

Original Article

A Review of Risk Factors for Adverse Neurologic Outcome After Cardiac Surgery

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Abstract: Although the incidence of overt sequelae has traditionally been higher in patients undergoing isolated intracardiac procedures such as valve replacement or repair, recent studies show that the incidence of stroke for intracardiac procedures now approximates that for isolated coronary artery bypass grafting (CABG), in the range of 1 to 4%. In both intracardiac and extracardiac surgery, macroemboli (>200 μm in diameter) and microemboli (<40 μm in diameter) seem to be responsible for most neurologic complications. The risk of overt stroke is clearly increased in patients who undergo more complicated, combined procedures such as CABG plus valve replacement or CABG plus carotid endarterectomy. For isolated CABG, preoperative risk factors include advanced patient age, proximal aortic atherosclerosis, hypertension, previous stroke or transient ischemic attack, diabetes, and female gender. One area of controversy and current research concerns whether hypothermia is better than

normothermia during cardiopulmonary bypass (CPB). Another debatable issue is whether CPB itself results in neurologic damage, owing to nonpulsatile perfusion, complement activation and the “inflammatory response,” or a greater propensity for platelet activation and aggregation into microemboli in this setting. Strategies for preventing adverse neurologic outcome (new paradigms for managing intra-aortic plaque and controlling the cerebral reperfusion temperature) and for acute intervention (using specific cerebral protective agents) are under investigation. Further research into techniques for preventing or mitigating cerebral injury, particularly in high-risk patients, is clearly mandated. **Keywords:** cardiopulmonary bypass, complications, stroke, cardiac surgery, combined cardiovascular procedures, coronary artery bypass grafting, carotid endarterectomy, risk factor analysis. *JECT. 2002;34:4–10*

An adverse neurologic outcome is a debilitating potential complication of successful cardiac surgery. According to recent prospective studies, perioperative overt stroke occurs in approximately 1–4% of patients who undergo isolated coronary artery bypass grafting (CABG) (1–8). Although the incidence of overt sequelae has traditionally been higher in patients undergoing such isolated intracardiac procedures as valve replacement or repair (9–13), recent studies show that the incidence of stroke for intracardiac procedures now approximates that for isolated CABG (14–17). In both intracardiac and extracardiac surgery, macroemboli (>200 μm in diameter) and microemboli (<40 μm in diameter) seem to be responsible for most

neurologic complications (1–9, 11, 14, 15, 18). Macroemboli are believed to cause focal defects, whereas particulate microemboli (consisting of white cell and platelet aggregates, fat, or air bubbles) may be implicated in more subtle diffuse cerebral dysfunction (19). Regardless of size, the eventual destination of the embolic material is critical in determining the severity of cerebral injury (20–22).

The risk of overt stroke is clearly increased in patients who undergo more complicated, combined procedures such as CABG plus valve repair or replacement (9, 14, 18) or CABG plus carotid endarterectomy (10, 23–27).

INCIDENCE OF NEUROLOGIC COMPLICATIONS

CABG Plus Intracardiac Surgery

In a large, single-institution review of nearly 7000 patients, multivariate analysis showed that a combined car-

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diac surgical procedure confers independent neurologic and mortality risks (14). A multicenter prospective study confirmed this finding, in that one out of six cardiac surgical patients suffered an overt cerebral injury, which resulted in prolonged intensive care and in-hospital stays, an increased need for long-term specialized care, and a significantly higher mortality (18). Because more than 200,000 patients worldwide undergo open-heart procedures annually, of which approximately 100,000 such procedures are combined with CABG, it is estimated that 15,000 to 30,000 of these patients will suffer serious cerebral events (18). Patients who undergo a combined operation may have complications associated with each separate procedure, including emboli related to proximal aortic atherosclerosis, intracardiac thrombus, valvular vegetation, or air bubbles (9).

