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Does Off-Pump Coronary Artery Bypass Surgery Reduce the Risk of Brain Injury?

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ABSTRACT

Documented evidence indicates that cardiopulmonary bypass (CPB) is an independent risk factor for end organ injury, particularly brain injury, following heart surgery. Because CPB and aortic cannulation are not performed during off-pump coronary artery bypass (OPCAB), it is expected that the incidence of brain injury attributable to these factors should be reduced with OPCAB. The mechanisms contributing to post-CPB neuropsychological deficits are uncertain. However, three major interrelated etiologic factors, hypo-perfusion, the systemic inflammatory response, and embolism are obvious suspects.

It is assumed that coronary artery bypass graft (CABG) surgery without CPB will diminish the potential for emboli. In essence, the avoidance of CPB during CABG surgery would be expected to reduce cerebral injury by reducing the cerebral embolic load, resulting in improved clinical outcomes. The number of ultrasonically detectable macroemboli delivered to the brain is the best predictor of neurobehavioral deficits. This article considers the results of studies indicating that a substantial portion of microemboli result from shed blood being reinfused via the CPB circuit.

Despite these expectations, recent studies examining the cerebroprotective effect of OPCAB procedures versus conventional coronary artery bypass (CCAB) have yielded inconsistent results. This article reviews the results of some of these studies and concludes that, collectively, the studies identify no clear superiority of either the OPCAB or the CCAB technique. Instead, they clearly suggest that patients undergoing these two procedures are not clinically similar. Whether the differences are due to the avoidance of CPB, patient selection bias, or a reduction in the number of coronary anastomoses in OPCAB patients remains unclear.

Until systematic, blinded, prospective studies are conducted comparing CABG with and without CPB, it cannot be positively concluded that CPB is an independent risk factor of cerebral complications following heart surgery. Although specific CPB components may be associated with increased risk of brain injury, it may be that other factors independent of CPB (e.g., blood product utilization or aortic manipulation) may impart a greater independent risk than CPB alone.

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BACKGROUND

Coronary artery bypass graft surgery (CABG) was first performed without the use of cardiopulmonary bypass (CPB) or the "heart-lung machine" in the 1960s. However, following the advent and acceptance of CPB in association with the development of methods of myocardial protection, this technique was soon abandoned. Forty years later, direct myocardial revascularization without the use of CPB is being resurrected due to new technological developments and the documented evidence that CPB is an independent risk factor for end organ injury, particularly brain injury, following heart surgery [Benetti 1991, Diegeler 1997, Calafiore 1998].

In off-pump coronary artery bypass procedures (OPCAB), surgery is performed on a beating heart with the use of instruments to stabilize the coronary artery and surrounding surgical field. The heart and lungs continue to function throughout the surgery, and CPB is not used. Reardon et al. noted that in performing this procedure, the surgeon must consider (1) the accuracy and patency of the anastomosis vis-à-vis conventional CAB (CCAB), (2) issues of incomplete revascularization, and (3) long-term out-

come [Reardon 1997]. Nevertheless, because CPB and aortic cannulation are not performed during OPCAB, the incidence of brain injury attributable to these procedures should be reduced.

MATERIALS AND METHODS

Neurobehavioral Deficits in OPCAB Versus CCAB Patients

Recent studies examining the cerebroprotective effect of OPCAB procedures versus CCAB have yielded inconsistent results. Watters et al. conducted a prospective, unblinded study comparing 10 CABG patients with CPB and 10 OPCAB patients and found that patients undergoing multiple-vessel OPCAB had markedly fewer cerebral emboli, detected intraoperatively by transcranial Doppler (TCD) examination of the right middle cerebral artery, than patients undergoing CABG with CPB [Watters 2000]. OPCAB patients had a median of 3 emboli (with a range from 0 to 18), while CABG patients had a median of 79 emboli (with a range of 38 to 876). In the patients undergoing CABG and CPB, although noticeable increases in embolic signals occurred during aortic manipulations, embolic signals also occurred throughout the period of CPB. The few emboli in the OPCAB group occurred only on removal of the side-biting clamps.

