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Inflammatory Responses and CNS Injury: Implications, Prophylaxis, and Treatment

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Early detection of perioperative stroke is essential if there is to be any opportunity to improve outcome. If there is suspicion of cerebral embolic stroke, scanning with computerized tomography can rule out acute hemorrhage and demonstrate diagnostic changes in a majority of patients within 5 hours of onset of symptoms [Nabavi 2002]. Strategies for reperfusion of ischemic tissue may include intraarterial thrombolysis in select patients with acute ischemic stroke even after recent cardiac operation. In one series, 13 patients with acute ischemic stroke within 12 days of cardiac operation underwent intraarterial thrombolysis within 6 hours of stroke symptom onset [Moazami 2001]. Recanalization was complete in 1 patient and partial in 5, and 7 patients had low flow. Neurologic improvement occurred in 5 patients (38%). One patient needed a chest tube for hemothorax; 2 others received transfusions for low hemoglobin. No operative intervention for bleeding was necessary.

In addition to thrombolysis, mechanical clot removal may be attempted [Chapot 2002]. Thromboaspiration requires favorable anatomy and a fresh nonadhesive clot. It reduces the time for recanalization, has no hemorrhagic risk, and may prevent distal clot migration. Thromboaspiration may be attempted as an adjunct or alternative to intraarterial fibrinolysis for basilar artery recanalization. If massive cerebral gas embolism is suspected and hyperbaric facilities are available, confirmation can be obtained by early single-photon emission tomography (SPET) and hyperbaric oxygen therapy instituted. This process was successfully undertaken in a case of paradoxical air embolism in a patient undergoing percutaneous nephrolithotripsy in the prone position and presenting with blindness and neurological deficits 8 hours later. Treatment with hyperbaric oxygen therapy was successful in this case [Droghetti 2002].

Adjunctive measures are also important. One important consideration is the avoidance of cerebral hyperthermia such as commonly occurs in the postoperative period. There is compelling experimental evidence demonstrating an almost exponential increase in the extent of neuronal cell death associated with an ischemic insult in the presence of a 2- or 3-degree increase in brain temperature compared with normothermia [Dietrich 1990]. Animal studies have further demonstrated the susceptibility of ischemic brain to even delayed hyperthermia, with temperature elevations even 24 hours after injury and after a normothermic interval, resulting in increased areas of cerebral infraction [Kim 1996]. Consistent with this finding, in a prospective study by Nathan et al, avoidance of cerebral hyperthermia in the immediate postoperative period after cardiac surgery was shown to result in improved cognitive outcomes in comparison to conventional temperature management for patients undergoing coronary artery bypass (CAB) surgery [Nathan 2001]. Fever has also been shown to worsen prognosis in acute stroke [Azzimondi 1995], strongly suggesting that postoperative fever must be treated aggressively especially in perioperative patients in whom cerebral injury is either suspected or demonstrated. Moderate hypothermia is also undergoing clinical trials in acute stroke patients [Krieger 2001] and has been demonstrated clinically to decrease glutamate, glycerol, lactate, and pyruvate levels in the "tissue at risk" area of cerebral infarct [Berger 2002].

Neutrophil accumulation and neutrophil-mediated tissue damage in the postischemic brain have been well documented in numerous animal studies and in humans during the past 3 decades. Activation of vascular endothelial cells and leukocytes by local and humoral factors increases the cell surface expression of a family of adhesion molecules termed selectins, which promote low-affinity leukocyte rolling over the surface of endothelial cells. This process is an obligatory preliminary step leading to subsequent firm attachment, at which point leukocytes can exert numerous cytotoxic effects leading to microvascular plugging, stasis, and thrombosis [Tilton 2002]. In an animal model, it has been demonstrated that mild hypothermia significantly reduces endothelial adhesion molecule expression, acute (neutrophil) and subacute (monocyte) leukocyte infiltration, and microglial activation up to 7 days following an acute cerebral ischemic insult [Wang 2002].

Activation of platelets and leukocytes has been demonstrated during CPB as a part of a systemic inflammatory response [Colman 1990]. That such nonspecific activation may exacerbate the impact of focal cerebral ischemia such as may follow microgaseous or macroatheromatous cerebral emboli can be surmised based on responses seen in animal studies. Following 3 hours of middle cerebral artery occlusion and 1 hour of reperfusion in a baboon occlusion/reperfusion model, del Zoppo et al demonstrated capillary-obstructing polymorphonuclear leukocytes in the microvascular bed

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following middle cerebral artery reperfusion during focal ischemia [del Zoppo 1991]. In another study white blood cell (WBC) involvement in the generation of cerebral infarcts was evaluated following ischemia and reperfusion injury in the rat [Heinel 1994]. Control and leukopenic rats (induced by vinblastine, WBC counts <1500/mm^3) were compared in a global forebrain ischemic model after 1 hour of ischemia and 1 hour 15 minutes of reperfusion. They demonstrated that the area infarcted in leukopenic rats was significantly less than infarcts generated in corresponding controls (21% ± 16% versus 70% ± 16%). In addition, electroencephalographic activity was preserved in all leukopenic animals when compared to controls, both during ischemia and after reperfusion. Both these studies indicate a key role for white blood cells in the generation of cerebral damage after a cerebral ischemic insult.

