Postoperative hypoxia is a contributory factor to cognitive impairment after cardiac surgery

S. M. Browne, MD, FAFRM^a
P. W. Halligan, PhD, DSc^b
D. T. Wade, MD^c
D. P. Taggart, MD, PhD, FRCS^a

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944 and 1087.

Objective: Cognitive dysfunction and postoperative hypoxia are common sequelae of coronary artery bypass grafting, but there has been no study to determine whether there is any relationship between them.

Methods: Arterial blood gas measurements were performed before surgical intervention and on the second and fifth postoperative day, and neuropsychological assessments were performed before surgical intervention and 5 days and 3 months postoperatively by using a battery of 10 psychometric tests in 175 patients undergoing coronary artery bypass grafting. An estimate of overall performance on the battery at each assessment point was provided by a simple aggregate cognitive index score calculated from the mean *z* scores of 4 normally distributed test variables. Multiple regression analysis was performed by using the cognitive index score at day 5 as the dependent variable, with age, sex, duration of the operation, presence or absence of cardiopulmonary bypass, preoperative cognitive index score, and arterial oxygenation and percentage of saturation at day 5 as independent variables.

Results: The mean cognitive index score decreased significantly in 115 (66%) patients who agreed to neuropsychological test battery assessment on the fifth postoperative day but improved significantly beyond baseline at 3 months. Mean arterial oxygen tension and percentage of saturation decreased significantly 2 days after the operation and, although improving over the following 3 days, remained decreased at day 5. Decreased cognitive index scores at day 5 strongly predicted cognitive impairment at 3 months ($r = 0.36$). The only significant independent predictors of the day 5 cognitive index score in the multiple regression analysis were preoperative cognitive index score and arterial oxygenation tension at day 5 ($r = 0.24$, $P < .03$).

Conclusions: We report a significant correlation between postoperative cognitive dysfunction and hypoxia 5 days after coronary artery bypass grafting. This finding might have therapeutic implications because early postoperative cognitive dysfunction influences long-term impairment.

Cognitive dysfunction is a well-documented complication of cardiac surgery. It is characterized by a marked deterioration on neuropsychological test performance in around two thirds of patients early after surgical intervention, and in many cases the deficits can last for several months or even years.¹ Recently, early postoperative neuropsychological impairment has been identified as a strong predictor of late cognitive deterioration.²

From the Oxford Heart Centre,^a John Radcliffe Hospital; the School of Psychology,^b Cardiff University; and Rivermead Rehabilitation Centre,^c Oxford, United Kingdom.

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Address for reprints: D. P. Taggart, PhD, FRCS, Consultant Cardiothoracic Surgeon, Oxford Heart Centre, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom (E-mail: david.taggart@orh.anglo-nhs.uk).

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TABLE 1. Mean (SD) Pao₂ cognitive index score, and percentage of saturation at each assessment point on the basis of 110 patients

	Assessment points			
	Preoperative	2 d	5 d	3 mo
Pao ₂ (kPa)	10.7 (1.1)	7.5 (1.2)*	9.2 (1.0)*	
% Saturation	95.8 (1.2)	89.9 (4.0)*	94.4 (1.7)†	
Cognitive index	+0.03 (0.74)		−0.26 (0.85)‡	+0.14 (0.77)‡

*Change from preoperative Pao₂ mean: paired *t* tests, *P* < .001.

†Change from preoperative percentage of saturation: paired *t* tests, *P* < .001.

‡Change from preoperative cognitive index mean: paired *t* tests, *P* < .005.