Ricci et al. performed a retrospective, nonrandomized study of 269 octogenarians who underwent CABG, 172 with CPB and 97 without [Ricci 2000]. None of the patients in the OPCAB group sustained a postoperative stroke, whereas a 9.3% rate of stroke was encountered in the CPB group. In addition, there was a trend toward more extensive multivessel involvement in the CPB cohort (3.3) compared to the off-pump cohort (1.8). However, the 30-day mortality rate in the OPCAB group was nearly twice the rate in the CPB group, though this did not reach statistical significance. Similarly, a trend toward a higher risk-adjusted mortality rate was observed in the off-pump cohort than in the CPB cohort, even though the length of hospital stay was slightly lower in the off-pump group. This decrease in hospital stay was offset by an increase in the percentage of reoperations in the off-pump cohort, which was nearly four times greater than that of the CPB group (16.5% vs. 4.7%).

In a small study, Diegeler et al. demonstrated that off-pump CABG patients tend to have less central nervous system dysfunction following surgery [Diegeler 2000]. In a study of 40 patients randomized to CCAB or OPCAB, it was noted that no patient in the OPCAB group showed any pathologic score, while, remarkably, 90% of the patients in the CPB group showed deficient scores.

In a similar small study, Murkin et al. observed a cerebroprotective effect of OPCAB, wherein beating heart surgery patients demonstrated a significantly lower incidence of cognitive dysfunction at five days (66% vs. 90%) and three months postoperatively (5% vs. 50%) compared with CCAB surgery patients [Murkin 1999]. However, the study did note significant differences in the number of coronary anastomoses (3.2 CCAB vs. 1.1 OPCAB), total operating room time, time to extubation, and numbers of patients in whom sternotomy as opposed to thoracotomy incisions were used. It should be noted that a 90% cognitive deficit rate after CCAB is as much as two times greater than generally reported. This remarkably high incidence of brain injury needs to be examined in regard to patient selection and randomization procedures.

On the other hand, Arom et al., in a retrospective, consecutive review of 3,521 coronary bypass operation patients who underwent either isolated CCAB (n = 3,171) or OPCAB (n = 350), observed no significant differences between the groups on variables such as neurologic deficits, perioperative myocardial infarction (MI), or operative mortality [Arom 2000]. However, using the logistic regression preoperative predicted risk model provided by the Society of Thoracic Surgeons' national cardiac surgery database, Arom's group did observe a significant difference in predicted risk between the CCAB and OPCAB groups ($2.6 \pm 4.6\%$ vs. $4.3 \pm 7.4\%$, respectively; $p < 0.001$). Moreover, they also reported a significant difference in ejection fraction between the two groups ($56 \pm 14\%$ CCAB vs. $52 \pm 15\%$ OPCAB; $p < 0.001$). When reviewing the OPCAB group, the study found significantly fewer grafts per patient (2.1) compared to the CCAB group (3.2), and an increase in the recurrence of angina was noted in the OPCAB group at the end of one year. This observation may be related to incomplete bypass and the fewer grafts per patient. The notion of incomplete bypass in OPCAB patients has been suggested by others as well [Ricci 2000].

It is possible that the findings from these studies could be explained by dissimilarities in the risk factors between CCAB and OPCAB patients. To address this issue of comparability between OPCAB and CCAB patients, Iaco et al. examined the technical profile of 472 OPCAB patients and 290 CCABs [Iaco 1999]. They found that OPCAB patients had a lower incidence of left main coronary artery disease and redo operations and a lower ratio of anastomoses per patient. Mortality and cerebrovascular accident (CVA) incidence, both crude and risk-adjusted, were similar, whereas the incidence of bleeding, blood transfusion, and ICU and postoperative in-hospital stays was significantly lower in the OPCAB group.

