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Deformable Emboli and Inflammation: Temporary or Permanent Damage?

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Abstract: Neurologic sequelae after cardiopulmonary bypass have a multi-factorial etiology. Although it is typically thought that a neurologic dysfunction means a focal lesion, symptoms of a brain disorder can be initiated by metabolic disruption such as from hyper- or hypoglycemia, hypercalcemia, renal and hepatic injury, fatigue, and anesthesia. However, one of the most important causes of acute neurologic dysfunction is edema. Brain swelling is associated with the systemic inflammatory response and the passage of deformable microemboli. The larger question is whether acute symptoms associated with brain swelling because of a breakdown of the blood–brain barrier contributes to a long-term negative outcome caused by cell loss. **Keywords:** cardiopulmonary bypass, microemboli, brain injury. *JECT. 2007;39: 289–290*

INTRODUCTION

Remarkable strides have been made in reducing death and stroke during and after cardiac surgery. As the etiologic factors associated with neurologic injury have been identified and eliminated, the patient's chance of escaping life-saving surgical intervention with an intact brain has greatly improved over the last decade.

However, although significant improvements have been made in the design of the extracorporeal circuits, cardiopulmonary bypass (CPB) remains associated with a risk for non–life-threatening neurologic complications. The injurious cascade related to CPB includes complement activation, adherent neutrophils, transmigration of leukocytes, production of oxygen-derived free radicals and proteolytic enzymes, embolic infarctions, and vasogenic edema, all of which possibly contribute to impaired neurobehavioral function postoperatively. However, emboli, both particulate and deformable, in the form of gaseous (1) and lipid microemboli, seem to be more of a major contributor to long-term neurologic dysfunction than previously appreciated.

The traditional view of how an embolus causes damage is by the occlusion of a vessel on the arterial side. The resultant lesion volume is affected by factors such as collateral circulation, capillary density, metabolic rate, and temperature of the ischemic tissue at the time of the occlusion. The key factor predicting the level of damage was presumed to be the focal cessation of flow to a fixed location, affecting a finite volume of tissue, in a specific arterial distribution and/or watershed area.

In an effort to describe the mechanism associated with ischemia/re-perfusion injury, most animals models of stroke or infarct revolved around stopping blood flow to a vascular bed by constricting a vessel using ligatures or floating a thread into a major vessel until it restricted downstream flow or even strangling the subject. What was seldom used in these experiments were actual emboli, or at least biologic emboli. These models are designed to eventually evaluate treatment strategies, as opposed to prevention of injury, the only adequate form of neuroprotection.

Microspheres have been substituted for biologic emboli for the purpose of causing a repeatable injury and volume of lesion. Of course, most of these studies are performed on young rodents with a perfectly smooth cortex, thus providing heuristic instead of practical insights into potential mechanisms of cerebral ischemia, at least in rats. The question has to be asked as to whether any of these models reflect real-life events in old people undergoing CPB.

The difficulty with most traditional models of embolization is that emboli behave differently depending, not only on their composition, but how they were manipulated before their delivery to a vascular bed. For example, normobaric microbubbles at normothermia will be absorbed according to the ideal gas law, but agitated, aspirated air bubbles in a protein bath (i.e., blood) will become "foam" with a lipoprotein sheath. Thus, an air bubble is transformed into a particulate embolus with a gas core and will not be absorbed until the sheath breaks down. Furthermore, the exact same embolus will behave differently in

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the gut, which has arterio-venous shunts, than it will in the cerebral vasculature, which has neither shunts nor a lymph system to remove metabolic waste. The brain does not have the ability to regenerate itself as do other organ systems, making cell loss secondary to microembolic insult a much more significant injury to the brain.

In a closed container such as the skull, the brain has a very limited ability to maintain adequate perfusion in the face of edematous challenge and an increase in intracranial hypertension. As deformable emboli transit, or are "extruded," through the cerebral circulation, the resultant breakdown of the blood–brain barrier (BBB) causes marked brain edema and cellular stress, as evidenced by heat shock protein and potential cell loss. Instead of an ischemic infarct, cell loss is initiated, which may eventually result in sufficient loss of mass that the ventricles will be noticeable enlarged (2). A generalized loss of brain mass will result in reduced brain function but not crisp, easily identified neurologic syndromes such as aphasia or a visual field cut.

BBB dysfunction has been suggested to be associated with the transient brain edema shown by magnetic resonance imaging after CPB and increased ventricular volume in long-term follow-up studies (2–5).

The BBB ensures an optimally controlled homeostasis of the brain's internal environment by regulating the transport of water, blood cells, and solutes through unique cerebral intercellular junctions: adherence junctions, tight junctions, gap junctions, and complexus adherentes. The passage, almost in the form of an extrusion, of microemboli through the vascular bed cause an endothelial disruption and initiate the inflammatory cascade. The final product is the loss of brain mass as damaged neurons die over the following months (2). This scenario potentially explains why patients often show acute symptoms that abate, but at the end of a year, these same patients are performing at a reduced level compared with patients who did not exhibit short-term deficits (6,7).

One of the consequences of the systemic inflammatory response to CPB is the activation of endothelial cells and their subsequent dysfunction (8). This process of endothelial dysfunction implies functional changes in the physiology of blood vessels, which may lead to problems of tissue perfusion. Of importance to the development of endothelial injury is the interaction between endothelial cells and neutrophils. After CPB, blood vessels are prone to leak. The resultant extravasation of fluid from the vascular compartment decreases shear forces within the blood vessels and increases contact between endothelial surfaces and circulating leukocytes. Because there are also increased levels of inflammatory cytokines and other vascular stimuli (e.g., complement anaphylotoxins, inflammatory lipids) in patients with atherosclerosis, both endothelial cells and leukocytes express cellular adhesion molecules on their surface. These adhesion molecules regulate the movement of leukocytes from the vascular compartment into the perivascular and interstitial compartments (9). Activated leukocytes further contribute to the endothelial injury by releasing oxygen radicals and degradative enzymes at the endothelial surface.

Our research suggests that to best protect the brain we must protect the endothelium. Traditionally, it is thought that an embolus must occlude a vessel to cause an ischemic infarct. Unfortunately, it is more complicated. We believe it is the interaction between the patient's preoperative endothelial health and intraoperative embolic events that precipitate the systemic inflammatory response, including breakdown of the BBB.

In addition, we have shown that gaseous and lipid microemboli can initiate endothelial dysfunction by being "extruded" through the microvascular bed. An activated endothelium is much more susceptible to injury. If a particulate embolus is captured earlier in its progression through a vascular bed, which has been activated by the previous passage of a deformable embolus, it will cause a larger ischemic lesion. The passage of microbubbles will initiate the adhesion of neutrophils in the capillary bed, which retard blood flow and substrate delivery. In addition to the transmigration of the leukocytes into the brain substance that cause brain swelling, the white cells are metabolically active and compete for a reduced supply of O_2 and glucose.

The only truly effective protection for the brain from the ravages of CPB-induced inflammation and microembolization is prevention through improvements in CPB technology and methods.

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