With intracardiac procedures, the prevalence of air emboli is increased, because air bubbles commonly remain trapped within the heart even after the affected chamber is closed. Padayachee and associates (28) have noted that, in patients undergoing valve replacement surgery, the number of emboli measured with transcranial Doppler echocardiography in the middle cerebral artery distribution is high, even exceeding that associated with myocardial revascularization. Regarding particulate emboli, patients undergoing combined procedures tend to be older and, therefore, are more likely to be at risk for atherosclerotic emboli (14, 18). In fact, one study of combined cardiac procedures identified aortic atherosclerotic plaque, intracardiac thrombus, and cardiac vegetation, as well as intermittent aortic cross clamping, as predictors of stroke (18). Thus, the extraordinary risk associated with combined procedures is due to the combination of risks inherent in each separate procedure.

CABG Plus Carotid Endarterectomy

The incidence of an adverse neurologic outcome is also higher in patients who undergo combined CABG plus carotid endarterectomy than in those who undergo isolated CABG. In several large studies, carotid stenosis has been associated with an increased risk of perioperative stroke (10, 23–27). Traditionally, the association between carotid stenosis and stroke in cardiac surgery patients was thought to result from inadequate cerebral blood flow during cardiopulmonary bypass (CPB). The principal justification for performing a carotid endarterectomy in cardiac surgery patients with known carotid stenosis was to prevent cerebral hypoperfusion during CPB. Of course, surgical correction of a carotid stenosis would have benefited the patient only if a perioperative neurologic insult would otherwise have resulted from the stenotic carotid artery itself (e.g., because of hypoperfusion or embolization).

More recently, it has been argued that carotid disease may be a marker for severe generalized atherosclerotic disease, thereby increasing the probability of ascending

aortic disease and of embolization from that source. Surgical correction of a carotid stenosis would be unlikely to benefit the patient if a perioperative insult were to originate from atherosclerosis in the proximal aorta.

Current practice generally adheres to the following guidelines (29). If the patient has symptoms of presumed carotid disease and is about to undergo cardiac surgery, a noninvasive carotid artery study is performed. If a high-grade carotid stenosis is detected and the patient has stable coronary symptoms, a carotid endarterectomy is usually performed before cardiac surgery. However, in patients with asymptomatic carotid stenosis (even a documented, high-grade lesion), either no prophylactic endarterectomy is performed or combined CABG plus carotid endarterectomy is performed, particularly if the patient has unstable angina or left main coronary disease.

A meta-analysis of 16 studies that had previously compared the results of combined versus staged CABG plus carotid endarterectomy showed that the combined procedure may be associated with a higher risk of stroke or death than the staged procedures (30). However, because many institutions select patients for a combined procedure on the basis of their particularly high risk for stroke or death, this conclusion may not be valid. Unfortunately, there have been no randomized trials of simultaneous CABG plus carotid endarterectomy versus CABG alone in patients with asymptomatic carotid disease.

RISK FACTORS FOR ISOLATED CABG

Preoperative Risk Factors

Preoperative risk factors for isolated CABG include advanced patient age, proximal aortic atherosclerosis, hypertension, previous stroke or transient ischemic attack (TIA), diabetes, and female gender.

Advanced Age: Advanced age, a well-known risk factor, is obviously important because of the tendency to operate on ever-older patients (1–8). In the mid-1980s, Gardner and co-workers (31) examined the incidence of major neurologic complications in CABG patients. The risk of stroke increased as the mean age of the patient population increased. For patients 41–50 years old, the incidence of stroke was 0.4%; for patients older than 75 years, the incidence increased to 7.1%.

In 1992, Tuman and associates (32) demonstrated the impact of advancing age on the probability of a neurologic complication after CABG, particularly in patients age 70 and older. Those who had a postoperative neurologic deficit also had a ninefold increase in mortality. Interestingly, cardiac complications (defined as myocardial infarction or a low cardiac output state) were not more common in older patients.

In 1996, Roach and colleagues (1) confirmed that older age (>70 years) is a leading predictor of an adverse cere-

bral outcome. In their series, the in-hospital incidence of severe overt outcomes (stroke, transient ischemic attack, or coma) was 3.1%. Again, patients with such postoperative neurologic deficits had a tenfold increase in mortality.

