Delirium and Cognitive Decline after Cardiac Interventions

Delirium en cognitieve achteruitgang na cardiale interventies
(met een samenvatting in het Nederlands)

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door

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Introduction

Chapter 1.1

General Introduction

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) effectively relieve symptoms of angina pectoris. Although the overall rate for coronary revascularization slightly declined over the last decade, CABG is still among one of the most commonly performed surgical procedures and in 2010, an estimated 954 000 PCI procedures and 397 000 bypass procedures were performed for inpatients in the United States alone.[1] In this period, hospital mortality rate declined for CABG and remained stable for PCI despite increased prevalence of comorbidity in patients who received these procedures. Both treatment strategies, however, are associated with neurocognitive complications that include postoperative delirium and cognitive decline.

Central nervous system injury in the immediate postoperative period may present as delirium. Derived from the Latin word 'delirare' (being deranged/deviating from track), delirium is an acute confusional state characterized by a disturbance in attention, and awareness with an additional disturbance in cognition, that is not explained by a preexisting neurocognitive disorder, and that is a direct physiological consequence of another medical condition.[2] While most clinicians will recognize increased arousal and hyperactivity as prominent features of hyperactive delirium, it is often overlooked that also a hypo-active form of delirium exists and that patients' mental state may fluctuate between both extremes within one episode. Not only is delirium extremely distressing to a patient and the family, it is now also recognized that the occurrence of delirium is associated with adverse outcomes.[3-6]

When physical recovery progresses and the initial postsurgical discomforts subsided, patients sometimes experience unanticipated cognitive problems. Lack of concentration, diminished speed of comprehension and sometimes even changes in personality are reported by patients and their spouses in the postoperative trajectory. These adverse out- comes were originally attributed to the effects of general anesthesia but it is now clear that the pathological basis of these symptoms is multifactorial and may include a combination of procedural and patient factors. Fortunately, postoperative cognitive impairment is often mild and transient, but when it is more profound or even permanent it can prevent return to work, and interfere with performing tasks of daily life. In recent years, improvements in surgical techniques and perioperative care have significantly reduced perioperative mortality. A consequence of these advances in medical care is that increasingly frail elderly patients become eligible for major surgery, thus enlarging the population at risk for cognitive decline.[7,8]

The aim of this thesis was to investigate early and late neurocognitive complications of cardiac interventions, encompassing the influence of various coronary revascularization strategies, the effect of an anti-inflammatory drug treatment and the influence of postoperative delirium on subsequent cognitive decline in cardiac patients.

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Chapter 1.2

Outline of the thesis

In the introduction section of this thesis, a general overview of cerebral outcomes after cardiac surgery is provided and the definition and prevalence of postoperative cognitive decline (POCD) and underlying pathophysiology and risk factors are described.

Next, in chapter 1.3, the difficulties of determining POCD in a research setting are discussed. In the chapters following the introduction it is investigated whether different cardiac revascularization strategies have a different effect on post-operative cognitive performance, whether an anti-inflammatory drug treatment affects postoperative delirium, and whether postoperative delirium has an effect on subsequent cognitive decline.

In chapter 2, the relation between preoperative differences in the cardiac vascular condition and postoperative cognitive outcome is examined in patients treated with conventional and off-pump coronary artery bypass grafting (CABG).

In chapter 3, the results of the long-term cognitive follow-up in patients treated with percutaneous coronary intervention (PCI) with stent placement compared to off-pump CABG are presented.

In chapter 4, brain integrity through detection of brain metabolites N-acetylaspartate and choline by magnetic resonance spectroscopy (MRS) in both cardiac intervention strategies are compared and the relation between brain metabolites and volume of white matter lesions and overall cognitive performance is examined.

In chapter 5, the effects of dexamethasone compared to placebo on the incidence of postoperative delirium are presented.

In chapter 6, the effects of postoperative delirium on postoperative cognitive performance are examined and additionally the relation between pre-operative cognitive functioning and the risk of developing postoperative delirium is described.

In the last section, the results presented in this thesis are summarized and discussed together with their implications for the individual patient and for future research in this area.

Chapter 1.3

Postoperative cognitive decline

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ABSTRACT

Memory loss and lack of concentration are symptoms that frequently occur in patients who have undergone a surgical procedure. Although cognitive function can be assessed using neuropsychological tests, reliable diagnosis of postoperative cognitive decline (POCD) appears to be difficult. Therefore, the true incidence of POCD is unknown. Severe POCD, which is apparent even without neuropsychological testing, is reported most frequently after cardiac and hip-replacement surgery. In these cases, POCD probably reflects microembolic brain injury. Apart from the nature of the surgical procedure, advanced age is the most important risk factor for POCD. The anesthetic technique is not a determinant of POCD: the risk of POCD appears to be similar after both general and regional anesthesia.

Introduction

After a surgical procedure, patients frequently report memory loss and lack of concentration. Some patients indicate that they are "just not the same" even if they underwent their surgery several years previously. Symptoms of subtle cognitive decline after surgery are usually described as "postoperative cognitive decline (POCD)". Patients often attribute these symptoms to their anesthesia.

Cognition

Cognitive functions such as perception, language processing, attention and memory functions, and abstract thinking are crucial for daily life activities, varying from everyday tasks such as driving and cooking to complex social interaction. One speaks of cognitive dysfunction when these processes do not go smoothly. Patients often describe their dysfunction as memory loss, lack of concentration, or slowness in executive and abstract functions.

Measuring cognition

There are many tests to measure cognitive performance.[1,2] These vary from the well-known "mini mental state examination (MMSE)" to more advanced and sometimes computerized neuropsychological tests. Examples are the measurements of reaction time or verbal and nonverbal memory. Every test, however, has its limitations. The MMSE has a ceiling effect: most patients obtain the maximum score and this test is therefore not suited to detect subtle cognitive decline. Often a series of five to ten different neuropsychological tests are used to measure different domains of cognitive functioning. These domains may include verbal and language skills, memory and learning, attention, concentration and perception, visual and spatial skills, visual motor and manual skills, numerical skills, executive functions, and composite measures.[3] There are even neuropsychological tests for aboratory animals; for example, tests measuring the time a thirsty rat needs to track down drinking water.[4] These tests are used in experimental settings to study disturbances in learning and memory functions, attributed to, for example, the use of anesthetics. Definition and prevalence of POCD After the patient has completed one or more neuropsychological tests, the presence or absence of POCD needs to be determined.[1] For some tests, tables are available with normal values, allowing a comparison of the patient's performance with that of groups similar in age, sex, and educational level. In daily practice patients are often tested only when the suspicion of POCD has arisen after the operation. For research purposes, patients are tested several times before and after an operation to determine the presence or absence of POCD. The postoperative performance will then be compared to the preope- rative performance. However, a person's cognitive performance varies by nature and so will the scores obtained by repeated neuropsychological testing in that person. Besides the phenomena of natural fluctuation in cognitive test performance and regression to the mean there can be learning effects as well, as seen in the frequently used word-learning tasks.[1] To correct for these effects information is needed about test-retest reliability and parallel versions of the tests used. Moreover, there is no consensus about the extent of the decline in test performance that is needed to speak of POCD. Therefore the prevalence of this condition depends on the definition used.[5-7] Some researchers even state that POCD rarely occurs, but is only diagnosed based on wrongful interpretations of the results of neur- opsychological tests.[8] An alarming prevalence of POCD, of more than 30% at 1 year after coronary bypass surgery, decreases to 10% when applying a more conservative definition.[6,9] By including nonsurgical controls in a study, who repeatedly undergo the same neuropsychological tests, the natural fluctuation in test results can be corrected for. In this way a more reliable estimate of the prevalence of POCD can be obtained. In a well-designed observational study in 1218 patients more than 65 years of age, undergoing major, noncardiac surgery, the incidence of POCD was quantified.[10] The authors also recruited 321 controls, who did not undergo an operation, but who were also repeatedly tested with neuropsychological tests. One week after the operation a prevalence of POCD of 26% was found. This decreased to 10% at 3 months postoperatively. A similar preva- lence was found 12 months after the operation. At every time interval an incidence of POCD of 3%, according to the definition used, was found in the nonsurgical controls. Other studies show that from 1 year after surgery onward the prevalence of POCD increases again. However, it is unknown whether this can be attributed to the surgery or to natural aging effects and other unrelated factors.[11]

