Characteristics, incidence, and pathomechanisms of neurological damage during cardiac surgery

H. P. Grocott

Departments of Anesthesiology and Surgery, University of Manitoba, Winnipeg, Manitoba, Canada

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Modern-day cardiac surgery, made possible by the advent of cardiopulmonary bypass (CPB) almost six decades ago, continues to be challenged by the risk of neurologic injury. While catastrophic injury was common in the early days of CPB, advances in perfusion, anesthetic and surgical techniques now allow the vast majority of patients to undergo surgery without major morbidity or mortality. However, variable degrees of cerebral injury (ranging in severity from the most subtle to the most severe) still occur. With over 1,000,000 patients worldwide undergoing various cardiac operations annually, understanding the incidence, significance and etiology with the subsequent development of neuroprotective strategies is of paramount importance.

Incidence and significance

Neurologic injury after CPB represents a group of variably occurring deficits ranging from neurocognitive dysfunction, occurring in approximately 25 - 80% of patients, to overt stroke occurring in 1-5% of patients (1-5). The significant disparity between studies in the incidence of these adverse cerebral outcomes relates in part to their definition as well as other methodological differences (such as the timing of neurologic examination) in the determination of both neurologic and neurocognitive outcome. For example, cognitive deficits range as high as 80% of patients at discharge, 10-35% six or more weeks after CABG, with 10-15% present more than a year after surgery. A recurrence of higher rates of cognitive deficits occurs 5 years after surgery where as many as 43% of patients have documented deficits (2). In addition, retrospective versus prospective assessment of neurologic deficits account for a significant portion of this inconsistency, as well as the experience and expertise of the examiner.

The significance to the patient of neurologic injury cannot be over emphasized. To have a patient's heart successfully treated by the planned operation only to discover that the patient no longer functions as well cognitively or is immobilized from a stroke, can have substantial quality of life and financial consequences (4-6). In addition, mortality following CABG, although having reached relatively low levels in the past decade (approximately 1% overall), is now increasingly attributable to cerebral injury (5).

Risk Factors

Risk factors for cerebral injury vary depending on whether one considers stroke or neurocognitive injures. Most studies outlining risk factors have focused principally on stroke with few describing risk factors for neurocognitive dysfunction. The preoperative risks of post-cardiac surgery cognitive loss include factors such as a poor baseline (preoperative) cognitive state, years of education (i.e., with a more advanced education being protective), age, diabetes, and CPB time are frequently described (7,8).

Stroke is better characterized and although various studies differ as to all the risk factors, certain patient characteristics consistently demonstrate an increased risk for cardiac surgery-associated neurologic injury. In a study of 2,108 patients from 24 centers in a study conducted by the Multicenter Study of Perioperative Ischemia (McSPI), incidence of adverse cerebral outcome after CABG surgery was determined and the risk factors analyzed. Two types of adverse cerebral outcomes were defined: Type I – non-fatal stroke, transient ischemia attack (TIA), stupor or coma at time of discharge, or death caused by stroke or hypoxic encephalopathy; and Type II – new deterioration in intel-

lectual function, confusion, agitation, disorientation, memory deficit without evidence of focal injury. 129 of the 2,108 (6.1%) patients had an adverse cerebral outcome in the perioperative period. Type I outcomes occurred in 66 of 2,108 (3.1%) patients with Type II outcomes occurring in 63 of 2,108 (3.0%) patients. Stepwise logistic regression analysis identified 8 independent predictors of Type I outcomes and 7 independent predictors of Type II outcomes.

In a subsequent analysis from the same study database, a stroke risk index using preoperative factors was developed. This risk index allowed for the preoperative calculation of the stroke risk based on the weighted combination of the preoperative factors including age, unstable angina, diabetes mellitus, neurologic disease, prior coronary cardiac surgery, vascular disease, and pulmonary disease (9). Of all the factors in the McSPI analysis, as well as in multiple other analyses (4,5,10-13), age appears to be the most overwhelmingly robust predictor of both stroke as well as neurocognitive dysfunction after cardiac surgery. Indeed, Tuman et al. have described that age has a greater impact on neurologic outcome than it does on perioperative myocardial infarction and/or low cardiac output states after cardiac surgery (13). The influence of gender on adverse perioperative cerebral outcomes after cardiac surgery has recently been evaluated. Women appear to be at higher risk for stroke after cardiac surgery than men (14). With respect to adverse cognitive outcome after cardiac surgery, Hogue et al. have described that although the frequency of cognitive dysfunction after cardiac surgery is similar for women and men, women appear more likely to suffer deficits in the visuospatial cognitive domain (15).