Collectively, these studies identify no clear superiority of either the OPCAB or the CCAB technique. Instead, they clearly suggest that patients undergoing these two procedures are not clinically similar. The majority of studies have shown that OPCAB patients tend to have fewer coronary anastomoses. Of those studies reporting all perioperative variables, most show that OPCAB patients spend less time in the operating room and intensive care unit and CCAB patients tend to have more major complications such as bleeding and unstable angina. Whether these differences are due to the avoidance of CPB, patient selection bias, or a reduction in the number of coronary anastomoses remains unclear.

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Physiological Mechanisms of Injury

The mechanisms contributing to post-CPB neuropsychological deficits are uncertain. However, three major interrelated etiologic factors, hypoperfusion, the systemic inflammatory response, and embolism are obvious suspects. Emboli can be divided into macro and micro categories according to size. Macroemboli occlude flow in arteries 200mM or greater in diameter, while microemboli obstruct flow in smaller arteries, arterioles, and capillaries. Each category will have a different clinical manifestation: a single macroembolus can result in hemiplegia, but a single microembolus is unlikely to have a noticeable effect except in very susceptible tissue such as the retina.

The subject of cerebral microemboli during CPB has been reviewed by a number of investigators [Padayachee 1987, Pugsley 1994, Blauth 1995, Clark 1995]. Focal neurologic deficit can occur secondary to embolism of a large bolus of air as a result of starting cardiac pulsation without completely evacuating air in the cardiac chambers, but this is rare. Focal neurologic deficit can also occur secondary to local hypoperfusion and particulate macroemboli (atherosclerotic plaque disruption at the site of aortic cannulation, calcium or vegetation particulate from valve manipulation, other debris from field aspirated blood, or clots). Diffuse neurologic and neuropsychological deficits are presumably due to global hypoperfusion or widespread microemboli. Microembolic agents could be platelet aggregates, chylomicrons, tiny air bubbles, glove powder, tube fragments, silicone antifoam materials, or phospholipid remnants of damaged red blood cells or lipid microemboli from the surgical field returned to the patient via cardiotomy suction [Brooker 1998].

The number of ultrasonically detectable macroemboli delivered to the brain is the best predictor of neurobehavioral deficits [Pugsley 1994, Clark 1995, Hammon 1997]. We have demonstrated that the number of emboli delivered to the brain during CPB can be decreased by reducing cerebral blood flow (CBF) during periods of maximum risk for embolus production [Jones 1990]. In a canine model of CPB we showed that hypothermic CPB will reduce brain blood flow to 1/3 of normothermic CPB levels and reduce the number of emboli that are delivered to the brain by over 50%. Since the microembolic load delivered to an organ is proportional to blood flow, reducing CBF during surgery will minimize the number of emboli delivered to the brain. In humans, this should result in fewer neurobehavioral manifestations for two reasons: (1) fewer emboli, and (2) the neuroprotective effect of hypothermia.

During an investigation of degenerative changes in the brain vasculature, an oily material was discovered in the afferent microvessels of patients who had recently undergone CPB. This exogenous material was first called small capillary and arteriolar dilatations (SCADs) [Moody 1990]. SCAD density appears to be associated with the use of cardiotomy suction and return of shed blood to the CPB circuit. In a canine model, Brooker et al. reported that dogs exposed to CPB with blood returned via cardiotomy suction exhibited significantly more SCADs than dogs undergoing right-heart vent, lower-extremity CPB, or hypothermic CPB without the return of cardiotomy suction [Brooker 1998]. Their results suggest that a substantial portion of microemboli result from shed blood being reinfused via the CPB circuit and that current venous and arterial filters inadequately protect patients from lipid microemboli.

