Off-pump surgery and cerebral injury

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Despite improvements in the conduct and clinical outcome of cardiac surgery during the last decade, cerebral injury remains a particularly important limitation for the patient, the physician, and—increasingly—the lay press. Furthermore, as patients of advanced age and those with other risk factors for neurologic complications increasingly constitute the surgical population, the challenge of minimizing cerebral injury will continue to grow. Cerebral injury can be broadly classified, in a decreasing spectrum of severity, as stroke, delirium (encephalopathy), or cognitive dysfunction. Although these patterns of injury constitute distinct clinical entities regarding pathophysiology, incidence, and clinical consequences, they also share certain common pathologic etiologies.¹

To date, most studies of cerebral injury have concentrated on stroke and cognitive dysfunction, while the incidence and consequences of delirium have been less well defined. Stroke is relatively uncommon but has a major adverse effect on postoperative mortality and morbidity.²⁻⁴ On the other hand, cognitive dysfunction is common,⁵ and although it has no obvious immediate undesirable impact on clinical outcome, it does correlate with late impairment in quality of life measures.⁶ Between these extremes lies delirium, which has traditionally been considered a self-limiting condition. Any such complacency is, however, sharply dispelled by three recent prospective studies summarized in Table 1.²⁻⁴ Stroke affects around 3% of patients undergoing coronary artery bypass grafting (CABG) and increases hospital mortality 10-fold, whereas delirium occurs in 3% to 7% and increases mortality 5-fold. Both at least double the hospital stay among survivors, before even considering their long-term functional and economic impacts.

In this issue of the *Journal*, the highly respected, experienced, and pioneering Leipzig group⁷ present a prospective study of delirium in a cohort of 16,000 cardiac surgical patients through a 5-year period. In addition to being the largest study of its kind in the literature, it explores preoperative and intraoperative (but not postoperative) risk factors for delirium. Most important, it examines the highly topical question of whether off-pump surgery reduces the risk of delirium and, by inference, the risk of cerebral injury.

The overall incidence of delirium was 8%, and the study confirms its adverse clinical consequences with increased risks of respiratory insufficiency and sternal instability and prolonged durations of intensive care and hospital stay (although we are not told what proportion of these patients died). The frequency of delirium varied markedly, however, depending on the type of surgery. It was 8% among 8917 patients undergoing conventional on-pump CABG, 11% among 5424 patients undergoing any open procedure, and 2% among 1847 patients undergoing off-pump CABG (OPCAB) through a median sternotomy or lateral thoracotomy. Consequently, the authors conclude that OPCAB “should be considered as one of the strategies for minimizing cerebral injury during cardiac operations.”⁷ In view of the size of the study this conclusion carries considerable weight and raises two questions. First, is it justified from the data presented? Second, is it consistent with other evidence that OPCAB reduces the risk of cerebral injury?

Even before attempting to answer these questions, it should be appreciated that to classify CABG procedures simply as on- or off-pump is overly simplistic in current practice, because both encompass a variety of techniques, with differing implications for the risk of cerebral injury. For example on-pump CABG can be performed on the beating heart without the need for a crossclamp and at various

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Received for publication Sept 15, 2003; revisions requested Sept 15, 2003; revisions received Sept 16, 2003; accepted for publication Sept 18, 2003.

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J Thorac Cardiovasc Surg 2004;127:7-9
0022-5223/\$30.00

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doi:10.1016/j.jtcvs.2003.09.006

TABLE 1. Mortality and morbidity resulting from stroke and delirium

Reference	No.	Operation	Cerebral injury	Incidence (%)	Mortality (%)	Hospital stay (d)
Roach et al, ² 1990	2108	CABG	None	94	2	10
			Stroke	3.1	21	25
			Delirium	3.0	10	21
McKhann et al, ³ 2003	2711	CABG	None	91	1.4	6.6
			Stroke	2.7	22	17.5
			Delirium	6.9	7.5	15.2
Wolman et al, ⁴ 1999	273	Open with or without CABG	None	84	7.4	15.4
			Stroke	8.4	30.4	30.6
			Delirium	7.3	5.0	22.7

temperatures, whereas the use of composite arterial grafting can minimize aortic manipulation in on-pump CABG and eliminate it entirely in OPCAB. And although this issue was not explored in the Leipzig study, avoidance of aortic manipulation is at least as important as the avoidance of cardiopulmonary bypass (CPB) in reducing the risk of cerebral injury.⁸

