjunction with other therapies, further reduce the inflammatory sequelae (53,54).

Complement/Neutrophil Activation

Neutrophil activation can occur after complement activation by immunologic (antibody mediated: IgM, IgG-antigen activation) or nonimmunologic (heparin-protamine, endotoxin) pathways (1). C5a interacts

with specific high-affinity receptors on white blood cells and platelets, initiating leukocyte chemotaxis, aggregation, and activation. Investigators have implicated neutrophil activation in producing the clinical manifestations of transfusion reactions, pulmonary vasoconstriction after protamine reactions, and transfusion-related acute lung injury (TRALI) (1). New anticomplement strategies using a monoclonal antibody (Pexelizumab) against C5a represent a promising modality of antiinflammatory therapy (55).

Therapeutic Approaches to the Inflammatory Response

Therapeutic strategies can be directed at modulating multiple aspects of the inflammatory response, including coagulation, contact activation, cytokines, neutrophils, intracellular molecular targets, and surface protein strategies (e.g., adhesion molecules) (56–60). Aprotinin is a serine protease inhibitor derived from bovine lung that inhibits trypsin, chymotrypsin, plasmin, tissue plasminogen activator, and kallikrein. The precise mechanism of action of aprotinin in reducing blood loss and transfusion requirement is not clear, but there appears to be a dose dependency in its antiinflammatory effects. Reduction of allogeneic blood transfusions are also important as part of antiinflammatory strategies, and aprotinin has been shown to consistently reduce bleeding and the need for transfusions. Although corticosteroids have been studied as antiinflammatory agents, controlled, placebo-controlled studies have not demonstrated efficacy in cardiac surgical patients, although they are indicated in patients with asthma and reactive airway disease. Aprotinin has a different mechanism of action and may attenuate other aspects of the inflammatory response to CPB, including inhibiting neutrophil adhesion and activation. Aprotinin has been demonstrated to be highly effective in reducing bleeding and transfusion requirements in high-risk patients undergoing repeat median sternotomy or in patients who are taking aspirin. Results from multicenter studies of aprotinin show there is no greater risk of early graft thrombosis, myocardial infarction (MI), or renal failure in aprotinin-treated patients (59–61). From the study of aprotinin in repeat coronary artery surgery, the incidence of stroke was significantly lower in aprotinin-treated patients (59). Aprotinin also selectively blocks the proteolytically activated thrombin receptor on platelets, the protease-activated receptor 1 (PAR1) (61,62). Aprotinin also appears to affect novel antiinflammatory targets. Aprotinin has been shown to exert an antiinflammatory effect by preventing the capacity of leukocytes to transmigrate through vascular endothelium (63,64).

Other novel strategies in current development include complement inhibition. Myocardial injury and dysfunction in acute infarction and during cardiac surgery with CPB produces undesirable inflammatory responses in which the complement cascade plays a major role. Pexelizumab is a humanized, monoclonal, single-chain antibody fragment that inhibits C5 by blocking its cleavage into active forms. Prospective, randomized, double-blind, placebo-controlled trials using pexelizumab during percutaneous coronary intervention after acute myocardial infarction (AMI), or in patients undergoing coronary artery bypass graft (CABG) with CPB, have demonstrated a reduction in morbidity and mortality. Thus, pexelizumab represents a promising therapeutic option with sustained benefit both in AMI and during CABG with CPB (55,64).

The Future

Inflammation is increasingly being recognized as an important cause of perioperative morbidity and mortality with wide-ranging manifestations. Coagulation and inflammation are closely linked via a network of both humoral and cellular components including proteases of the clotting and fibrinolytic cascades. The challenge for the future will be to identify a pharmacologic agent or other technique that will decrease inflammatory injury, coagulation, and eventually improve patients' outcomes. Future research will be directed at finding the unique pharmacologic and/or biologic agents or combinations that may effectively attenuate these pathological responses.

References

1. Levy JH. Anaphylactic reactions in anesthesia and intensive care, 2nd ed. Stoneham: Butterworth-Heinemann, 1992.
2. Delves PJ, Roitt IM. Advances in immunology: the immune system. N Engl J Med 2000;343:37–49,108–17.
3. Kay AB. Advances in immunology: allergy and allergic diseases. N Engl J Med 2001;344:30–7.
4. Marcus AJ. Thrombosis and inflammation as multicellular processes: significance of cell-cell interactions. Semin Hematol 1994;31:261–9.
5. Walport MJ. Advances in immunology: complement—first of two parts. N Engl J Med 2001;344:1058–66.
6. Walport MJ. Advances in immunology: complement—second of two parts. N Engl J Med 2001;344:1140–4.
7. Warltier DC, Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology 2002;97:215–52.
8. White FA, Bhangoo SK, Miller RJ. Chemokines: integrators of pain and inflammation. Nat Rev Drug Discov 2005;4:834–44.
9. Mojcik C, Levy JH. Systemic inflammatory response syndrome and anti-inflammatory strategies. Ann Thorac Surg 2001;71:745–54.
10. Cheng DC, Bainbridge D, Martin JE. Off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. Anesthesiology 2005;102:188–203.
11. Davie EW, Fujikawa K, Kisiel W. The coagulation cascade: initiation, maintenance, and regulation. Biochemistry 1991;30:10363–70.