Risk factors

Over the years a number of risk factors for the development of POCD have been identified. Cardiac surgery and specific orthopedic procedures are interventions with a relatively high incidence of POCD.[11-13] In general, larger and more invasive operations, such as abdominal, thoracic, and vascular surgery, present a larger risk than smaller, simpler procedures, such as outpatient surgery.[14] Irrespective of the type of surgery, advanced age is a major determinant of POCD.[10-12,15] Only few studies have looked at younger populations. In a study of 508 patients between 40 and 60 years of age a prevalence of 6% was reported 3 months after noncardiac surgery, while the prevalence reported in the 183 nonsurgical controls was 4%.[16] Hardly any studies of POCD are conducted in patients younger than 40 years of age. Oxygen saturation and blood pressure frequently drop during operations and in the first days and nights postoperatively. Although this has been subjected to extensive research, these parameters do not seem to be determinants of POCD.[10] Genetic make-up, such as the presence of apolipoprotein-E4 (the "Alzheimer") allele, appears to play no evident role as a risk factor for POCD either.[17,18] Several other risk factors, including lower educational level, a history of previous cerebral vascular accident, POCD at hospital discharge,[15] the postoperative pain treatment regimen,[19] and a history of alcohol abuse[20] are reported to influence the occurrence and severity of POCD at varying postoperative intervals.

Pathophysiology

It is a tempting idea to attribute POCD to the use of intravenous or volatile anesthetics. Although the regularly used hypnotics and analgesics cannot be traced in the blood anymore within a few days after an operation, it is conceivable that they may cause structural changes to the nerve system, which remain present for a longer period of time. Some evidence has been found in animal studies, and in in vitro experiments, that volatile anesthetics contribute to POCD through enhancement of the oligomerization and cytotoxicity of Alzheimer disease-associated peptides.[21,22] The theory that anesthetics may modulate new cell production and lead to POCD through anesthetic-induced suppression of neurogenesis has been disproved by Tung et al.[23] However, there are no clinical studies supporting these in vitro findings so far. A surprising, but consistent, finding which argues against general anesthetics as a cause of POCD is the fact that the incidence of POCD after regional anesthesia and after general anesthesia is similar.[24,25] In 19 trials patients were randomized to general or regional techniques. In only 1 of these studies a small difference in the incidence of POCD was detected, in favor of patients allocated to regional anesthesia.[25] A limitation of these studies is the fact that patients operated under regional anesthesia frequently received sedatives, usually low-dose benzodiazepines or propofol. Nevertheless, these findings suggest that factors other than anesthetic agents are responsible for the development of POCD. POCD after hip replacement procedures is associated with fat emboli arising from the bone marrow of the femur during insertion of the prosthesis.[26] Mostly emboli get stuck in the lung capillaries, but they can also end up in the brain. This most likely coincides with an open foramen ovale, which can be found in around 25% of the population. POCD after cardiac surgery is attributed to the use of cardiopulmonary bypass (CPB).[27] The use of CPB itself or manipulation of the aortic root can cause microemboli. Just as in the

example of hip replacement surgery, emboli can be detected intraoperative in the carotid artery or the arteria cerebri media with the use of Doppler echography. Magnetic resonance imaging and postmortem findings in patients after cardiac surgery reveal multiple small defects in the brain, most likely caused by these microembolic processes.[27] In a clinical trial comparing coronary bypass operations with and without CPB, POCD was also found in patients randomized to off-pump coronary bypass surgery.[9,28] Thus, the role of CPB in the development of POCD is probably not as crucial as always suspected. There is conflicting evidence on the effect of the processing of cardiotomy blood with a cell saver versus direct reinfusion through the cardiotomy suction reservoir. A study done by Djaiani et al.[29] showed a significant reduction in POCD with a cell saver, but a study done by Rubens et al.[30] failed to show the benefit of a cell-saver on cognitive outcome. Independent of the kind of surgical procedure (cardiac or noncardiac) or anesthetic regimen, it is known that surgery-induced tissue damage activates the peripheral immune system, resulting in the release of inflammatory mediators. This inflammatory response contributes to POCD through the per- and postoperative secretion of cortisol, cytokines, and other inflammatory mediators.[31-33]

Consequences for the patient

A small proportion of patients experience severe cognitive decline after their operation, without the focal signs consistent with cerebral infarction.[12,13] These patients are sometimes unable to resume their work, or they have to be admitted to long-term care facilities. After cardiac surgery the incidence of this severe POCD is about 3%.[12] The percentage of patients with severe POCD after noncardiac surgery is unknown, but is probably lower. A high proportion of patients self-report postoperative cognitive impairment through q uestionnaires. This impairment does not necessarily affect their daily activities. Compared with the strict criteria based on neuropsychological testing, subjective reporting overestimates the incidence of POCD.[16,34] Depression is often associated with subjective cognitive decline.[16,34] However, no clear association has been established between depression and POCD according to neuropsychological tests.[16] Also, there is no apparent relationship between a decline in neuropsychological test results and quality of life.[9,12] This confirms that the diagnosis "POCD", as established by means of neuropsychological tests, has little significance in real life for the individual patient, but is merely an outcome measure in research settings.

Conclusion

Cognitive functioning is a soft outcome measure, and it is extremely difficult to measure subtle differences in cognitive performance. The true prevalence of POCD is therefore uncertain. Cardiac surgery and certain orthopedic interventions in particular can be complicated by cognitive decline. After these procedures, POCD is probably a result of microembolic injury. There is little evidence that POCD is caused by general anesthesia.

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2

Delirium and cognitive decline after cardiac interventions

Chapter 2

Presence of coronary collaterals is associated with a decreased incidence of cognitive decline after coronary artery bypass surgery

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ABSTRACT

Objective

Coronary artery bypass grafting (CABG) is associated with significant cerebral morbidity, usually manifested as cognitive decline or stroke. The underlying mechanism leading to cognitive decline is still unclear. Presence of coronary collateral arteries, which may reflect an overall better cardiovascular condition, recently appeared to relate to a better cardiac outcome after CABG. In this study, we investigated the hypothesis that presence of coronary collaterals is associated with less cognitive decline after coronary artery bypass grafting.

Methods

Data from 281 patients undergoing first-time coronary artery bypass grafting were used. Presence of coronary collaterals was determined on the preoperative angiogram. Cognitive function was evaluated before the operation, at 3 and 12 months and 5 years thereafter by standardized neuropsychological assessment. Cognitive decline in individuals was determined by calculating the reliable change score, a cognitive change score corrected for natural testing variability and practice effects.

Results

Cognitive decline was found in 19 (8%) patients at 3 months, in 31 (12%) patients at 12 months and in 82 (34%) at 5 years follow-up. Presence of coronary collaterals was independently associated with a better cognitive outcome at both 3 months (odds ratio (OR) 0.30; 95% confidence interval (CI) 0.09—0.95; p = 0.04) and 12 months (OR 0.42; 95% CI 0.18—0.97; p = 0.04) after coronary artery bypass grafting. At 5 years, the OR was 0.57 (95% CI 0.31—1.05; p = 0.07).

Conclusions

In patients undergoing first-time coronary artery bypass grafting, presence of coronary collaterals is associated with a decreased risk of cognitive decline at both 3 and 12 months of follow-up. This trend persists at 5-year follow-up. Preoperative differences in the cardiac vascular condition may therefore predict cognitive outcome in patients undergoing coronary artery bypass grafting.