The recognition that serine protease inactivators can significantly decrease various aspects of the inflammatory response has shed new light on prospective mechanisms whereby these agents may act to decrease the magnitude of a cerebral ischemic insult [Murkin 1997]. The demonstration that administration of urinary trypsin inhibitor modulated the effect of ischemia-reperfusion injury in rats and resulted in a significant decrease in neutrophil infiltration in the ischemic hemisphere compared with saline control, is further evidence suggestive of efficacy [Yano 2003]. In a clinical study of patients undergoing CPB, low-dose aprotinin administration was found to have an antiinflammatory effect similar to that of methylprednisolone in blunting release of systemic tumor necrosis factor and neutrophil integrin CD11B up-regulation, a marker of white cell activation, in comparison to untreated controls [Hill 1995]. Additionally, in patients after major vascular surgery, activation of neutrophils manifesting as increased superoxide production and impaired chemotaxis has been shown to be significantly suppressed by aprotinin administration [Lord 1992]. In CPB patients, aprotinin has also been shown to suppress the rise of the inflammatory mediator and leukocyte activator interleukin-6 during CPB in comparison to a control group [Whitten 1992]. Using intravital microscopy of rat omentum, suppression of leukocyte capillary transmigration by clinically relevant dosages of aprotinin has been demonstrated [Asimakopoulis 2000].

The demonstration by Poullis and colleagues that aprotinin inhibits thrombin-induced platelet activation by preventing proteolysis of the protease activated receptor (PAR-1) provides another potential mechanism for serine protease inactivator-induced cerebroprotection [Poullis 2000]. The localization of PARs in brain regions particularly vulnerable to ischemic insults as well as distinct alterations in the expression pattern of PARs after experimental ischemia support the notion of an important role of extracellular serine proteases and PARs in cerebral ischemia [Striggow 2001]. As such, the further demonstration of the wide-spread distribution of PAR receptors on a variety of endothelial surfaces, as well as on platelets and neurophils, is evidence of another possible locus of action of serine protease inactivators [Dery 1998, Yano 2003]. Further work identifying an essential role of PAR1 in thrombin-induced microglial activation provides further impetus for strategies aimed at blocking thrombin signaling through PAR1, acknowledging that these may be therapeutically valuable for diseases associated with cerebral vascular damage and significant inflammation with microglial activation [Suo 2002].

These findings suggests several possible mechanisms of action for aprotinin, consistent with the results from several clinical trials. Overall, a significantly lower incidence of stroke was found in aprotinin-treated patients in 2 meta-analyses utilizing the North American database of randomized controlled, double-blind trials of full-dose aprotinin versus placebo [Smith 1996, Murkin 2002]. In the meta-analysis of Smith and Muhlbaier, 2.4% of the placebo group experienced stroke compared to only 1.0% in the treatment group [Smith 1996]. The more recent analysis showed that of 1867 patients, 2.6% of control patients versus 1.0% of aprotinin treated patients were identified as having a cerebrovascular accident as an adverse event [Murkin 2002].

In a recent multicenter prospective observational study by Mangano [Mangano 2002] of 5065 CABG patients, the effect of perioperative aspirin therapy on mortality and various adverse outcomes was examined. The incidence of stroke in the group who received aspirin (up to 650 mg) within 48 hours after revascularization was 1.3% compared with 2.6% in the nonaspirin group. Whether this difference reflects the antiinflamatory properties of aspirin acting via inhibition of cyclo-oxygenase–related pathways, or reflects more of an antithrombotic mechanism in such patients after cardiac surgery as may have aortic cannulation-related intimal flap and thrombus formation [Ura 2000], or even the relative avoidance of postoperative fever and cerebral hyperthermia [Kim 1996, Nathan 2001] is currently unclear. It does appear as though such therapies can be expected to have a salutary effect on the incidence of central nervous system injury and now need to be rigorously evaluated in randomized prospective trials.

REFERENCES

Asimakopoulis G, Thompson R, Nourshargh S, et al. 2000. An anti-inflammatory property of aprotinin discovered at the level of leukocyte extravasation. J Thorac Cardiovasc Surg 120:361-9.

Azzimondi G, Bassein L, Nonino F, et al. 1995. Fever in acute stroke worsens prognosis. A prospective study. Stroke 26:2040-3.

Berger C, Schabitz WR, Georgiadis D, Steiner T, Aschoff A, Schwab S. 2002. Effects of hypothermia on excitatory amino acids and metabolism in stroke patients: a microdialysis study. Stroke 33:519-24.

Chapot R, Houdart E, Rogopoulos A, Mounayer C, Saint-Maurice JP, Merland JJ. 2002. Thromboaspiration in the basilar artery: report of two cases. AJNR Am J Neuroradiol 23:282-4.