Notwithstanding this caveat, the answer to the first question is predicated both on certainty about the diagnoses and an assumption of homogeneity of risk factors for delirium in patients undergoing the different procedures. The diagnosis of delirium was made by physicians involved in the daily clinical care of patients according to the American Psychiatric Association definition as being of “acute onset characterised by global impairment of cognitive functions, reduced level of consciousness, attention abnormalities, increased or decreased psychomotor activity, and disordered sleep-wake cycle.”⁷ As some or all of these features apply to most patients shortly after awakening from general anesthesia, some authors recommend that a diagnosis of delirium not be made until 24 hours after surgery.³ Because the overall incidence of delirium in the Leipzig study is consistent with those in other contemporary reports, we must assume that similar time criteria were applied.

Most important, were the three surgical groups similar with respect to the risk factors for delirium? Multivariate logistic regression analysis identified 10 independent risk factors for delirium and 2 variables associated with a lower risk (younger age and avoidance of CPB). The 10 risk factors for delirium (essentially other indicators of vascular disease, impaired ventricular function, and complex surgical procedures) are in effect generic for any adverse outcome after cardiac surgery, neurologic or otherwise. And herein lies the major weakness of the Leipzig study. Because most of the risk factors for delirium were significantly lower in the OPCAB group, it is not surprising that they should have

a lower incidence of this complication. The authors were in effect comparing surgical populations with inherently different risks for delirium, and no amount of multivariable analysis can truly account for differences between apples and oranges.

Is there other supportive evidence that OPCAB reduces the risk of stroke or cognitive dysfunction? There are now several large observational studies reporting that OPCAB reduces the risk of stroke.⁹⁻¹¹ Although critics will argue, legitimately, that these do not carry the same weight as randomized trials, the absence of such trials cannot be used simply to ignore strong circumstantial evidence in favor of a neuroprotective effect of off-pump surgery. Absence of proof, in the absence of randomized trials, is not proof of absence. Indeed, an analogous situation existed for the internal thoracic artery graft, which is now widely accepted as the best conduit for CABG on the basis of strong circumstantial evidence rather than randomized trials. In any event, organization of such a trial would now present almost insurmountable difficulties. To demonstrate a 50% reduction in the risk of stroke from 3% would require several thousands of patients, and avoidance of both aortic manipulation and CPB would need to be factored into the randomization. Even more importantly, patients at the highest risk of stroke (those of advanced age with a history of cerebrovascular disease) are the very patients who would be most likely to be excluded from such a trial by surgeons confident with OPCAB and “no-touch” aortic techniques.

At the other end of the spectrum, evidence that OPCAB reduces cognitive dysfunction is conflicting, with reports of marked,¹² modest,¹³ and no¹⁴ benefits. This is not entirely surprising, as my own group previously reported, somewhat against intuition, that cognitive deficits appeared to be as common in patients undergoing OPCAB as on-pump CABG and that CPB therefore could not be the sole cause of such impairment.¹⁵ Other reports of cognitive deficits in

nonsurgical populations confirm our observations.^{16,17} However, paradoxically, before CPB is completely cleared of causing cognitive dysfunction, a note of caution needs to be sounded. Magnetic resonance imaging studies continue to confirm a high incidence of new infarcts in the brains of patients after CPB,^{18,19} and recent transcranial Doppler ultrasonographic studies confirm that patients undergoing on-pump CABG not only have a far higher number of cerebral microembolic events than do patients undergoing OPCAB but that a significantly higher proportion of these appear to represent particulate rather than gaseous debris.²⁰ Assuming that these sophisticated imaging techniques are indicating a real adverse effect of CPB on the brain, it is possible that the reason for failure of neurocognitive testing to detect real differences between on- and off-pump populations is simply that the noise to signal ratio is too high.²¹

In the absence of randomized trials, this study from the Leipzig group is an important and timely contribution to the literature. According to intuition, the authors are almost certainly correct that OPCAB reduces the risk of cerebral injury, but because of marked differences in their patient groups, their study cannot provide conclusive proof. It is, however, another incremental piece of evidence supporting the hypothesis that OPCAB is an important strategy to reduce the risk of cerebral injury.

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