Another consistent risk factor for stroke after cardiac surgery relates to the presence of cerebrovascular disease, and in a related way, atheromatous disease of the aorta. With respect to cerebrovascular disease, patients who have had a prior stroke or TIA are more likely to suffer a perioperative stroke (14,16-18). Indeed, even in the absence of symptomatic cerebrovascular disease, such as the presence of a carotid bruit, the risk of stroke increases with the severity of the carotid disease. Breslau et al. reported that Doppler-detected carotid disease increased the risk of stroke after cardiac surgery by threefold (19). Similarly, Brener et al. described that a carotid stenosis > 50% increased the risk of stroke from 1.9% to 6.3% (20).

Although the presence of cerebrovascular disease is a risk factor for perioperative stroke, it does not always correlate well with the presence of significant aortic atherosclerosis (21). Atheromatous disease of the ascending, arch, and descending thoracic aorta has been consistently implicated as a risk factor for stroke in cardiac surgical patients (22-25). The increased use of transesophageal echocardiography (TEE) and epiaortic ultrasonography has added new dimensions both to the detection of aortic atheromatous disease and in the understanding of its relationship to stroke risk. It has allowed the diagnosis of atheromatous disease to be made in a more sensitive and detailed manner contributing greatly to the information regarding potential stroke risk. The risk of cerebral embolism from aortic atheroma was described early in the history of cardiac surgery (26) and has repeatedly been described in detail since (4,5,27-30). For example, Katz et al. found that the incidence of stroke was 25% in patients with a mobile atheromatous plaque in the aortic arch compared with a stroke rate of 2% in those with limited atheromatous disease (31). Studies have consistently reported higher stroke rates in patients with increasing atheromatous aortic involvement (particularly the ascending and arch segments) (32).

Etiology

Stroke and neurocognitive dysfunction are frequently grouped together when considering etiology; this likely misrepresents the differing etiologies of these injuries. The following section will deal with both stroke and cognitive injury with their respective etiologies being differentiated where appropriate.

Emboli, both macroemboli (such as atheromatous plaque) and microemboli (both gaseous and particulate) are generated during CPB, many of which find their way to the cerebral vasculature (33). Whereas macroemboli are responsible for stroke, microemboli are fundamental to the development of neurocognitive dysfunction. Sources for the microemboli are numerous and include those generated de novo from the interactions of blood within the CPB apparatus (platelet-fibrin aggregates, for example) and those generated within the body by the generation and mobilization of atheromatous material or entrainment of air from the operative field. Other sources for emboli include lipid-laden debris that can be added by the cardiotomy (34). Other gaseous emboli may be generated though injections into the venous reservoir of the CPB apparatus itself (35,36).

Numerous studies outline the relationship between emboli and cognitive decline after cardiac surgery (37-

39). However, one of the major limitations in understanding this relationship has been the relative inability to discern between gaseous and particulate microemboli. Typically, Doppler ultrasonography has been used to measure cerebral embolic signals. However, Doppler cannot reliably distinguish between gaseous and particulate emboli (40). In addition to Doppler evidence, Moody et al. (33) have performed histologic analyses on brains from cardiac surgical patients describing the presence of millions of cerebral emboli represented as small capillary arteriolar dilations (SCADs).

The impact of aortic atheroma on cognitive decline is incompletely understood. Where it is widely known (both from non-surgical and cardiac surgical studies) that there is a clear relationship between the presence of aortic atheroma and stroke (22, 41-43), the relationship between cognitive outcome and cerebral atheroma is much less uncertain. Several studies describe differing results (44,45). Whereas there is some data that suggests that with the higher degree of atheroma in the ascending aorta present, the more likely there are to be cerebral emboli (46), there is a relative failure demonstrating that these atheroma correspond to cognitive decline (44). Part of the discordance between these two findings may be due to the previously outlined limitation of Doppler technology to discriminate between gaseous and particulate emboli, thereby possibly misrepresenting somewhat the actual cerebral embolic load (47).