Proximal Aortic Atherosclerosis: A risk factor closely related to age is proximal aortic atherosclerosis. Ultrasonographic scanning has shown that between 14 and 20% of patients older than age 65 have moderate or severe atherosclerotic disease (33–40). Surgical palpation of the ascending aorta underestimates the presence of atherosclerotic disease (33, 37, 40). Intraoperative transesophageal and/or epiaortic echocardiography has been used to scan the thoracic aorta to identify patients at risk (33, 36, 37). In current practice, it is debatable whether epiaortic scanning is routinely necessary for cardiac surgery patients (41, 42). One approach may be to obtain views of the descending thoracic aorta, which are nearly always excellent, and to grade the pathologic findings. Patients with advanced atheromatous disease, including those with a mobile atheroma of the descending aorta, would be good candidates for epiaortic scanning and/or extra care during intraoperative manipulation of the aorta (43). Another approach may be to induce a 40- to 50-mm Hg decrease in the systemic pressure and then to palpate the aorta gently but thoroughly (44, 45). When moderate-to-severe atherosclerosis is suspected, additional diagnostic measures or a modified surgical technique can be used (29, 43, 45).

In the large, prospective study conducted by Roach and co-workers (1), the most important predictor of stroke was moderate-to-severe proximal aortic atherosclerosis, as identified by means of surgical palpation. Neither careful transesophageal echocardiography nor epiaortic scanning of the proximal aorta was performed in this study. Even so, intraoperative aortic palpation by the surgeon, although certainly less sensitive, was adequate for identifying moderate-to-severe disease; in patients with palpable disease, the incidence of perioperative stroke was more than fourfold higher than in patients without palpable disease.

Dislodgement of atherosclerotic debris from the proximal aorta is most likely to occur during aortic cannulation, aortic clamping and unclamping, and construction of proximal vein graft anastomoses. These intervals have been identified by transcranial Doppler technology as periods of high risk for embolization to the middle cerebral artery (43, 46–48).

To prevent macroembolization from the ascending aorta, one must avoid cross clamping the aorta in areas of severe or moderate atherosclerotic disease, because manipulation and clamping of such areas may release large particulate emboli. It also may be necessary to use a “no-touch” surgical technique, which involves modification of the aortic cannulation site, use of a single aortic cross clamp, different placement of the proximal anastomoses,

or maximal use of pedicled arterial grafts such as internal mammary artery grafts (45). Another solution is “off-pump” coronary revascularization, which completely avoids the need for cannulation and cross clamping (45). Moreover, if only internal mammary grafts are used in off-pump CABG, there is no need for a “partial occluding” or “side-biting” clamp during creation of the proximal anastomoses. Patients with severe atherosclerosis of the ascending aorta may be particularly suited for off-pump CABG, because the procedure may be performed without touching the aorta, possibly eliminating a major cause of stroke in these patients.

Hypertension: Another risk factor is preoperative hypertension, particularly “poorly controlled” hypertension (49–51). Elevation in the cerebral autoregulatory pressure threshold for patients with chronic hypertension has been described in the literature (52, 53). However, it is probably unnecessary to maintain a higher mean arterial pressure during nonpulsatile, hypothermic, hemodiluted CPB. Most of the recent studies that have retrospectively examined the influence of the mean arterial pressure and/or of hypotension during CPB have found little or no relationship between these factors and an adverse neurologic outcome (54–57). One report by Gold and co-authors (58) suggests that the mean arterial pressure may influence the neurologic outcome; however, the authors selectively pooled the combined mortality, neurologic, and cardiac outcome data and claimed that the overall morbidity and mortality was significantly lower in the high-pressure group than in the low-pressure one. Also, no data were provided regarding the incidence of postbypass or postoperative hypotension. In a separate publication, Hartman and colleagues (43) focused on a subset of patients from the same study. The authors pointed out a trend indicating that, in patients with documented high-grade atherosclerosis, fewer strokes may occur when relatively high mean arterial pressures (80–100 mm Hg) are maintained during CPB. However, this finding did not reach statistical significance.

It is possible that embolic phenomena and hypoperfusion often coexist and that their pathophysiology may be interactive (59). Sungurtekin and colleagues (60) recently reported that cerebral microembolization during normothermic CPB impairs cerebral autoregulation, increasing the dependence of the cerebral blood flow on the mean arterial pressure. Reduced perfusion limits the ability of the bloodstream to clear or wash out emboli and microemboli and reduces the available blood flow to regions rendered ischemic by emboli that block nutrient arteries (59). The brain border zones (the “watershed” areas) are a favored destination for microemboli that are not cleared by the bloodstream (49). Impaired washout seems to be an important but neglected concept that is intertwined with hypoperfusion, embolization, and brain infarction (59).