Colman RW. 1990. Platelet and neutrophil activation in cardiopulmonary bypass. Ann Thorac Surg 49:32-4.

del Zoppo GJ, Schmid-Schonbein GW, Mori E, Copeland BR, Chang CM. 1991. Polymorphonuclear leukocytes occlude capillaries following middle cerebral artery occlusion and reperfusion in baboons. Stroke 22:1276-83.

Dery O, Corvera CU, Steinhoff M, Bunnett NW. 1998. Proteinase-activated receptors: novel mechanisms of signaling by serine proteases. Am J Physiol 274:C1429-52.

Dietrich WD, Busto R, Valdes I, Loor Y. 1990. Effects of normothermic versus mild hyperthermic forebrain ischemia in rats. Stroke 21:1318-25.

Droghetti L, Giganti M, Memmo A, Zatelli R. 2002. Air embolism: diagnosis with single-photon emission tomography and successful hyperbaric oxygen therapy. Br J Anaesth 89:775-8.

Heinel LA, Rubin S, Rosenwasser RH, Vasthare US, Tuma RF. 1994. Leukocyte involvement in cerebral infarct generation after ischemia and reperfusion. Brain Res Bull 34:137-41.

Hill GE, Alonso A, Spurzem JR, et al. 1995. Aprotinin and methylprednisolone equally blunt cardiopulmonary bypass-induced inflammation in humans. J Thorac Cardiovasc Surg 110:1658-62.

Kim Y, Busto R, Dietrich WD, Kraydieh S, Ginsberg MD. 1996. Delayed postischemic hyperthermia in awake rats worsens the histopathological outcome of transient focal cerebral ischemia. Stroke 27:2274-80.

Krieger DW, De Georgia MA, Abou-Chebl A, et al. 2001. Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. Stroke 32:1847-54.

Lord RA, Roath OS, Thompson JE, et al. 1992. Effect of aprotinin on neutrophil function after major vascular surgery. Br J Surg 79:517-21.

Mangano DT, Multicenter Study of Perioperative Ischemia Research Group. 2002. Aspirin and mortality from coronary bypass surgery. N Engl J Med 347:1309-17.

Moazami N, Smedira NG, McCarthy PM, et al. 2001. Safety and efficacy of intraarterial thrombolysis for perioperative stroke after cardiac operation. Ann Thorac Surg 72:1933-7.

Murkin JM. 1997. Cardiopulmonary bypass and the inflammatory response: a role for serine protease inhibitors? J Cardiothorac Vasc Anesth 11:19-23.

Murkin JM, Maurer J, Niemcryk S. 2002. Full dose aprotinin administration is associated with a significant decrease in perioperative stroke in patients undergoing elective cardiac surgery: a meta-analysis. Ann Thorac Surg 73:S374.

Nabavi DG, Kloska SP, Nam EM, et al. 2002. MOSAIC: multimodal stroke assessment using computed tomography: novel diagnostic approach for the prediction of infarction size and clinical outcome. Stroke 33:2819-26.

Nathan HJ, Wells GA, Munson JL, Wozny D. 2001. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial. Circulation 104(12 suppl 1):I85-91.

Poullis M, Manning R, Laffan M, Haskard DO, Taylor KM, Landis RC. 2000. The antithrombotic effect of aprotinin: actions mediated via the proteaseactivated receptor 1. J Thorac Cardiovasc Surg 120:370-8.

Smith PK, Muhlbaier LH. 1996. Aprotinin: safe and effective only with the full-dose regimen. Ann Thorac Surg 62:1575-7.

Striggow F, Riek-Burchardt M, Kiesel A, et al. 2001. Four different types of protease-activated receptors are widely expressed in the brain and are upregulated in hippocampus by severe ischemia. Eur J Neurosci 14:595-608.

Suo Z, Wu M, Ameenuddin S, et al. 2002. Participation of protease-activated receptor-1 in thrombin-induced microglial activation. J Neurochem 80:655-66.

Tilton RG, Berens KL. 2002. Functional role for selectins in the pathogenesis of cerebral ischemia. Drug News Perspect 15:351-7.

Ura M, Sakato R, Nakayama Y, et al. 2000. Ultrasonic demonstration of manipulation-related aortic injuries after cardiac surgery. J Am Coll Cardiol 35:1303-10.

Wang GJ, Deng HY, Maier CM, Sun GH, Yenari MA. 2002. Mild hypothermia reduces ICAM-1 expression, neutrophil infiltration and microglia/monocyte accumulation following experimental stroke. Neuroscience 114:1081-90.

Whitten CW, Latson TH, Allison PM, et al. 1992. Does aprotinin inhibit cardiopulmonary bypass-induced inflammation? [abstract] Anesthesiology 77:A266.

Yano T, Anraku S, Nakayama R, Ushijima K. 2003. Neuroprotective effect of urinary trypsin inhibitor against focal cerebral ischemia-reperfusion injury in rats. Anesthesiology 98:465-73.

Yano T, Anraku S, Nakayama R, Ushijima K. 2003. Neuroprotective effect of urinary trypsin inhibitor against focal cerebral ischemia-reperfusion injury in rats. Anesthesiology 98:465-73.