INTRODUCTION

Coronary artery bypass grafting (CABG) effectively relieves angina, but is complicated by postoperative cognitive decline. The incidence of cognitive decline varies from 3 to 50%, depending on patient characteristics, definition of decline, and timing of neuropsychological assessment.[1] Only in about 3% of CABG patients can the cognitive decline be attributed to perioperative stroke.[1,2] Although the degree of cognitive decline, as measured with extensive test batteries, does not always affect patients in functional terms, a proportion of patients experiences difficulties during postoperative rehabilitation or problems with return to employment .[1] Cerebral damage following CABG procedures has mainly been attributed to the use of cardiopulmonary bypass. To address these limitations of conventional bypass surgery (on-pump CABG), beating heart bypass surgery (off-pump CABG) has been reintroduced in clinical practice. In the Octopus trial, a small beneficial effect on cognitive outcome of off-pump CABG was demonstrated 3 months after surgery, but this effect became negligible after 12 months.[3,4] However, we recently demonstrated that patients with coronary collateral circulation who underwent off-pump CABG had a better cardiac outcome both perioperative and at 1 year than patients without coronary collaterals.[5] This may be attributed to the nature of the off-pump technique, during which the target vessel is temporarily occluded. In the presence of coronary collateral vessels this temporary occlusion most likely results in less cardiac ischemia and thus in a better overall cardiovascular condition. Consequently, we hypothesized that patients with extensive coronary collateral circulation might also have an improved capacity to maintain adequate cerebral perfusion, resulting in less cognitive decline than in patients without collaterals. We therefore reanalyzed the neurocognitive data from the Octopus trial[3] and studied, to our knowledge for the first time, if there is also a relationship between the presence of coronary collaterals and postoperative neurocognitive test performance.

METHODS

Study population

The study population consisted of the patients enrolled in the Octopus study.[3] In this study, 281 patients were randomly assigned to on-pump or off-pump CABG. Patients were eligible if referred for first-time isolated CABG and if the off-pump procedure was technically feasible. The study was approved by the institutional review committees of the three participating centers and was performed according to institutional guidelines. All subjects gave informed consent before participation. The present analysis was based on data from all 281 patients and adjustment was made for type of surgery (i.e. on-pump or off-pump treatment) as a possible confounder in the multivariable analysis.

Coronary collaterals

The presence of coronary collaterals was defined by visual assessment of the baseline angiogram using the Rentrop criteria (0, no filling of collaterals; 1, filling of collaterals without any filling of the epicardial artery; 2, partial filling of the epicardial artery; and 3, complete filling of the epicardial artery) .[6] Collaterals were considered present in case of filling of the epicardial artery (Rentrop > 1). The angiograms were independently graded in random order by two cardiologists who were blinded to clinical and each other's data. The reproducibility of the Rentrop score has been described as high ($k = 0.85$, 95% CI 0.77—0.93).[6]

Cognitive outcome

Patients underwent a battery of 10 neuropsychological tests 1 day before, 3 and 12 months and 5 years after the operation. All tests were administered in the participating hospitals by trained neuropsychologists. In accordance with the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery,[7] the battery included tests for motor skills, verbal memory capacity, and attention. In addition, tests were included to assess speed and capacity of working memory, visuospatial capacity, selective and sustained attention, and information processing. Each test yielded 1 or more variables, with different ranges per variable. Eleven main variables were chosen a priori to be used in the analyses. The cognitive domains that were covered, the tests, and the main variables are listed in Table 1. Administration of the tests lasted approximately 100 min. To limit practice effects, 6 of the 10 tests were also administered 2 weeks before baseline assessment and, wherever possible, parallel forms of the tests were used in the consecutive assessments. To determine the absence or presence of cognitive decline, each individual patient's postoperative cognitive performance was compared to his or her preoperative cognitive performance. The presence of cognitive impairment in individuals was determined by calculating a reliable change (RC) score, a standardized cognitive change score corrected for natural testing variability and practice effects.[4,8,9] To calculate an RC score, parallel cognitive test data from a non-operated control group were used. This control group has been described in detail elsewhere.[4] For each patient, scores at baseline, 3 and 12 months and 5 years postoperatively from each test were used to calculate the RC score as follows: RC = (postoperative score - baseline score) - (practice effect estimated from controls)/(standard deviation of difference scores estimated from control group). Cognitive decline was defined as a composite RC equal to or less than -1.96 or an RC equal to or less than -1.96 in two or more main variables. For analytical purposes, patients who had a stroke or had developed severe dementia were considered to have cognitive decline. In the original report of the Octopus trial, a different definition of cognitive decline (a decrease in an individual's performance of at least 20% from baseline, in at least 20% of the main variables; the 'standard' definition) was used.[3] This definition was later shown to overestimate the incidence of cognitive decline.[4]

Data analysis

The association between presence of collaterals and cognitive decline after 3 and 12 months and 5 years was examined by first calculating a crude odds ratio (95% confidence interval). Then the distribution of the most important confounders (i.e. age, sex, diabetes, hypertension, number of coronary artery grafts, postoperative myocardial infarction and off-pump vs on-pump treatment) across the patients with and without collaterals was quantified. We also quantified the association of these potential confounders with the outcome. Finally, we estimated the association between the presence of collaterals and the outcome, adjusted for the potential confounders using multivariable logistic regression analysis. Risks are presented as odds ratios (OR) with 95% confidence interval. All reported probability values are two-sided. Probability values <0.05 were considered statistically significant. All data were analyzed using SPSS for Windows v12.0.

Domain	Test	Main variable
Verbal memory, learning	Rey auditory verbal learning	Total score trial 1ó 5
Verbal memory, retrieval	Rey auditory verbal learning	Delayed recall score
Motor capacity	Grooved pegboard	Time dominant hand (s)
Divided attention	Trail making tests parts A and B	Time trail B (s)
Working memory speed	Sternberg memory comparison	Time 4-character chart (s)
Visuospatial capacity	Line orientation test	Total score
Selective attention	Stroop colour word test	Time Có time B (s)
Sustained attention	Continuous performance task	Mean reaction time (ms)
Working memory	Self-ordering tasks	Sum score
Visual working memory	Visuospatial working memory	Average distance (cm)
Information processing	Symbol digit modalities test	Total score

Table 1. Cognitive domains and neuropsychological tests

RESULTS

Baseline characteristics of the patients are shown in Table 2. Coronary collaterals were present on the angiogram in 46% of the patients. Possible confounders were equally distributed over the determinant categories, with exception of myocardial infarction (Table 2). As reported previously by Nathoe et al.,5 myocardial infarction occurred more often in the group without coronary collaterals. Three patients suffered from a perioperative stroke: two in the group with collaterals and one in the group without collaterals. The mean interval between operation and 3-month follow-up was 94 (SD 14) days, 379 (SD 57) days at 12-month follow-up, and 62 (SD 3) months at 5-year follow-up. Three months after surgery, 19 (8%) of 248 patients available for follow-up had cognitive decline. At 12 months, cognitive decline was present in 31 (12%) of 252 patients available for follow-up. Five years after surgery, 82 (34%) of 240 patients available for follow-up had cognitive decline. Relation between coronary collaterals and cognitive outcome (Tables 3 and 4) At 3 months, cognitive decline occurred in 4 (3%) of the patients with coronary collaterals, versus 15 (12%) of the patients without collaterals (OR 0.26; 95% CI 0.09—0.82; $p = 0.02$). After adjusting for age, sex, diabetes, hypertension, number of grafts, treatment type (i.e. on-pump or off-pump surgery) and myocardial infarction, the OR was 0.30 (95% CI 0.09—0.95; $p = 0.04$). At 12 months, cognitive decline was present in 9 (7%) of the patients with coronary collaterals, compared to 22 (17%) of the patients without collaterals (OR 0.40; 95% CI 0.18—0.90; $p = 0.03$). After adjusting for age, sex, diabetes, hypertension, number of grafts, treatment type and myocardial infarction, the association between collaterals and cognitive decline remained (OR 0.42; 95% CI 0.18—0.97; $p = 0.04$). At 5 years, cognitive decline was present in 31 (27%) of the patients with coronary collaterals, compared to 51 (41%) of the patients without collaterals (OR 0.55; 95% CI 0.31—0.95; $p = 0.04$). After adjusting for age, sex, diabetes, hypertension, number of grafts, treatment type and myocardial infarction, there was still a trend towards an association between collaterals and cognitive decline, although not significant (OR 0.57; 95% CI 0.31—1.05; $p = 0.07$).