Cardiopulmonary bypass (CPB) is still considered to be the primary cause of cognitive deterioration after coronary artery bypass grafting (CABG),² although similar cognitive dysfunction is also observed after CABG without CPB³ and other major types of noncardiac surgery.^{4,5} Consequently, nonspecific factors, such as general anesthesia, the neurohumoral response to surgical intervention, and postoperative pain and sleep deprivation, need to be considered when discussing causality.³⁻⁵

In 1993, we reported that hypoxia was an invariable complication of CABG surgery and that 6 days after the operation, one quarter of patients still had severe respiratory impairment (defined as an arterial oxygen tension [Pao₂] of less than 8 kPa [60 mm Hg] while breathing room air).⁶ Using the same criteria, we recently found that 18% of patients undergoing CABG still had severe postoperative respiratory impairment.^{7,8} Consequently, we hypothesized that postoperative hypoxia might contribute to cognitive dysfunction after CABG.

Methods

We previously reported neuropsychological results in a cohort of 75 patients from a study population of 175 patients undergoing CABG surgery at our institution.³ In brief, 150 patients were taking part in a randomized placebo-controlled trial of a new anti-inflammatory agent, and the remaining 25 patients underwent CABG surgery without CPB.⁷ There were no favorable or detrimental effects in patients treated with the anti-inflammatory agent regarding postoperative oxygenation or cognitive performance, and hence the treatment groups were combined.

Serial neuropsychological assessments were performed before surgical intervention, before discharge, and 3 months postoperatively by a battery of 10 psychometric tests.³ A simple aggregate score, termed the "cognitive index," provided an estimate of a patient's overall performance on the battery at each assessment point. It represented the mean of a patient's scores on 4 of the 10 tests examining different cognitive domains. These included Test A from the Adult Memory Information Processing Battery (a test of information-processing speed), Trail-Making Test B (TMTB; a set-shift thinking test), Delayed Recall from the Auditory Verbal Learning Test (a memory test), and the Verbal Fluency Test (a test

of executive functioning). In all cases the raw data were normally distributed except for TMTB (in which data were normalized by taking the natural log because the raw scores were positively skewed).

We did not include several other tests in the aggregate score for a variety of reasons. These included the Immediate Recall component of the Auditory Verbal Learning Test (this added nothing significant to the Delayed Recall component used in isolation), Trail-Making Test A (this correlates strongly with TMTB and gives an effect of doubling up), the Bell test (prone to measurement error in relation to perceived time the subject had for test completion), the Orientation Memory Concentration test (only a gross screening test), Digit Span (unable to normalize the forwards and backwards component), and the Pegboard test (essentially a test of motor function, whereas our study was essentially aimed only at higher cognitive function).

Arterial blood gas samples were obtained before surgical intervention and 2 and 5 days postoperatively (with the patient breathing room air). Patients undergoing neuropsychological testing on postoperative day 5 had the arterial blood gas sample taken immediately on completion of testing. No patient was receiving supplemental oxygen on day 5. Patients with pre-existing pulmonary disease were excluded from the study.

Multiple regression analysis (forward stepwise with probability of *F* to enter = 0.05) was performed by using the cognitive index score at day 5 as the dependent variable. Independent variables entered into the analysis were age, sex, duration of the operation, presence or absence of CPB, preoperative cognitive index score, and arterial oxygenation tension at day 5.

Results

One hundred fifteen patients agreed to predischARGE assessment on the fifth postoperative day. A total of 156 patients completed neuropsychological testing before discharge and at 3 months.

The mean cognitive index score decreased significantly at the 5-day assessment but improved significantly beyond baseline at the 3-month assessment (Table 1). Mean arterial oxygen tension decreased significantly 2 days after the operation, and although it improved over the following 3 days, it remained significantly lower than the preoperative value (Table 1). Sixty percent of patients were hypoxic (Pao₂ of <8 kPa) at day 2, and 12% were hypoxic at day 5.

