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Objective: To describe the association between cognitive outcome in the first postoperative week and that at three months after both off-pump and on-pump coronary bypass surgery, and to make a direct comparison of early cognitive outcome after off-pump versus on-pump surgery.
Design: Randomised trial with an additional prediction study within the two randomised groups.
Setting: Three centres for heart surgery in the Netherlands.
Patients: 281 patients, mean age 61 years.
Interventions: Participants were randomly assigned to off-pump or on-pump coronary bypass surgery.
Main outcome measures: Cognitive outcome, assessed by psychologists who administered neuropsychological tests one day before and four days and three months after surgery. A logistic regression model was used to study the predictive association between early cognitive outcome, together with eight clinical variables, and cognitive outcome after three months.
Results: Cognitive outcome in the first week after surgery was determined for 219 patients and was a predictor of cognitive decline after three months. This association was stronger in on-pump patients (odds ratio (OR) 5.24, $p < 0.01$) than in off-pump patients (OR 1.80, $p = 0.23$). Early decline was present in 54 patients (49%) after off-pump surgery and 61 patients (57%) after on-pump surgery (OR 0.73, $p = 0.25$).
Conclusions: In patients undergoing first time coronary bypass surgery, early cognitive decline predicts cognitive outcome after three months. Early cognitive decline is not significantly influenced by the use of cardiopulmonary bypass.

Coronary artery bypass surgery (CABG) may affect cognitive function.[1] This may occur in up to 50% of patients, depending on the type of patient and the timing and method of neuropsychological assessment.[1–3] Cognitive decline after CABG has largely been attributed to the use of cardiopulmonary bypass (CPB),[4] but other determinants have been recognised as well. These include advanced age,[1 5–7] female sex,[8] diabetes,[8] history of stroke,[9] peripheral vascular disease, and manipulation of the ascending aorta.[5 8]

The octopus trial recently showed that at three months, the incidence of cognitive decline was 29% after on-pump CABG and 21% after off-pump CABG ($p = 0.15$).[10] The present analysis describes the incidence of early cognitive decline (that is, in the first week) after off-pump and on-pump surgery. Furthermore, as various studies have shown an association between early cognitive decline and after several months or years,[1 3 11] we studied such a relation in the present patient sample. This association was also assessed after accounting for other known predictors of cognitive decline.

METHODS

Patients and procedures

The design, methods, and patient characteristics of the octopus randomised trial have been described in detail elsewhere.[12] In brief, patients were eligible if referred for first time isolated CABG and an off-pump procedure was deemed technically feasible. The ethics committees of the three participating centres approved the study and written informed consent was obtained from all participants. A total of 281 patients were randomly assigned to off-pump or on-pump CABG. Ten patients randomly assigned to off-pump surgery underwent CABG with CPB because progression of symptoms required emergency surgery or because technical problems were encountered during the procedure. One other off-pump patient underwent coronary angioplasty. In five patients assigned to on-pump CABG, an off-pump procedure was performed.

During off-pump procedures, the octopus method[13] was used to stabilise the target coronary artery. During on-pump procedures, CPB was managed according to the α stat principle, with a minimum nasopharyngeal temperature of 32℃ and a non-pulsatile perfusion of 2.0–2.4 l/m^2/min. In the on-pump group 99% of the patients received total intravenous anaesthesia, including high dose opioids, whereas in the off-pump group 54% of the patients received thoracic epidural anaesthesia combined with low dose opioids.

Outcome

To establish early cognitive outcome, patients underwent a battery of six neuropsychological tests, one day before and four days after surgery. In accordance with the ''Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery''[14] the battery tested motor skills, verbal

Abbreviations: CABG, coronary artery bypass surgery; CI, confidence interval; CPB, cardiopulmonary bypass; OR, odds ratio

Table 1 Patients characteristics at baseline

Characteristic	All patients (n = 281)	Off-pump group (n = 142)	On-pump group (n = 139)
Age, mean (SD) (years)	61.2 (9.0)	61.7 (9.2)	60.8 (8.8)
Education, mean (SD) (years)	9.5 (2.6)	9.3 (2.4)	9.7 (2.8)
Male sex (%)	68	66	71
Peripheral vascular disease (%)	10	7	13
Diabetes (%)	13	9	17
History of stroke (%)	3	4	3
Hypertension (%)	42	40	44
Pulmonary disease (%)	9	9	10