Missing data

Cognitive outcome data could not be obtained in 33 (12%) patients at 3 months, in 29 (10%) patients at 12 months and in 41 (15%) patients at 5 years of follow-up. Reasons for not obtaining neuropsychological test data are summarized in Table 5. The characteristics of the patients who were available for analysis of cognitive outcome were comparable to the patient characteristics of the entire sample, indicating that the missing data were completely random. Still, to determine whether there was some bias in our data due to selective loss to follow-up, we imputed all missing cognitive outcomes by means of multiple imputation available in S-plus for Windows v7.0. After imputation, the odds ratios for cognitive decline at 3 months (OR 0.29; 95% CI 0.10—0.86), 12 months (OR 0.42; 95% CI 0.19—0.95) and 5 years (OR 0.60; 95% CI 0.34—1.05) were comparable to the odds ratios of the complete case analysis.

	All patients (n = 281)	Collaterals present (n = 129)	Collaterals absent (n = 152)	OR	p value *
Age	61.3 (9.0)	60.5 (8.9)	62.0 (9.1)	-	0.17
Female	89 (32)	40 (31)	49 (32)	0.95	0.90
Diabetes	36 (13)	13 (10)	23 (15)	0.63	0.22
Hypertension	118 (42)	50 (39)	68 (45)	0.78	0.33
Number of grafts				1.14	0.70
0	4 (1)	2 (2)	2 (1)		
1	46 (16)	22 (17)	24 (16)		
2	90 (32)	36 (28)	54 (36)		
3	102 (36)	50 (39)	52 (34)		
4	32 (11)	17 (13)	15 (10)		
5	5 (2)	1 (1)	4 (3)		
6	2 (1)	1 (1)	1 (1)		
Myocardial infarction	16 (6)	1 (1)	15 (10)	0.07	0.001
On-pump treatment	139 (49)	58 (45)	81 (53)	0.72	0.19

Table 2. Baseline patient characteristics and distribution of possible confounders between patients with and without collaterals

Age is displayed as mean (SD); all other variables are number (%). OR: odds ratio (unadjusted); (*) using Fisher's exact test.

	3-month cognitive outcome (n = 248)				1-month cognitive outcome (n = 252)				5-year cognitive outcome (n = 240)			
	Decline	No Decline	OR	p	Decline	No Decline	OR	p	Decline	No Decline	OR	p
Age	60.9(10.2)	60.7 (9.0)	-	0.92	63.9 (8.4)	60.6 (9.1)	-	0.06	65.1 (8.2)	58.5 (8.7)	-	<0.001
Female	7 (10)	65 (90)	1.47	0.44	10 (14)	62 (86)	1.22	0.63	23 (28)	43 (27)	1.04	0.89
Diabetes	3 (10)	27 (90)	1.40	0.61	4 (13)	27 (87)	1.61	0.22	14 (17)	17 (11)	1.71	0.17
Hypertension	7 (7)	90 (93)	0.90	0.83	16 (15)	88 (85)	1.06	0.91	33 (40)	62 (39)	1.04	0.88
Number of grafts			-	0.58			-	0.55			-	0.92
0	1 (0.4)	0 (0)			1 (0.5)	0 (0)			0 (0)	1 (1)		
1	37 (16)	2 (11)			34 (15)	4 (13)			11 (13)	27 (17)		
2	76 (33)	9 (47)			71 (32)	12 (39)			27 (33)	55 (35)		
3	83 (36)	5 (26)			83 (38)	10 (32)			32 (39)	52 (33)		
4	26 (11)	2 (11)			27 (12)	3 (10)			10 (12)	19 (12)		
5	4 (2)	1 (5)			3 (1)	2 (6)			1 (1)	3 (2)		
6	2 (1)	0 (0)			2 (1)	0 (0)			1 (1)	1 (1)		
Myocardial infarction	0 (0)	12 (100)	0.00	0.61	1 (7)	13 (93)	0.53	1.00	6 (7)	7 (4)	1.70	0.35
On-pump treatment	14 (12)	106 (88)	3.25	0.03	15 (12)	107 (88)	1.00	1.00	41 (50)	76 (48)	1.08	0.78

Table 3. Association between potential confounders and 3- and 12-month and 5-year cognitive outcome

Age is displayed as mean (SD); all other variables are n(%); OR: odds ratio(unadjusted); p: p-value using Student's t-test for age, and Fisher's exact test for all other variables.

3-month cognitive outcome (n = 248)					
	Decline	No decline	Crude OR	Adjusted OR	p value *
Collaterals	4	115	0.26	0.30	0.04
No collaterals	15	114			
12-month cognitive outcome (n = 252)					
	Decline	No decline	Crude OR	Adjusted OR	p value *
Collaterals	9	112	0.40	0.42	0.04
No collaterals	22	109			
5-year cognitive outcome (n = 240)					
	Decline	No decline	Crude OR	Adjusted OR	p value *
Collaterals	31	83	0.55	0.57	0.07
No collaterals	51	75			

Table 4. Association between coronary collaterals and cognitive outcome
OR: odds ratio; (*) of adjusted OR, using multivariable logistic regression analysis.

REASON	Number of patients at 3-month analysis	Number of patients at 12-month analysis	Number of patients at 5-year analysis
Patient appeared to be unsuitable for neuropsychological testing	2	2	1[a]
Withdrawal immediately after inclusion	3	3	3
Withdrawal after baseline assessment but before surgery	6	6	3[b]
Failure to administer baseline tests (logistic)	3	3	3
Mortality at time of cognitive follow-up	2	3	20
Readmission to hospital or too ill for postoperative assessment	5	2	1
Failure to administer tests at time of cognitive follow-up (logistic)	1	1	0
Unable to come for follow-up (holiday or caring for ill partner)	5	0	0
Not motivated for follow-up/withdrawal	6	9	10
Total number of patients missing neuropsychological assessment	33	29	41

Table 5. Reasons for missing neuropsychological assessment
At 5-year follow-up, five patients (1.9%) were unable to undergo neuropsychological testing because severe dementia (n = 3) or because of a non-fatal stroke (n = 1) or a fatal stroke (n = 1). These five patients were included in the cognitive analyses and were considered to have cognitive decline.

a. One patient who was unsuitable for neuropsychological testing at baseline had died at 5-year follow-up.
b. Three patients who had initially refused future cognitive assessments, appeared to be motivated to undergo 5 year follow-up.