The concept that global cerebral hypoperfusion during CPB may lead to neurologic and neurocognitive complications originates from the earliest days of cardiac surgery when significant (both in degree and time) systemic hypotension was a relatively common event. Although making intuitive sense – that hypotension would lead to global cerebral hypoperfusion – studies that have examined the relationship between mean arterial pressure and cognitive decline after cardiac surgery have generally failed to show any significant relationship (8,48,49). This failure is not the case for stroke, however, where Hartman et al. (29), and Gold et al. (50), demonstrated a link between hypotension and the presence of a significantly atheromatous aorta with increased stroke. This is not a clear relationship, however, and likely represents an interaction between macroembolism and global cerebral hypoperfusion. It is likely for example, that if one area of the brain that is being perfused by a cerebral vessel becomes occluded by an atheromatous embolus, it may be more susceptible to hypoperfusion if collateral perfusion is compromised by concomitant systemic hypotension (51). Other evidence for global cerebral hypoperfusion comes from Mutch et al. (52), who examined magnetic resonance imaging (MRI) assessments of cerebral blood flow (CBF) showing progressive decreases in CBF during the course of experimental CPB in pigs.

The impact of CPB temperature (i.e., hypothermia) on outcome is addressed further in the chapter. However, with the various trials of hypothermia during CPB and with detailed temperature monitoring having been performed, the observation has been made that *hyperthermia* can also occur during certain periods during and after cardiac surgery. During rewarming from hypothermic CPB, there can be an overshoot in cerebral temperature due to aggressive rewarming generally aimed at decreasing time on bypass and overall operating room time. This cerebral hyperthermia may well be responsible for some of the injury that occurs in the brain (53).

The post-operative period is also a critical time whereby hyperthermia can contribute to brain injury (54,55). Grocott et al. (54), demonstrated that the peak temperature in the post-operative period (24 hours after surgery) was related to cognitive decline six weeks after cardiac surgery. It is not clear whether this hyperthermia causes de novo injury or whether it exacerbates injury that has already occurred (such as that injury that might be induced by cerebral microembolization or global cerebral hypoperfusion). Also one must be cautious in concluding whether these relationships are ‘temporal’ or ‘causal.’ However, if one assumes that the brain is injured during CPB, and as experimental brain injury is known to cause hyperthermia (secondary to hypothalamic injury (56)), then the hyperthermia that is demonstrated in the post-operative period may very well be due to the occurrence or extent of brain injury. However, if hyperthermia occurs due to the inflammatory response to bypass, then this hyperthermia itself may induce or exacerbate cerebral injury.

Although well known that blood interacts with the foreign surfaces of the pump-oxygenator to stimulate a profound inflammatory response (57), the systemic end-organ effects of this inflammatory response are less clearly defined. Much of the data relating organ dysfunction, in this case, the CNS, to the inflammatory response in the cardiac surgical patient has focused on indirect evidence, both experimentally and clinically. It is not entirely clear whether a cerebral inflammatory response occurs as a result of CPB in humans.

Hindman et al. reported that cyclooxygenase mRNA was upregulated following CPB suggesting that, on the molecular biologic level, CPB induces an over expression of this pro-inflammatory gene in the brain (58). What is not clear was whether this was a primary event (i.e., as a direct result of the pro-inflammatory effects of CPB) or a secondary event as a result of other injurious effects of CPB (such as microembolization etc.) In settings other than cardiac surgery, inflammation has been demonstrated to directly injure brain (such as is the case in sepsis-mediated encephalopathy) (59), but it is also known to result as a response to various cerebral injuries (such as ischemic stroke) (60).

Whereas there is no direct evidence that inflammation causes cardiac surgery-associated adverse cerebral outcome, there is some supportive indirect evidence. For example, Mathew at al. demonstrated a relationship between poor cognitive outcome and an impaired immune response to circulating endotoxin (that inevitably translocates from the gut into the blood stream due to alterations in splanchnic blood flow during CPB) (61). It is known that having a low antibody response to circulating endotoxin is paradoxically associated with an over-stimulated inflammatory response (62). Thus, demonstrating the relationship between low endotoxin antibodies and poor cognitive outcome may be mediated by an augmented inflammatory response. There is no other *direct* data linking cognitive dysfunction with inflammation after cardiac surgery at the present time.