A decreased cognitive index scores at day 5 was a strong predictor of cognitive impairment at 3 months (partial correlation coefficient (*r*) = 0.36 when controlling for preoperative cognitive index). The preoperative cognitive index score and the Pao₂ at day 5 (or the percentage of saturation at day 5 levels as a substitute variable because one is derived from the other) were the only significant independent predictors of the day 5 cognitive index score in the multiple regression analysis (Table 2). Pao₂ and the percentage of saturation at day 5 both produced a partial correlation coefficient of 0.024 (*P* < .03) with the day 5 cognitive index score. Because saturation is derived from oxygen level, only one of these variables could be entered as

TABLE 2. Predicting day 5 cognitive index score (multiple regression analysis) on the basis of results in 110 patients

	Variable	B	Significance of <i>t</i> value
Variables in the equation	Preoperative cognitive index	0.958	.0000
	Day 5 oxygen	0.106	.0120
	Constant	-1.273	.0012
Variables not in the regression equation	Age		.16
	Sex		.13
	Operation time		.39
	CPB		.96

Regression equation: $F = 150.6$; significance of $F = 0.0000$.

an independent variable into the multiple regression equations in Table 2. Age, sex, duration of the operation, and presence or absence of CPB did not predict day 5 cognitive impairment.

Discussion

These findings suggest that postoperative hypoxia is a contributory factor to early postoperative cognitive deterioration after CABG and that the severity of cognitive impairment might be related to the degree of hypoxia at the time of the assessment.

Given that early postoperative cognitive impairment has been shown to be an indicator of long-term cognitive impairment,² an observation confirmed in the present study, our results raise concerns that postoperative hypoxia might contribute to long-term cognitive impairment. Recent studies have demonstrated that neuropathologic changes, particularly those in the hippocampal structures, are associated with cognitive impairment caused by hypoxia.⁹ Our speculation also receives support from similar widespread patterns of neuropsychological impairment (disorders of memory, attention, or concentration; decreased mental processing speed; or both) found in other conditions that produce variable degrees of cerebral hypoxia,¹⁰ including chronic obstructive pulmonary disease,¹¹ adult respiratory distress syndrome,¹² cardiac and respiratory arrest,⁹ and obstructive sleep apnea syndrome.¹³ Furthermore, the current findings are also consistent with our report of a similar level of cognitive dysfunction in patients undergoing CABG operated on with and without CPB³ in whom there is a similar severity of postoperative hypoxia.⁷

Although the extent of the association between hypoxia and cognitive impairment in our study is statistically significant, the overall correlation ($r = 0.24$) is relatively weak. It is possible, however, that our study underestimates the strength of this association because only two thirds of patients agreed to assessment on day 5, and it is the more severely impaired patients who are least likely to cooperate with postoperative assessment.¹⁴ Furthermore, because the mean age of our population was relatively young (62 years), a stronger association might be anticipated in older patients,

in whom there is a higher incidence of postoperative cognitive impairment.¹

In contrast to our findings, Moller and colleagues⁵ reported no relationship between postoperative hypoxia and cognitive impairment in the International Study of Postoperative Cognitive Dysfunction (ISPOCD).⁵ However, there are several differences in the designs and populations of these studies, which might explain the differing conclusions. Only 10% of the patients in the ISPOCD experienced hypoxia (defined simply by percentage of saturation change and not absolute arterial oxygen tension), and that study did not include patients undergoing cardiac surgery. This is particularly relevant because patients undergoing CABG experience more severe postoperative hypoxia than patients undergoing noncardiac surgery.⁶

In contrast to other studies, age and duration of operation were not significant predictors of early (day 5) cognitive impairment. The most likely explanation for this observation was the relatively narrow spectrum (mean $\pm$ SD) of both age (62 ± 8 years) and duration of CPB (65 ± 15 minutes). The failure to identify avoidance of CPB as protective against the occurrence of cognitive impairment is probably a result of the relatively small number of patients and the fact that these patients also experience cognitive impairment.³

If hypoxia contributes to cognitive morbidity after CABG, then preventing postoperative hypoxia with supplemental oxygenation might be a simple way to reduce postoperative cognitive dysfunction. Because of logistic difficulties in providing supplemental oxygen for such an extended postoperative period, a randomized trial to confirm our findings would be necessary.

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