DISCUSSION

We found an association between the presence of coronary collaterals and a lower incidence of postoperative cognitive decline at 3 and 12 months and 5 years after surgery in coronary artery bypass surgery patients. This association remained significant after adjustment for the most important possible confounders at 3 and 12 months, but not at 5 years of follow-up. Nevertheless this indicates that the absence of coronary collaterals might be relevant to cognitive outcomes in both short and long term. Previous studies on coronary collaterals have either looked at possible determinants of their presence or focused on their effect on cardiac outcomes.[5,10-13] The forming rate of coronary collaterals has been demonstrated to increase with the severity of stenotic disease of the coronary arteries.[14] Also, several mechanisms have been identified that enhance coronary collateral formation, most of which appear to have a genetic basis.[15-17] From the available evidence it seems likely that different patients will have different 'phenotypes' of vascular plaque formation and stability, leading to varying stimuli for collateral vessel formation. On the outcomes level, the presence of collaterals increases myocardial viability following infarction and recent studies have shown that coronary collateral circulation favors long-term cardiac outcome in patients undergoing percutaneous cardiac interventions and off-pump cardiac surgery.[5,13] However, the association between coronary collaterals and cognitive outcome has never been studied before. Little is known of the relationship between the presence of coronary collaterals on the one hand and the ability to utilize collateral pathways in the brain on the other. In patients with significant stenosis in the carotid or vertebral arteries, alternative routes of blood flow to specific brain regions are utilized. These collateral pathways may involve the circle of Willis, leptomeningeal vessels, the ophthalmic artery and other more rare connections. Often, cardiovascular disease has affected multiple vessels and organs in patients scheduled for CABG. For example, concomitant carotid artery stenosis is present in up to 50% of these patients.[18-20] It is thus conceivable that coronary artery disease is, at least in part, related to cerebrovascular pathology and that the ability to create collaterals in the heart is associated with the same process in the brain. Cerebral injury after cardiac surgery has been largely attributed to either insufficient brain perfusion or multiple cause embolism during the procedure.[21,22] Consequently, a sufficiently developed intracranial collateral blood supply theoretically reduces cerebral injury by protecting watershed areas that are most susceptible to infarction, and by limiting the size of an ischemic area following embolic vessel occlusion. In parallel with the results obtained in cardiac studies,[5,13] the presence of intracranial collateral circulation in patients with severe carotid artery stenosis has been associated with a better clinical outcome: these patients have a lower risk of stroke or transient ischemic attacks, and generally a better functional recovery following an ischemic event.[23] It is therefore conceivable that the presence of cerebral collaterals will also positively influence neurocognitive outcome following cardiac surgery. From another perspective, it can also be argued that coronary collaterals preserve myocardial function, and consequently lead to a better cardiac output. During and after surgery, a favorable cardiac output will most likely improve end-organ perfusion, and thus cerebral blood flow. This leads to a lower risk of insufficient brain perfusion and to reduced injury from embolic events, which in turn results in a better cognitive outcome. One step beyond, in patients with symptomatic systemic atherosclerotic disease, collateral vessel formation will probably be enhanced in both cardiac and cerebral tissue, by either recruitment of pre-existing pathways or by formation of new vessels. At least on the level of the smaller vessels, genetic predisposition in favor of formation of new vessels could play an important role here. This could be one of the mechanisms underlying the observed association between coronary collaterals and a better cognitive outcome in our study.[24] In the present study population, the only genetic polymorphisms that were assessed are variants of the apolipoprotein E (ApoE) gene locus. However, no association could be demonstrated between either cardiac collaterals or cognitive outcome and ApoE polymorphisms in this group of patients (data not shown). In the current analysis, data were used from all patients originally included in the Octopus study (i.e. patients from both the on-pump and the off-pump treatment arms). Although for a long time cerebral injury following CABG has mainly been attributed to the use of cardiopulmonary bypass, several recent randomized studies (including our own) were unable to demonstrate a beneficial effect of off-pump CABG on cognitive outcome.[3,25] We therefore believe that using data from both on-pump and off-pump patients is justifiable, as long as treatment type (i.e. on-pump or off-pump surgery) is corrected for in a multivariable analysis. In contrast with the original report of the Octopus study, we have now applied a more conservative definition of cognitive decline for the analysis of cognitive test scores. Using this definition, cognitive performance in operative patients is compared to cognitive performance in simultaneously tested patients in a matched non-operative control group, to take into account natural fluctuations in test performance.[3] In a recently published re-analysis of the Octopus data[4] as well as in other recent reports[9] it was shown that the previously used standard definition may overestimate the incidence of cognitive decline. Because misclassification of patients with cognitive decline decreases statistical power, we chose to use this more conservative definition of cognitive decline in the current analysis. A limitation of this study is that the study population may not be representative for the average patient population undergoing CABG. The young age (61 years on average),[3] the patients' eligibility for off-pump surgery and the relatively low incidence of cognitive decline during the follow-up period, disclose that the study population was at a relatively low risk for postoperative complications and cognitive deterioration. Another limitation is that, due to the relatively long testing time (100 min), subjects could have underperformed on the baseline tests, resulting in a too low estimate of the true incidence of cognitive decline. Finally, we had no information on the presence of carotid or vertebral artery stenosis in these patients. Patients with haemodynamically significant stenosis in the cerebropetal vessels may have been more at risk of cognitive deterioration after CABG. Although the associations found in this study are strong, there is always the risk that this observation is a statistical phenomenon rather than the clinical result of an underlying mechanism by which coronary collaterals relate to a decreased risk of postoperative cognitive decline. The present study is based on a post-hoc analysis and the original Octopus study was not designed to evaluate the possible association between coronary collaterals and cognitive outcome. Therefore, these results must be interpreted with care, and must be considered primarily hypothesis generating. Future studies need to clarify possible underlying mechanisms, and should confirm whether or not this association is clinically useful in predicting the risk of cognitive deterioration after CABG. We conclude that in patients undergoing first-time CABG surgery, presence of coronary collaterals is associated with a decreased risk of cognitive decline at both 3 and 12 months of follow-up. Moreover, a trend remained present at 5 years. Preoperative differences in the cardiac vascular condition may therefore predict cognitive outcome in patients undergoing CABG surgery.

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Chapter 3

Cognitive Outcomes 7.5 Years After Angioplasty Compared With Off-Pump Coronary Bypass Surgery

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ABSTRACT

Background

Off-pump coronary artery bypass grafting and percutaneous coronary intervention are both associated with cognitive decline, but limited data are available on long-term outcomes. This study compared long-term cognitive outcomes between patients managed with percutaneous coronary intervention and off-pump coronary artery bypass grafting.

Methods

A multicenter trial in the Netherlands randomized 280 patients to percutaneous coronary intervention or off-pump coronary artery bypass grafting. Cognitive performance 7.5 years after randomization was assessed through a battery of 9 neuropsychologic tests and summarized into a combined Z-score.

Results

After 7.5 years, cognitive assessment could be performed in 81% of the 249 surviving patients. Better cognitive performance was observed in the off-pump coronary artery bypass grafting group (combined Z-score 0.11 for off-pump coronary artery bypass grafting versus -0.17 for percutaneous coronary intervention; difference 0.28, 95%confidence interval 0.08 to 0.47, $p < 0.01$). However, this difference became not significant (Z-score difference 0.14, 95% confidence interval -0.01 to 0.29, p (0.08) after multivariable adjustment for potential confounders.

Conclusions

At 7.5 years follow-up, off-pump coronary artery bypass grafting patients had a similar or perhaps even better cognitive performance compared with percutaneous coronary intervention patients.

INTRODUCTION

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) effectively relieve symptoms of angina pectoris.[1] Both treatment strategies, however, may be associated with some degree of cognitive decline, possibly due to cerebral emboli during the intervention.[2,3] Emboli after CABG have been attributed to the use of cardiopulmonary bypass (CPB) and off-pump CABG without CPB reduces cerebral emboli.[4] Embolic complications after PCI may arise from manipulation of the atheromatous wall of the aortic arch or introduction of air bubbles by coronary catheters.[2] The specific impact of CPB use during CABG on postoperative cognitive health remains controversial given that off-pump CABG surgery has not been shown to translate into better long-term cognitive outcome.[5-8] In 1, non-randomized, cohort study that compared long-term cognitive outcome among 3 groups of cardiac patients (those undergoing off-pump CABG, those undergoing on-pump CABG, and those not requiring CABG), underlying factors such as patient age and level of education accounted for long-term cognitive outcome far more than whether the patient underwent CABG surgery with or without CPB.[6] The Octopus Study randomized 280 patients who were candidates for PCI with bare metal stenting to receive either PCI or an off-pump CABG and found after 1 year that stenting was more cost-effective than off-pump surgery while maintaining comparable cardiac outcome and quality of life.[9] However, cognitive outcomes have never been reported for these patients. Given the current controversy of whether the choice of revascularization strategy influences long-term cognitive outcome, we sought to compare long-term cognitive outcomes between patients who were managed with PCI with those who were managed with off-pump CABG.

MATERIAL AND METHODS

Design and Patients

The 280 study subjects in the Octostent arm of Octopus Study consisted of patients from 3 Dutch centers who were referred between 1998 and 2000 for a PCI procedure where either PCI or off-pump CABG was deemed technically feasible. Patients were randomized to PCI with bare metal stent implantation or off-pump CABG. Details of the Octopus Study methods and 1-year results have been published elsewhere.[9] This report describes the results of a long-term follow-up study of cognitive outcomes in patients enrolled in the Octopus Study. Ethics committee approval for this long-term study was obtained from each participating center and written informed consent was obtained from all patients.

