Cerebral dysfunction – Pathophysiology of central nervous functions

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Technological advancements and innovations in surgical and anesthetic technique have allowed surgical treatment of cardiovascular disease to be offered to an increasing number of elderly patients that suffer from a significant number of comorbidities. It is this group of patients that is at greatest risk for neurological injury after cardiac surgery. Neurologic injury can be classified as cerebral vascular accidents such as stroke and coma (incidence 1-5%) and neurocognitive dysfunction (incidence 8% to 40%). All of these can result in loss of independence or may limit the improvement in quality of life that these patients usually experience after heart surgery.

The exact etiology of cardiac surgery-associated cerebral injury remains incompletely understood. Cerebral embolism and hypoperfusion exacerbated by ischemia/reperfusion injury are likely to be the primary underlying causes [1]. Inflammation (both cerebral and systemic), cerebral edema, blood brain barrier dysfunction, hyperthermia, and a genetic susceptibility to injury or genetically defined inability to repair following injury have all been implicated [2-5]. Embolization of particulate and gaseous material into the cerebral microvasculature resulting in focal areas of cerebral ischemia has been well studied [6,7], but evidence showing a direct association between cerebral microembolic load and post-operative cognitive dysfunction is conflicting [7-10]. It may be that quality rather than quantity of cerebral emboli plays a more important role in the pathogenesis of cerebral injury. Global cerebral hypoperfusion may result from the non-pulsatile nature of cardiopulmonary bypass (CPB) [11], and cerebral edema has been demonstrated by MRI in the post-operative period [12]. Cerebral and systemic inflammatory pathways can be activated during CPB leading to direct and indirect injury of brain cells [5,13,14].

Perioperative cerebral injury following cardiac surgery appears to be a multifactorial disorder with significant inter-patient variability in the susceptibility to cerebral injury as well as in the recoverability after these injuries, and poorly predicted by clinical and procedural risk factors. The variability may in part be due to genetic differences among patients. The apolipoprotein genotype (APOE) was one of the first genetic variants linked to cognitive decline after cardiac surgery when Tardiff et al. showed a significant association between the presence of APOE ε4 allele and change in cognitive test score in measures of short-term memory at 6 weeks post-operatively [15]. It has also been shown to be a factor affecting a number of other types of cerebral injury including Alzheimer's disease and traumatic brain injury [16-18]. However, when Steed et al. attempted to replicate the findings of Tardiff et al. with a larger sample size, they found no association between post-operative cognitive decline and either individual APOE genotypes or the presence or absence of the ε4 allele [19]. The general consensus is that APOE is one of hundreds of variants that may play a role in post-operative cerebral injury, but its individual effect is unlikely to be clinically significant. In more recent studies, prothrombotic and proinflammatory genetic polymorphisms including CRP and IL-6 single nucleotide polymorphisms (SNP) have been implicated in both post-cardiac surgery stroke and cognitive decline [5,20]. Most recently, two candidate gene polymorphisms with additive effects associated with a reduction in the evidence of cognitive decline following cardiac surgery were identified. In 513 patients, logistic regression revealed that in addition to age, baseline cognition, and years of education, a CRP 1059 G/C SNP and a SELP (P-selectin) 1087 G/A SNP were significantly associated with postoperative cognitive decline [5]. Functionally, these CRP and SELP SNPs were associated with reductions in serum CRP and platelet activation respectively, suggesting that therapies aimed at reducing the perioperative inflammatory and prothrombotic state may be beneficial. In summa-

ry, these findings suggest that specific genes may modulate the incidence and variability of cerebral injury after cardiac surgery.

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