12. Cicala C, Cirino G. Linkage between inflammation and coagulation: an update on the molecular basis of the crosstalk. Life Sci 1998;62:1817–24.
13. Levi M, van der Poll T, Buller HR. Bidirectional relation between inflammation and coagulation. Circulation 2004;109: 2698–704.
14. Levi M. Current understanding of disseminated intravascular coagulation. Br J Haematol 2004;124:567–76.
15. Levi M, van der Poll T. Two-way interactions between inflammation and coagulation. Trends Cardiovasc Med 2005;15:254–9.
16. Bar-Shavit R, Kahn A, Wilner GD. Monocyte chemotaxis: stimulation by specific exosite region in thrombin. Science 1983;220:728.
17. Struova SM, Dugina TN, Khgatian SV, et al. Thrombin-mediated events implicated in mast cell activation. Semin Throm Hemost 1996;22:145.
18. ten Cate H, Schoenmakers SH, Franco R, et al. Microvascular coagulopathy and disseminated intravascular coagulation. Crit Care Med. 29(7 Suppl):S95–7.
19. Verrier ED, Boyle EM, eds. Endothelial cell injury in cardiovascular surgery. Ann Thorac Surg 1997;64:4.
20. Reinhart K, Bayer O, Brunkhorst F, Meisner M. Markers of endothelial damage in organ dysfunction and sepsis. Crit Care Med 2002;30(5 Suppl):S302–12.
21. Johnson K, Choi Y, DeGroot E, et al. Potential mechanisms for a proinflammatory vascular cytokine response to coagulation activation. J Immunol 1998;160:5130–5.
22. Rittner HL, Machelska H, Stein C. Leukocytes in the regulation of pain and analgesia. J Leukoc Biol 2005 Oct 4; In Press.
23. Nicholson AC, Nachman RL, Altieri DC, et al. Effector cell protease receptor-1 is a vascular receptor for coagulation factor Xa. J Biol Chem 1996;271:28407–13.
24. Esmon CT. Cell mediated events that control blood coagulation and vascular injury. Ann Rev Cell Biol 1993;9:1–26.
25. Hoffman M, Monroe DM 3rd. A cell-based model of hemostasis. Thromb Haemost 2001;85:958–65.
26. Coughlin SR. Protease-activated receptors in vascular biology. Thromb Haemost 2001;86:298–307.
27. Versteeg HH, Peppelenbosch MP, Spek CA. The pleiotropic effects of tissue factor: a possible role for factor VIIa-induced intracellular signalling? Thromb Haemost 2001;86:1353–9.
28. Edgington TS, Mackman N, Brand K, Ruf W. The structural biology of expression and function of tissue factor. Thromb Haemost 1991;66:67–79.
29. Esmon CT. Role of coagulation inhibitors in inflammation. Thromb Haemost 2001;86:51–6.
30. Jordan JE, Zhao ZQ, Vinten-Johansen J. The role of neutrophils in myocardial ischemia-reperfusion injury. Cardiovasc Res 1999;43:860–78.
31. Drake TA, Morrissey JH, Edgington TS. Selective cellular expression of tissue factor in human tissues. Am J Pathol 1989; 134:1087–97.
32. Levi M, de Jonge E, van der Poll T, ten Cate H. Advances in the understanding of the pathogenetic pathways of disseminated intravascular coagulation result in more insight in the clinical picture and better management strategies. Semin Thromb Haemost 2001;27:569–75.
33. Boyle EM Jr, Canty TG Jr, Morgan EN, et al. Treating myocardial ischemia-reperfusion injury by targeting endothelial cell transcription Ann Thorac Surg 1999;68:1949–53.
34. Levitsky J, Gurell D, Frishman WH. Sodium ion/hydrogen ion exchange inhibition: a new pharmacologic approach to myocardial ischemia and reperfusion injury. J Clin Pharmacol 1998;38: 887–97.
35. Vinten-Johansen J, Yellon DM, Opie LH. Postconditioning: a simple, clinically applicable procedure to improve revascularization in acute myocardial infarction. Circulation 2005;112: 2085–8.
36. Déry O, Corvera CU, Steinhoff M, Bunnett NW. Proteinase-activated receptors: novel mechanisms of signaling by serine proteases. Am J Physiol 1998;274:C1429–52.
37. Vu TK, Hung DT, Wheaton VI, Coughlin SR. Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. Cell 1991;64:1057–68.
38. Sugama Y, Tiruppathi C, Offakidevi K, et al. Thrombin-induced expression of endothelial P-selectin and intercellular adhesion molecule-1: a mechanism for stabilizing neutrophil adhesion. J Cell Biol 1992;119:935–44.