Cognitive Assessment

Data regarding baseline neuropsychologic status was not available given that the evaluation of long-term cognitive outcomes was not considered when the Octopus study was first conceived. Cognitive status at the 7.5 years follow-up was evaluated using a battery of 9 neuropsychologic tests that were deemed, on a priori basis, to yield 11 different test variables (Appendix). This battery of neuropsychologic tests consisted of those recommended in the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery[10] and was supplemented with computerized tests from the CogHealth battery.[11] These tests evaluate the cognitive domains of verbal memory, motor capacity, divided attention, reaction time, decision making, working memory, and learning. Total test time was 60 to 90 minutes, depending on the patient's speed of comprehension and execution. To obtain an overall score of cognitive performance, we first calculated a Z-score for each raw test score of each patient, by subtracting the total group mean from the patient's individual score and dividing the residue by the group standard deviation. Scores of timed tasks were multiplied by $^{-1}$, so that a higher Z-score always indicates better cognitive performance. Then, an overall Z-score was calculated as the mean of the Z-scores of the 11 test variables, and used as an overall composite cognitive outcome measure.

Quality of Life

Quality of life was assessed at follow-up using the Short Form-36 (SF-36) questionnaire which is comprised of 9 different domains, each ranging in scores from 0 to 100. A higher score indicates a higher level of functioning or well-being.[12] Prior to each neuropsychologic evaluation, each patient was asked whether 1 or more of the following were present: sensory impairment; utilization of psychiatric or psychologic services; sleep or concentration problems; or short- or long-term memory loss.

Data Acquisition

The general practitioner of each patient who had participated in the Octopus Study was sent a letter to determine whether the patient was still alive. A study consultant subsequently invited these patients over the telephone to participate in the follow-up study. When either the patient or the general practitioner reported that a cardiovascular event (death, stroke, myocardial infarction, or coronary revascularization) had occurred, the attending physician was contacted and photocopies of original reports, letters, laboratory tests, and electrocardiograms were obtained for verification of the event. All neuropsychologic tests were administered at the patient's home to minimize patient burden and maximize the completeness of cognitive follow-up. Neuropsychologic testing was performed by 2 different bachelor degree-trained psychology assistants.

Each assistant received extensive training from an experienced neuropsychologist including a 3-month inpatient training period. An experienced neuropsychologist was available for consultation throughout the entire study period.

Each subject received a phone call and an informational letter prior to the planned visit. Prior to each assessment, home environments were adjusted as necessary by the evaluator to minimize distracting influences that included asking other individuals to leave the room and switching off telephones during the assessment.

Data Analysis

For the present follow-up study, we did not perform a power calculation because the sample size of the study is based on the power calculation of the original OctoStent Study, which compared major adverse events in the first year after PCI versus off-pump CABG. Data were analyzed according to the intention to treat principle; ie, based on randomization. Overall cognitive performance is presented as means with standard deviation and compared using a 2-sample test. Not normally distributed continuous values are presented as medians and were compared using the Mann-Whitney test. We performed a multivariable linear regression analysis to adjust for potential baseline differences between the 2 groups that were available for cognitive follow-up. The multivariable analysis was conducted with the aim to adjust for potential confounding factors. Therefore all variables were added into the analysis at once and no threshold criteria were used. We included the following potential confounders: age at time of neurocognitive testing; gender; level of education; diabetes; smoking; hypertension; hypercholesterolemia; renal dysfunction; extent of coronary disease; and left ventricular function. Additional sensitivity analyses were conducted excluding patients with impaired left ventricular function and stroke. We also performed a post hoc comparison of test scores with normative data. We considered scores in the second percentile or lower (Rey Auditory Verbal Learning and Trail Making Test), more than 2 standard deviations above the mean for timed tests (Grooved Pegboard, Continuous Monitoring task, Simple Reaction Time test, Choice Reaction Time test, 1-Back Working Memory task), or more than 2 standard deviations below the mean for accuracy (1-Back Working Memory task) impaired. Normative data for the complex reaction time test and associative learning task were not available. The analyses were performed using SPSS software, version 15 (SPSS Inc, Chicago, IL). Multiple imputation analysis to evaluate the possible effect of missing data was performed using R software version 2.8.1. The variables used for multiple imputation were randomization group, age at time of neurocognitive testing, gender, unstable angina, brain ischemia, obesity, renal dysfunction, extent of coronary disease, diabetes, smoking, hypertension, hypercholesterolemia, left ventricular function, use of side clamp, infarction, and the outcomes of the 9 separate cognitive tests. These variables differed slightly from those selected for the multivariable analysis; we did not use "level of education" in the imputation for technical reasons and the variables "use of side clamp," "infarction," and the outcomes of the separate cognitive tests were added as this led to better imputation modeling. All reported p-values are 2-sided.

RESULTS

Characteristics of the Patients and Completeness of Follow-Up

In the original study, 138 patients were randomized to receive PCI and 142 patients to receive off-pump CABG. The flow of patients throughout the trial is shown in Figure 1. The baseline characteristics of patients are summarized in Table 1. The time interval between the index treatment and the long-term cognitive assessment averaged 7.46 ± 0.5 (mean ± SD) years in the PCI group and 7.44 ± 0.4 years in the off-pump CABG group (p= 0.78). Overall, 31 of the 280 (11%) patients died during this period with the mortality rate being similar between the PCI (n= 12) and off-pump CABG (n= 19) groups (p= 0.21). Of the 249 surviving patients, 247 (99%) were contacted by letter or telephone. A total of 201 of these 247 (81%) patients agreed to undergo the neuropsychologic test battery. Of these patients, 4.5% of the patients failed to complete 1 of the tests and 5.0% of the patients failed to complete more than 1 test. Reasons for missing neurocognitive follow-up are shown in Figure 1. During the 7.5-year follow-up period 3 (2.2%) patients in the PCI and 3 (2.1%) patients in the off-pump CABG group experienced clinical symptoms of a stroke. The baseline characteristics of the 201 patients who underwent cognitive assessment at follow-up are also shown in Table 1. Table 2 shows the cardiovascular events that occurred after randomization in the patients available for cognitive follow-up. The proportion of patients who underwent at least 1 coronary reintervention was 33.7% in the PCI group and 17.0% in the off-pump CABG group, (p <0.01). The proportions of patients reporting psychiatric or psychologic help (12.4%), sleeping problems (10.9%), concentration problems (9.5%), short-term memory impairment (3.5%), and long-term memory impairment (10.4%) were balanced between both groups. When asked about sensory impairments, more patients in the PCI group reported hearing difficulties (24 [25.3%] vs 14 [13.2%], p <0.05), often requiring hearing aids.

Cognitive Outcome

The univariable analysis revealed that overall cognitive performance was better in the off-pump CABG group (combined Z-score 0.11 for off-pump CABG versus 0.17 for PCI; difference 0.28, 95% confidence interval [CI] 0.08 to 0.47, p <0.01). Cognitive outcomes were more favorable in the off-pump CABG group versus the PCI group for the domains of learning, motor capacity, and verbal memory (Table 3). For the 3 individual tests that showed better cognitive performance in the off-pump CABG patients, we performed a post hoc, explanatory analysis that was stratified for both age (younger versus older) and educational level (lower versus higher). We observed no significant heterogeneity across these subgroups. After multiple imputation for the patients who were alive but not available for cognitive follow-up, and for missing data of patients who did not complete the full test battery, the overall result remained similar (difference 0.25, 95% CI 0.08 to 0.42, p <0.01). However, the difference attenuated and statistical significance was lost when applying the multivariable linear regression model (difference 0.14, 95% CI -0.01 to 0.29, p= 0.08). Additional sensitivity analyses excluding patients with impaired left ventricular function and stroke showed similar results. Comparison of individual patient data against normative values showed the highest percentage of low values within the domains of verbal memory and motor capacity (see Table 4). With the exception of simple reaction time (11 [12.1%] in the PCI group versus 2 [1.9%] in the off-pump CABG group, p <0.01), no significant differences in number of patients with abnormally low scores were found.

Quality of Life

There were no differences between the 2 groups in 7 of the 9 domains of the SF-36 quality of life questionnaire. However, the domain "role limitations due to emotional problems" showed a higher score in the off-pump CABG group (mean 58 ± 45.2) compared with the PCI group (mean 44 ± 45.5, p= 0.02). Also, the domain "general mental health" showed a higher score in the off-pump CABG group, (mean 60 ± 8.2) compared with the PCI group (mean 58 ± 8.8, p= 0.02).