Previous Stroke or Transient Ischemic Attack: Another risk factor for a postoperative adverse neurologic outcome is a previous stroke or TIA (1, 2, 8, 10, 26, 31, 32, 61, 62). In a prospective analysis of 1000 consecutive patients, Redmond and associates (61) noted that 71 patients had a previous documented stroke. Of these patients, 8.5% developed a new stroke, and 35% had reappearance or worsening of a prior deficit. The combination of a previous stroke or TIA and a significant carotid stenosis (confirmed by noninvasive carotid scanning) confers a particularly high (18.2%) risk of postoperative stroke, compared with <5% in patients with only one of these two risk factors and <2% in patients with neither risk factor (26).

Diabetes: Numerous investigators (1, 5, 7, 8, 62) have cited diabetes as a significant risk factor for neurologic complications in CABG patients. Cerebral autoregulation may be impaired in diabetic patients, particularly during post-CPB rewarming (63). As with patients with cerebrovascular disease, diabetic patients may have more severe generalized atherosclerotic disease, including lesions of the ascending aorta and/or the carotid vessels. Although some animal data indicate that hyperglycemia may worsen the neurologic outcome after focal ischemia (64), clinical data from diabetic and nondiabetic patients have failed to confirm this finding, despite the presence of marked temporary hyperglycemia during CPB (57, 65).

Female Gender: One single-institution study (5) and one large multi-institution study examining the Society of Thoracic Surgery's National Cardiac Surgery Database (66) have shown that female gender is an independent risk factor for perioperative stroke. Although hormone replacement therapy has recently been shown to improve survival among women undergoing cardiac surgery, such therapy does not significantly improve the neurologic outcome (67). Further studies should address hormone replacement therapy, the management of concurrent diseases, and the timing of cardiac surgery, in an effort to decrease neurologic complications and other types of morbidity in female patients.

Intraoperative Risk Factors

Hypothermia vs. Normothermia: One area of controversy and current research concerns whether hypothermia is better than normothermia during CPB (4, 68–75). Certainly, it is well known that the brain is protected if it is in a hypothermic state at the time of an ischemic insult. However, induced hypothermia may be inadequate for brain protection during cardiac surgery. During routine CPB, hypothermia is always initiated after aortic cannulation and the onset of bypass. Also, patients are rewarmed before the termination of bypass. Macroembolization to the brain is unlikely during the hypothermic period, because the heart is excluded from the circulation by the aortic cross clamp. Actually, it is during the onset of CPB, as well as during aortic cannulation, cross clamping, unclamping,

and weaning from CPB that the brain is at the highest risk for micro- and macroembolization. During these periods, the brain is normothermic and vulnerable. Also, induction of hypothermia commits the surgeon to a later phase of rewarming, and there is some evidence that rapid rewarming is harmful (55, 76–79).

It is well known from animal studies and from clinical studies in stroke patients that hyperthermia is also harmful. Even small increases in the brain temperature (1–2°C) will exacerbate the severity of neurologic injury (80–84). Therefore, in one's zeal to cool the patient and to protect vital organs—particularly the brain—the rewarming phase must not be neglected. Another crucial aspect of the rewarming phase is the location of the temperature monitor(s). The jugular bulb venous blood temperature is somewhat higher than the nasopharyngeal or esophageal temperature (85, 86) and is dramatically higher than the bladder or rectal temperature; in fact, the temperature gradient between the bladder and the jugular bulb can vary by as much as 5°C (86).

To summarize these temperature issues, it is well documented in the neuroscience literature that even mild hypothermia (in the 33–35°C range) confers a protective effect. Even when induced after an ischemic event, mild hypothermia is thought to improve the neurologic outcome. Some clinicians wean high-risk patients from CPB at a slightly reduced temperature (approximately 35–36°C). Of course, this practice must be weighed against the potential risks of hemodynamic instability and bleeding. There is little question, however, that it is critical to avoid superheating the brain during the rewarming phase of CPB; to achieve this goal, one must avoid a nasopharyngeal or tympanic membrane temperature of 38–39°C. Rewarming should be started early enough to achieve stability of the desired nasopharyngeal or tympanic temperature, and the bladder and rectal temperatures should be ignored. Although an “afterdrop” in temperature always occurs after CPB, one should not risk causing cerebral hyperthermia in an effort to avoid this afterdrop.