Table 1. Stroke/CVA Pooled Trasylol Database

	Placebo p=.04	Trasylol
No Reinfusion	0/134 (0.0%)*	2/162 (1.2%)
Reinfusion	21/685 (3.1%)*	7/643 (1.1%)
Overall p=.02	21/819 (2.6%)#	9/805 (1.1%)#

* = $P \leq 0.04$; # = $P \leq 0.02$

Recently, Kincaid et al. further demonstrated that shed blood scavenged from the mediastinum is a source of cerebral lipid microemboli [Kincaid 1999]. They found that arterial line filters used individually or in combination with leukocyte depleting filters were ineffective at reducing the lipid embolic load. However, the use of a cell saver to retrieve and process shed blood resulted in a significant reduction of cerebral lipid microemboli. Further, the mechanism by which the cell-saver processed the shed blood appeared to influence the lipid embolic load returned to the patient.

Obviously, if we could reduce or eliminate the need to return shed blood, then treating the blood would be unnecessary. Lipid microemboli (LME) have been found in the brain of every CPB patient examined using the alkaline phosphatase method of staining the cerebrovasculature. It is unclear if LME contribute to the inflammatory response but there is evidence that LME cause focal ischemic changes. The quantity of LME is related to whether shed blood is returned to the subject during CPB. We hypothesize that reducing shed blood production would lessen the need to return it during CPB and protect the subject from LME.

In a study of six dogs we measured the volume of shed blood during CPB. The animals were randomized to receive full dose aprotinin or a placebo infusion [Stump 1999]. All animals received a standard surgical insult. Only cut vessels were cauterized and no bone wax was used. At the end of CPB the volume of shed blood was measured and 850 ml was returned to the non-aprotinin (n = 3) group. Despite the minimal efforts to control bleeding, aprotinin resulted in a 25% reduction in the volume of shed blood during the surgery. In particular bleeding from cut bone surfaces, which is believed to be a major source of LME, was reduced. The return of 850 ml of shed blood was associated with a higher LME count in the cerebral microvasculature when compared to no return.

Unfortunately, we had not measured the amount of cardiotomy suction blood we had returned to our study patients and could not demonstrate any relationship between shed blood and outcome. The only large group of patients we could find in which shed blood was monitored was in the trasylol database. Bayer kindly provided us access.

In a preliminary analysis, the CABG patients in the trasylol database were separated into two categories: those who received shed blood and those who received none. There was a striking difference in the neurologic complication rate between the groups, with the group receiving shed blood having over three times the number of strokes and CVAs (Table 1, ◎). Also of interest, only 18% of patients receiving trasylol had over 300 ml of shed blood returned compared to 46% of the placebo group. This data further supports the premise that the return of shed blood has a negative effect on patient outcome. The reported neuroprotective benefits of off-pump surgery may be partially due to the reduction in bleeding and use of blood products.

SUMMARY

It is assumed that CABG surgery without CPB will diminish the potential for emboli, particularly those associated with the disruption of atheromatous plaques due to cannulation, cross-clamping, and manipulation of the aorta. Moreover, the generation of gaseous microemboli from the CPB circuit and microparticulate emboli from the pump tubing would likewise be avoided. In essence, the avoidance of CPB during CABG surgery would be expected to reduce cerebral injury by reducing the cerebral embolic load, resulting in improved clinical outcomes.

OPCAB surgery is becoming more commonplace, particularly with the availability of new techniques for exposure of the target coronary artery and improvements in artery stabilization devices. CPB and aortic cannulation are not utilized with this technique, and therefore the incidence of brain injury that may be related to CPB should be reduced. However, when comparing OPCAB to conventional CAB patients, intraoperative variables and postoperative complications as well as follow-up are not well-documented. CPB patients tend to have greater mean numbers of coronary anastomoses, suggesting stark contrasts to OPCAB patients.

It seems plausible that patients having less coronary artery disease may, likewise, have less cerebrovascular disease and aortic atherosclerosis, logically suggesting that they are less predisposed to subtle neurological insult following CABG surgery. Until systematic, blinded, prospective studies are conducted comparing CABG with and without CPB, it cannot be positively concluded that CPB is an independent risk factor of cerebral complications following heart surgery. Although specific CPB components may be associated with increased risk of brain injury, it may be that other factors independent of CPB (e.g., blood product utilization or aortic manipulation) impart a greater independent risk than CPB alone.

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