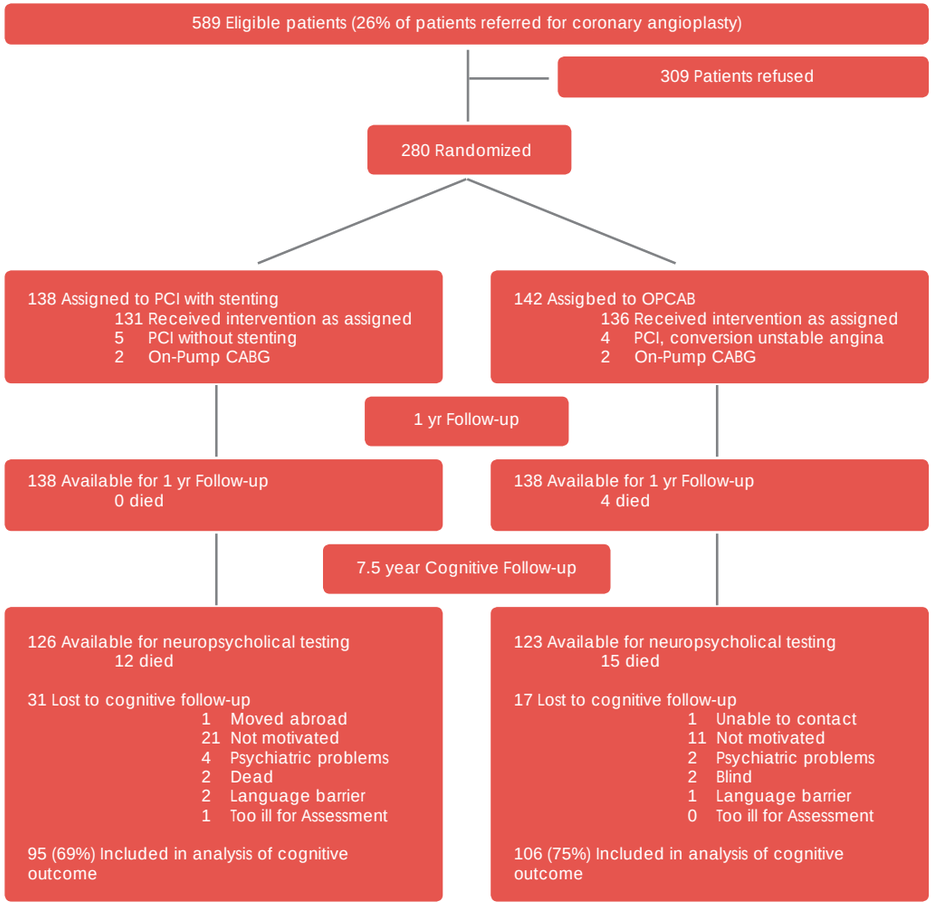

Figure 1. Flow of patients through the trial

CABG= coronary artery bypass grafting;
OPCAB= off-pump coronary artery bypass grafting;
PCI= percutaneous coronary intervention.

Variable	All randomized patients			Patients with cognitive tests		
	PCI (n=138)	OPCAB (n=142)	p-value	PCI (n=95)	OPCAB (n=106)	p-value
Age mean (SD) year	60 (9)	59 (10)	0.13	59 (8)	57 (9)	0.10
Male sex (%)	97 (70)	102 (72)	0.78	70 (73)	77 (73)	0.99
Education mean (SD) scorea	3.8 (1.5)	4.1 (1.3)	0.05	4.1 (1.4)	4.3 (1.3)	0.26
Previous conditions and risk factors						
Stroke or TIA (%)	8 (6)	10 (7)	0.67	5 (5)	5 (5)	0.86
Myocardial infarction (%)	34 (25)	33 (23)	0.78	25 (26)	24 (23)	0.55
Diabetes (%)	12 (9)	20 (14)	0.23	9 (9)	14 (13)	0.41
Hypertension (%)	46 (33)	44 (31)	0.67	32 (34)	34 (32)	0.81
Hypercholesterolemia (%)	81 (59)	85 (60)	0.94	59 (62)	66 (62)	0.98
Impaired LVF (%)	13 (9)	30 (21)	<0.01	10 (11)	23 (22)	0.03
Multiple-vessel disease (%)	44 (32)	37 (26)	0.28	28 (29)	29 (27)	0.35
Smoking (%)	34 (25)	27 (19)	0.20	29 (30)	23 (22)	0.23

Table 1. Baseline characteristics*
a Dichotomous data are presented as numbers with percentages in brackets.
b The level of education was classified according to Dutch norm data using the system of Verhage, ranging from 1 (no education) to 7 (university).

LVF= left ventricular function;
OPCAB= off-pump coronary artery bypass grafting;
PCI= percutaneous coronary intervention;
TIA=transient ischemic attack.

All Events	Patients with cognitive tests		
	PCI (n=95)	OPCAB (n=106)	p-value
Death from any cause	-	-	-
Stroke	0 (0)	1 (0.9)	0.34
Myocardial infarction	6 (6.3)	6 (5.7)	0.85
Repeated revascularization	32 (33.7)	18 (17.0)	0.01
CABG	7 (7.4)	2 (1.9)	0.06
PCI	27 (28.4)	17 (16.0)	0.03

Table 2. Major adverse events*
*Dichotomous data are presented as numbers with percentages in brackets.
CABG denotes coronary artery bypass grafting, PCI percutaneous coronary intervention.

Domain	Test Variable	PCI Group Raw Test Score Median (IQR)	PCI Group Z-score, Mean (SD)[a]	OPCAB Group Raw Test Score, Median (IQR)	OPCAB Group Z-score, Mean (SD)[a]	p-value[b]
Verbal memory	RAVL 1-5	27 (19-34)	-0.19 (1.07)	30 (22-37)	0.17 (0.90)	0.01
Verbal memory	RAVL DR	5 (3-7)	-0.17 (0.93)	5 (4-8)	0.14 (1.04)	0.06
Motor capacity	GP	97 (86-119)	-0.17 (1.69)	92 (78-107)	0.16 (0.91)	0.03
Divided attention	TMT-B	104 (78-161)	-0.13 (1.18)	104 (80-140)	0.12 (0.81)	0.55
Divided attention	MON	2.7 (2.6-2.8)	-0.96 (1.06)	2.7 (2.6-2.7)	0.09 (0.94)	0.17
Reaction time	SRT	2.5 (2.4-2.6)	-0.06 (1.10)	2.5 (2.5-2.6)	0.05 (0.90)	0.89
Reaction time	CRT	2.9 (2.8-2.9)	-0.07 (1.03)	2.9 (2.8-2.9)	0.06 (0.98)	0.46
Decision making	ChRT	2.7 (2.7-2.8)	-0.07 (1.09)	2.7 (2.7-2.8)	0.06 (0.92)	0.49
Working memory	OBK Acc	1.1 (1.0-1.3)	-0.11 (1.04)	1.2 (1.0-1.3)	0.09 (0.96)	0.18
Working memory	OBK RT	2.9 (2.8-3.0)	-0.11 (0.99)	2.9 (2.8-3.0)	0.10 (1.00)	0.18
Learning	AssL	0.7 (0.6-0.8)	-0.18 (1.48)	0.7 (0.6-0.8)	0.15 (0.04)	0.03
Overall Z-score*			-0.17 (0.78)		0.11 (0.60)	<0.01

Table 3. Neuropsychological test results and Z-scores at 7.5 year follow-up
a For each raw test score of every patient, a Z-score was calculated by subtracting the total group mean from the patient's individual score and dividing the residue by the group standard deviation. Scores of timed tasks were multiplied by -1, so that a higher Z-score always indicates better cognitive performance. The overall Z-score is the mean of the Z- scores of the 11 test variables.
b P-values are for the comparison of the median raw test scores between the PCI group and the OPCAB group by the Mann Whitney test.
* The overall Z-score of the two groups was compared using the 2-sample t test.
PCI denotes percutaneous coronary intervention, OPCAB off-pump coronary artery bypass grafting, IQR interquartile range.