Off-Pump CABG: Another debatable issue is whether CPB itself results in neurologic damage, owing to nonpulsatile perfusion, complement activation and the “inflammatory response,” or a greater propensity for platelet activation and aggregation into microemboli in this setting. In studying patients who died within 3 weeks after CPB, Brown and associates (87) found that an increased CPB duration was associated with an increased embolic load. Although some investigators have claimed that the cognitive outcome is improved by off-pump versus on-pump CABG (88–90), other investigators have observed no differences in these two techniques with respect to the cognitive outcome (91–94). This issue has not been studied in any large, randomized series.

Certainly, off-pump CABG can have a significant im-

pact on some, but not all, risk factors. For example, it is possible to avoid embolization of atherosclerotic debris in the proximal aorta by avoiding ascending aortic cannulation, aortic cross clamping, and even use of a "side-biter" clamp in certain patients with ideal coronary lesions. Recent evidence suggests that, as compared to traditional CABG, off-pump CABG is associated with fewer cerebral emboli, as detected by transcranial Doppler imaging (95). However, in most patients, the goal of complete revascularization would be sacrificed by using this no-touch technique, because it depends on use of the internal mammary arteries. Off-pump CABG helps avoid the whole issue of hypothermic versus normothermic CPB, the possible harm of rapid rewarming, and the certain harm of superheating the brain in the presence of an ischemic injury. It is largely unknown whether CPB inherently poses other risks to the brain or, conversely, whether off-pump CABG involves unique risks to the brain. Off-pump surgery often involves a relatively low mean arterial pressure, use of the Trendelenburg position, and some degree of venous occlusion, all of which may be additive in producing a low cerebral perfusion pressure. The decision to operate with or without CPB should be tailored to the individual patient, after one has considered all the risk factors, as well as the expected adequacy and longevity of revascularization.

Postoperative Risk Factors

A small, but definite, number of "delayed" strokes occur hours or days after surgery and are generally unrelated to CPB. For example, so-called "failure of the native circulation" (severe hypoperfusion shortly after CPB and during the early postoperative period) would be an important confounding factor in studies of adverse neurologic outcomes after CPB (54). Also, in many studies, the contribution of postoperative atrial fibrillation to the stroke risk may be underestimated, because the timing of the neurologic event is not taken into consideration. With respect to delayed stroke, Hogue and co-workers (5) recently noted a strong, previously undescribed interaction between postoperative atrial fibrillation and low cardiac output syndrome.

CONCLUSION

Only one report (62) has attempted to define a stroke risk index for patients undergoing isolated CABG, based on data obtained in a prospective multicenter observational study [the Multicenter Study of Perioperative Ischemia (McSPI)]. In this report, key predictor variables were patient age, diabetes, a history of previous neurologic disease, a history of vascular disease, a history of pulmonary disease, unstable angina, and redo coronary surgery. The first four factors are strongly weighted in the nomogram

that the authors developed to compute risk (62). These factors (age, diabetes, a history of neurologic disease, and a history of vascular disease) are commonly accepted risk factors and have been discussed in this review. Although repeat CABG consistently produces greater overall morbidity and mortality, its possible association with an increased risk of stroke is controversial (50, 51). Also, the mechanism by which unstable angina might increase the risk for stroke is unknown, but it may relate to the severity of atherosclerosis or the likelihood of atherosclerotic plaque instability (62). Furthermore, the extent to which a history of pulmonary disease may contribute to the risk of stroke is not yet clear. The above-mentioned risk index has yet to be tested prospectively to verify its accuracy in predicting stroke.

The annual cost of neurologic complications after cardiac surgery is estimated to be at least 2 to 4 billion dollars (1, 2). Strategies for preventing such complications (new paradigms for managing intra-aortic plaque and controlling the cerebral reperfusion temperature) and for acute intervention (using specific cerebral protective agents) are under investigation. Further research into techniques for preventing or mitigating cerebral injury, particularly in high-risk patients, is clearly mandated.

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