39. Church MK, Levi-Schaffer F. The human mast cell. J Allergy Clin Immunol 1997;99:155.
40. Galli SJ, Wershil BK. The two faces of the mast cell. Nature 1996;381:21–2.
41. Tannenbaum S, Oertel H, Henderson W, Kaliner M. The biologic activity of mast cell granules. I. Elicitation of inflammatory responses J Immunol 1980;125:325–35.
42. Kanwar S, Kubes P. Mast cells contribute to ischemia-reperfusion-induced granulocyte infiltration and intestinal dysfunction. Am J Physiol 1994;267:G316–21.
43. Enerback L. The differentiation and maturation of inflammatory cells involved in the allergic response: mast cells and basophils. Allergy 1997;52:4–10.
44. Valent P, Bettelheim P. The human basophil. Crit Rev Oncol Hematol 1990;10:327–52.
45. Costa JJ, Weller PF, Galli SJ. The cells of the allergic response: mast cells, basophils, and eosinophils. JAMA 1997;278:1815–22.
46. Beaven MA, Metzger H. Signal transduction by Fc receptors. Immunol Today 1993;14:222–6.
47. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. Chest 1997;112:676–92.
48. Vincent JL, Sun Q, Dubois MJ. Clinical trials of immunomodulatory therapies in severe sepsis and septic shock. Clin Infect Dis 2002;34:1084–93.
49. Levi M. Pathogenesis and treatment of DIC. Thromb Res 2005; 115(Suppl 1):54–5.
50. Kalter RD, Saul CM, Wetstein L, et al. Cardiopulmonary bypass: associated hemostatic abnormalities. J Thorac Cardiovasc Surg 1979;77:427–35.
51. Zaidan JR, Johnson S, Brynes R, et al. Rate of protamine administration: its effect on heparin reversal and antithrombin recovery after coronary artery surgery. Anesth Analg 1986;65: 377–80.
52. Hashimoto K, Yamagishi M, Sasaki T, et al. Heparin and antithrombin III levels during cardiopulmonary bypass: correlation with subclinical plasma coagulation. Ann Thorac Surg 1995;58: 799–805.
53. Levy JH, Despotis GJ, Szlam F, et al. Recombinant human transgenic antithrombin in cardiac surgery: a dose finding study. Anesthesiology 2002;96:1095–102.
54. Levy JH, Weisinger A, Ziomek CA, Echelard Y. Recombinant antithrombin, production and role in cardiovascular disorders. Semin Thromb Hemost 2001;27:405–16.
55. Fleisig AJ, Verrier ED. Pexelizumab: a C5 complement inhibitor for use in both acute myocardial infarction and cardiac surgery with cardiopulmonary bypass. Expert Opin Biol Ther 2005;5: 833–9.
56. Chaney MA. Corticosteroids and cardiopulmonary bypass: a review of clinical investigations. Chest 2002;21:921–31.
57. Barnes PJ. Molecular mechanisms of corticosteroids in allergic diseases. Allergy 2001;56:928–36.
58. Levy JH, Pifarre R, Schaff H, et al. A multicenter, placebo-controlled, double-blind trial of aprotinin to reduce blood loss and the requirement of donor blood transfusion in patients undergoing repeat coronary artery bypass grafting. Circulation 1995;92:2236–44.
59. Miller BE, Tosone SR, Tam VKH, et al. Hematologic and economic impact of aprotinin in reoperative pediatric cardiac surgery. Ann Thorac Surg 1998;66:535–40.
60. Alderman EL, Levy JH, Rich J, et al. International multi-center aprotinin graft patency experience (IMAGE). J Thorac Cardiovasc Surg 1998;116:716–30.

61. Landis RC, Asimakopoulos G, Poullis M, et al. The antithrombotic and antiinflammatory mechanisms of action of aprotinin Ann Thorac Surg 2001;72:2169–75.
62. Poullis M, Manning R, Laffan M, et al. The antithrombotic effect of aprotinin: actions mediated via the protease activated receptor 1. J Thorac Cardiovasc Surg 2000;120:370–8.
63. Asimakopoulos G, Thompson R, Nourshargh S, et al. An anti-inflammatory property of aprotinin detected at the level of leukocyte extravasation. J Thorac Cardiovasc Surg 2000;120:361–9.
64. Verrier ED, Stanton SK, Taylor KM, et al. Terminal complement blockade with pexelizumab during coronary artery bypass graft surgery requiring cardiopulmonary bypass: a randomized trial. JAMA 2004;291:2319–27.