memory capacity, and attention. Each test yielded one or more variables, with different ranges for each variable. Seven main variables were chosen a priori to be used in the analyses. (Table 2 lists the cognitive domains that were covered, the tests, and the main variables.) We defined "cognitive decline", according to commonly used criteria, as a decrease in the person's performance of at least 20% from baseline performance before surgery, in at least 20% (that is, two) of the main variables.[15] Patients who had had a stroke were considered to have cognitive decline. Early cognitive outcome could not be determined for 31 patients in each treatment group (22%). In the off-pump group, five patients appeared unsuitable for neuropsychological testing or withdrew from the study before surgery. Postoperatively, 26 other patients said they felt too weak or were physically unable to undergo the early neuropsychological assessment. In the on-pump group, nine patients appeared unsuitable for neuropsychological testing or withdrew before their surgery, and 22 were unable to undergo the early postoperative tests or claimed to be so. Three months after surgery, cognitive performance was determined with a more extended battery of 10 neuropsychological tests. Cognitive outcome at three months was determined for 248 patients.[10] For 210 patients, early cognitive outcome *and* the outcome at three months was established.

Data analysis

To estimate the predictive association between early cognitive outcome and cognitive outcome at three months, we calculated the odds ratio (OR) with 95% confidence interval (CI). This was done for the complete patient sample and for both treatment groups separately. To account subsequently for other possible predictors of three month cognitive outcome, multivariate logistic regression analysis was used. These other predictors were age, sex, diabetes, peripheral vascular disease, history of stroke or transient ischaemic attack, the number of diseased coronary arteries, perioperative use of aortic side clamps, and off-pump versus on-pump treatment. First the association between cognitive outcome at three months and each of the other possible predictors was quantified by univariate analysis. Then, all predictors with $p \leqslant 0.25$ in the univariate analysis were included in the multivariate model together with early cognitive decline.[16]

For the direct comparison of early cognitive outcome between the off-pump group and the on-pump group, data were analysed according to intention to treat. Incidences of early cognitive decline were compared by using the χ^2 statistic and the OR with 95% CI.

RESULTS

Patient characteristics

Mean age of the participating patients was 61 years and 68% were men (table 1). The mean number of distal anastomoses was 2.5. Baseline characteristics of the patients, including preoperative cognitive test performance, were balanced between the off-pump and on-pump groups (tables 1 and 2).

Association between early and three month cognitive outcome

Early cognitive decline was a predictor of cognitive decline after three months. This association was stronger in on-pump patients than in off-pump patients (table 3). Table 4 shows the results of the univariate and multivariate logistic regression analyses in the total sample. At three months, 62 of the 248 patients had "cognitive decline". Of the predictors other than early cognitive decline, we found only two weakly associated with three month cognitive decline in univariate analysis: on-pump versus off-pump treatment ($p = 0.15$), and use of side clamps ($p = 0.24$). However, in multivariate analysis combined with early cognitive decline, both were not significant at the 0.05 level such that the effect of early cognitive decline was the same as in univariate analysis (table 4). When this analysis was repeated for the off-pump and on-pump groups separately, early cognitive decline also was the only predictor of three month cognitive decline.

Direct comparison of early outcome in off-pump versus on-pump groups

Early cognitive decline occurred in 54 patients (49%) after off-pump CABG surgery and 61 patients (57%) after on-pump CABG surgery (OR 0.73, 95% CI 0.43 to 1.24, $p = 0.25$). The OR did not change after adjustment for

Table 2 Cognitive domains and neuropsychological tests at baseline and four days after surgery

Domain	Test	Main variable	Off-pump group Baseline	Off-pump group Day 4	On-pump group Baseline	On-pump group Day 4
Verbal memory, learning	Rey auditory verbal learning	Total score trial 1–5	36 (25–48)	35 (25–46)	36 (26–48)	35 (24–46)
Verbal memory, retrieval	Rey auditory verbal learning	Delayed recall score	6 (3–9)	6 (3–9)	6 (3–10)	5 (3–9)
Motor capacity	Grooved pegboard	Time dominant hand (s)	106 (88–137)	108 (90–161)	104 (91–141)	109 (92–142)
Divided attention	Trail making test part A and B	Time trail B (s)	83 (49–153)	83 (48–159)	84 (52–154)	89 (57–149)
Working memory speed	Sternberg memory comparison	Time 4 character chart (s)	59 (43–88)	56 (40–87)	57 (43–87)	54 (42–73)
Visuospatial capacity	Line orientation test	Total score	24 (17–29)	24 (17–29)	24 (18–28)	24 (18–29)
Selective attention	Stroop colour word test	Time C–time B (s)	43 (23–76)	44 (23–75)	40 (23–77)	39 (22–74)

All values are raw data and presented as medians, with 10th and 90th centiles in parentheses.

Table 3 Early cognitive decline as a predictor of cognitive decline at three months

	All patients (n = 210)		Off-pump group (n = 105)		On-pump group (n = 105)	
Predictor	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Early cognitive decline	3.07 (1.54 to 6.12)	<0.01	1.80 (0.69 to 4.66)	0.23	5.24 (1.8 to 15.21)	<0.01

OR >1.0 predicts cognitive decline at three months (< 1.0 absence).