Cerebral edema following CPB has been reported in several studies (63,64). The explanation for why cerebral edema may occur early in the post-bypass period is not clear. It may be due to cytotoxic edema secondary to global cerebral hypoperfusion or possibly secondary to hyponatremia-induced cerebral edema. Generalized cerebral edema due to increases in cerebral venous pressure secondary to cannula misplacement which frequently occurs during CPB, is another reason (65). Specifically, dual-stage venous cannula can often lead to cerebral venous congestion with vertical displacement of the heart during access to the posterior epicardial coronary arteries. It is not clear from these studies whether the edema results because of injury that occurs during CPB, thus leading to cognitive decline, or whether the edema itself directly causes the injury by consequent increases in intracranial pressure (ICP) with either global or regional decreases in CBF with resulting ischemia.

The function of the BBB is to aid in maintaining the homeostasis of the extracellular cerebral milieu protecting the brain against fluctuations in various ion concentrations, neurotransmitters, and growth factors that are present in the serum (66). The impact of CPB on the function and integrity of the BBB is not clearly known. Gillinov et al. were unable to show any changes in BBB dysfunction two hours after CPB in piglets as assessed using carbon 14-aminoisobytyric acid tracer techniques in post-bypass brain homogenates (67). More recently, however, Cavaglia et al., measuring the leakage of fluorescent albumin from blood vessels in brain slices following bypass, were able to demonstrate significant breaches in the BBB (68). Both of these studies looked at a single time point (i.e., immediately after CPB), and it is not known whether there are other temporal changes in the BBB integrity.

It is difficult to determine whether the changes in BBB integrity, if present at all, are a primary cause of brain dysfunction or simply a result of other initiating events such as ischemia (from cerebral microembolization) or a diffuse cerebral inflammatory event. Changes in the BBB could cause some of the cerebral edema that has been demonstrated or it could result from cerebral edema if the edema resulted in ischemic injury (from increases in ICP) (64).

Anesthetics themselves have recently been demonstrated to have some possible implications of cognitive loss after surgery. Experimental work studying cognitive outcome in rats exposed to anesthetics have demonstrated that relatively brief (several hours) exposure to isoflurane can lead to long-term cognitive changes in the animals (69). This, coupled with the demonstration in other experimental models of necrosis in neonatal brains exposed to certain anesthetic agents (isoflurane, midazolam, nitrous oxide) (70), added to data suggesting that corresponding proteomic changes can occur in the brain after exposure to anesthetics (71), serves to highlight this as a potential area for further research.

Genetics may play a role in either modifying the degree of CNS injury or in the ability of the brain to recover once an injury has occurred. There have been several investigations of the genetic influences of cerebral outcome after CPB. Thus far, the most commonly explored gene variant, or single nucleotide polymorphism (SNP), has been the ε4 allele of the Apolipoprotein gene. This gene has been reported to be responsible for increasing the risk of both sporadic and late onset Alzheimer's disease (as well as compli-

cating outcome after a variety of other head injuries) (72). Although early reports suggest that this may be an important influence (73), later reports have shed some doubt as to how robust this effect is (74). A second SNP examined relates to the PLA-II receptor polymorphism. This platelet integrin receptor polymorphism has been shown to be important in the etiology of acute coronary syndromes and other thrombotic disorders (75,76). A small study in cardiac surgery patients demonstrated worse impairments in the minimental status exam in the PLA-II positive patients versus PLA-II negative (77). Most recently, a study of neurocognition by Mathew et al, and one in stroke by Grocott et al. (78,79), have further described the differential influence of SNPs related to inflammatory and platelet function, highlighting again the role that inflammation may play in the complex injuries after cardiac surgery. Future work will further define these genetic influences.

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Address for corresponding: Hilary P. Grocott, MD, FRCPC, FASE, Professor, Departments of Anesthesiology and Surgery, University of Manitoba, IH Asper Clinical Research Institute, CR3008-369 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada, E-Mail: hgrocott@sbgh.mb.ca