Table 4 Three month cognitive outcome by logistic regression analysis

Predictor	All patients (n = 248)	Decline absent (n = 186)	Decline present (n = 62)	Univariate analysis		Multivariate analysis	
				OR	p Value	OR	p Value
Age, mean (SD) (years)	61 (9)	61 (9)	61 (9)	1.02*	0.90		
Female sex (%)	29	29	29	1.00	1.00		
Diabetes (%)	12	12	13	1.10	0.82		
Peripheral vascular disease (%)	8	8	8	1.00	1.00		
Previous stroke or TIA (%)	4	4	3	0.74	0.71		
Number of diseased coronary arteries	2.0	2.0	2.0	1.06	0.79		
Off-pump treatment (%)	49	52	42	0.65	0.15	0.87	0.68
Use of side clamp(s) (%)	42	40	48	1.42	0.24	1.74	0.10
Cognitive decline at day 4 (%)	52	46	72	3.07	<0.01	3.05	<0.01

OR >1.0 predicts cognitive decline at three months (<1.0 absence).
The 248 patients in this table are the patients for whom three month cognitive outcome was known.
TIA, transient ischaemic attack.
*OR per 10 years.

baseline differences in age, sex, diabetes, peripheral vascular disease, and number of diseased vessels (OR 0.73, p = 0.26) and increased slightly after adjustment for use of additional epidural anaesthesia (OR 0.88, p = 0.72).

DISCUSSION

In off-pump and on-pump coronary bypass group patients, we found an association between cognitive outcome in the first postoperative week and cognitive outcome at three months. In on-pump patients, other authors have found comparable results.[1 3 11] It is remarkable that in the present study, the association between early and late cognitive decline was stronger in patients who underwent surgery with CPB than in those without CPB.

A second finding is that clinical variables that were previously identified as predictors of cognitive decline were not associated with this outcome in the present patient sample. Advanced age is the least controversial demographic risk factor for cognitive decline,[1 5–7] but even this association could not be confirmed. One possible explanation is that the association between age and cognitive decline is curvilinear and that our relatively young patient group was on the flat part of this curve.

Finally, in a direct randomised comparison of off-pump versus on-pump patient groups, we found no significant effect of CPB on early cognitive outcome. The use of CPB is generally regarded as the main cause of cognitive decline.[4] In the same patient sample, we were unable to find a substantial cognitive benefit of off-pump surgery at three or 12 months.[10] It was anticipated, however, that early outcome would have been significantly improved. The only two other randomised studies on early cognitive outcome that have been carried out so far (n = 2 × 20 and n = 2 × 30) had a much better cognitive outcome after seven days with the use of off-pump CABG.[17 18] A major disadvantage of early neuropsychological assessment is that the patient's test performance may be determined by postoperative discomfort, pain, stress, and use of analgesics.[14] It has been shown, however, that neuropsychological testing is possible at two days[19] or even 18 hours[20] after CABG. Remarkably, the off-pump patients had a slightly quicker recovery (hospital discharge after six instead of seven days[21]), but this did not translate into better early cognitive outcome.

The present study has certain limitations. Since all definitions of cognitive decline are based on a comparison between preoperative and postoperative test performance, the association between early and late cognitive outcome may be explained by regression to the mean.[22] Patients who perform well—according to their own standards—on their preoperative assessment have a greater risk of performing worse on all future (postoperative) assessments and therefore may repeatedly meet the criteria of cognitive decline. Other limitations are single blinding and a 22% loss to follow up. Apart from the possible influence of postoperative discomfort on cognitive performance, this high dropout rate is a major disadvantage of early cognitive testing. As a concession to the limited physical abilities of the patients on the fourth day after surgery, we used a shorter battery of six neuropsychological tests for early cognitive assessment. The proportion of patients unable or unwilling to undergo neuropsychological testing on the fourth postoperative day was similar in the two groups. Also, the baseline characteristics of the patients who were lost to follow up and the fully observed patients were largely similar, suggesting no selective drop out. Another limitation of this study is that study participants were relatively young. The effects of an off-pump technique on early cognitive outcome may be more notable in older patients with more co-morbidity. A final limitation is that the anaesthetic management of the patients was different in the two groups because in the off-pump group 54% of the patients received thoracic epidural anaesthesia combined with a lower dose of opioids. This might have affected the cognitive performance in the immediate postoperative period.

We conclude that for patients undergoing first time CABG, early cognitive decline predicts cognitive outcome after three months. Early cognitive decline is not significantly influenced by the use of CPB.

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APPENDIX

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