Test variables

RAVL 1-5: Rey Auditory Verbal Learning test, total score trials 1 to 5
RAVL DR: Rey Auditory Verbal Learning test, delayed recall score
GP: Grooved Pegboard test, time dominant hand (s)
TMT-B: Trail-making test, time trail B (s)
MON: Continuous monitoring task, reaction time (Log10 ms)
SRT: Simple Reaction Time test, reaction time (Log10 ms)
CRT: Complex Reaction Time test, reaction time (Log10 ms)
ChRT: Choice Reaction Time test, reaction time (Log10 ms)
OBK RT: One Back working memory task, reaction time (Log10 ms)
OBK Acc: One Back working memory task, accuracy (arcsine of proportion correct responses)
AssL: Associative learning task, accuracy (arcsine of proportion correct responses)

Domain	Test Variable	PCI (n = 95)		OPCAB (n= 106)		p-value
Verbal memory	RAVL 1-5	36	(40.4)	36	(35.3)	0.463
Verbal memory	RAVL DR	14	(15.9)	18	(17.6)	0.102
Motor capacity	GP	29	(32.2)	29	(28.7)	0.599
Divided attention	TMT-B	8	(9.2)	6	(5.9)	0.386
Divided attention	MON	7	(7.7)	6	(5.8)	0.604
Reaction time	SRT	11	(12.1)	2	(1.9)	0.005
Reaction time	CRT	-	-	-	-	-
Decision making	ChRT	1	(1.1)	2	(1.9)	0.635
Working memory	OBK Acc	11	(12.1)	6	(5.8)	0.124
Working memory	OBK RT	1	(1.1)	2	(1.9)	0.635
Learning	AssL	-	-	-	-	-

Table 4. Numbers of patients with a low cognitive performance, per test*
*Dichotomous data are presented as numbers with percentages in brackets.
PCI denotes percutaneous coronary intervention, OPCAB off-pump coronary artery bypass grafting.

Test variables

RAVL 1-5: Rey Auditory Verbal Learning test, total score trials 1 to 5
RAVL DR: Rey Auditory Verbal Learning test, delayed recall score
GP: Grooved Pegboard test, time dominant hand (s)
TMT-B: Trail-making test, time trail B (s)
MON: Continuous monitoring task, reaction time (Log10 ms)
SRT: Simple Reaction Time test, reaction time (Log10 ms)
CRT: Complex Reaction Time test, reaction time (Log10 ms)
ChRT: Choice Reaction Time test, reaction time (Log10 ms)
OBK RT: One Back working memory task, reaction time (Log10 ms)
OBK Acc: One Back working memory task, accuracy (arcsine of proportion correct responses)
AssL: Associative learning task, accuracy (arcsine of proportion correct responses)

COMMENT

The present study is the first randomized trial comparing long-term cerebral outcomes between PCI and OPCAB. In the primary univariate comparison of the 2 randomized groups, we found a difference in cognitive performance favoring OPCAB, which remained present after imputation of missing cognitive data. However, in a multivariate model the difference was smaller and not statistically significant. The risk of symptomatic neurologic complications after PCI is 0.2% to 0.9%,[2,13] and 1% to 2% after bypass surgery.[14,15] In the present study there were no strokes in the perioperative period or the first year of follow-up. During the 7.5-years follow-up period 3 (2%) patients in each group experienced clinical symptoms of a stroke. Cognitive decline after coronary revascularization has been attributed to emboli from CPB and due to manipulation of the ascending aorta through cannulation and cross clamping in conventional CABG surgery and internally by coronary catheters in PCI. In the present study, the patients randomized to PCI with bare metal stenting had significantly more coronary revascularizations during follow-up than the patients randomized to off-pump CABG which may partially explain why cognitive performance was lower in this group. However, several recent studies have indicated that patient-related factors like advanced age, diabetes, a low level of education, and presence of cardiovascular disease are more important determinants of long-term cognitive outcome than the mode of coronary revascularization.[6,8,16,17] The overall cognitive performance of the off-pump CABG group was superior to the PCI group. Correction for known risk factors through a multivariable analysis attenuated this difference, supporting the hypothesis that some demographic variables may have more influence on long-term cognitive outcome than the mode of revascularization. Several limitations of our study should be mentioned. At the time of design of the trial no difference in cognitive outcome between off-pump CABG and PCI was expected[18] and therefore no baseline neuropsychologic assessment was performed before coronary intervention. This is a major limitation, because the 1994 consensus statement on the assessment of neurobehavioral outcomes after cardiac surgery[10] recommends applying such a baseline assessment. The lack of baseline testing affects what sort of conclusions can be drawn from the data. It is not possible to quantify the change in cognitive performance over time in both groups, but it is possible to answer the cross-sectional question of whether one group has a better cognitive performance than the other 7.5 years after the randomization. Further, patients were tested within their own home environment rather than at the hospital. This may have resulted in a less standardized and controlled testing environment. On the other hand, testing at home has contributed to the motivation of patients to undergo the evaluation, resulting in an excellent long-term cognitive follow-up of 81% of surviving patients, which is higher than in other randomized studies reporting long-term cognitive outcomes.[8,18] We used multiple imputation to test the strength of the results when correcting for the loss to follow-up. After imputation, the results remained similar. In conclusion, at 7.5 years follow-up, off-pump CABG patients had a similar or perhaps even better cognitive performance compared with PCI patients. In addition, it was shown that demographic variables are more important determinants of long-term cognitive outcome than mode of revascularization.

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APPENDIX

Test and Variable	Domain	Description
Rey auditory verbal learning (RAVL) - immediate recall, total score of 5 trials - delayed recall, number correct	Verbal memory	Fifteen monosyllabic words are presented in 5 trials. Each trial ends with a free recall. After 20 minutes, delayed recall is tested.
Grooved pegboard (GP) - time to completion dominant hand	Motor Capacity	Manual dexterity is tested which is a highly sensitive for improvements in motor function following stroke.
Trail-making test (TMT-B) - time trail B	Divided Attention	Shifting between concepts is operationalized.
Continuous monitoring task (MON) - reaction time	Divided Attention	Up and down movements of 5 cards is monitored. A spacebar has to be pressed when any card touches a border.
Simple reaction time (SRT) - reaction time	Reaction Time	A card is presented face down on a computer screen. When this card turns face up, participants are required to press the spacebar as quickly as possible.
Complex reaction time (CRT) - reaction time	Reaction Time	Participants are required to indicate whether two cards match in color or not by pressing one of two possible keys.
Choice reaction time (ChRT) - reaction time	Decision Making	Participants are required to indicate the color of a suit by pressing one of two possible keys.
One back working memory task (OBK) - reaction time - accuracy	Working Memory	Participants must indicate whether a new card is the same or different as the one that was just presented by pressing one of two possible keys.
Associative learning task (AssL) - accuracy	Learning	Participants must indicate whether a pair of cards matches any of the 5 pairs presented above face down. The central pair is not presented face down and serves as a control. Matching and non-matching pairs are presented.

Appendix. Description of the neuropsychologic tests

Chapter 4

Brain injury 7.5 years after angioplasty compared to off-pump coronary artery bypass surgery with magnetic resonance imaging and spectroscopy

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Submitted

ABSTRACT

Introduction

Subtle changes in brain integrity related to previous ischemic insults from percutaneous coronary intervention (PCI) with stent implantation or off-pump coronary artery bypass grafting (OPCAB) can be picked up by proton (hydrogen 1 [1H]) magnetic resonance spectroscopy (MRS), through detection of the brain metabolites N-acetylaspartate (NAA) and choline (Cho). We investigated the difference in metabolite levels between PCI and OPCAB and the relation to cognitive decline and volume of white matter lesions.

Methods

The MRI protocol of the 1.5-T Philips whole body imaging system consisted of T2-weighted, T1-weighted and FLAIR scans, covering the entire brain, with a spatial resolution of 1 x 1 x 4 mm^3. Volume of white matter lesions was measured with an automated probabilistic segmentation method. MR spectra were obtained using a single voxel PRESS sequence with an echo time (TE) of 144ms and repetition time (TR) of 2s and CHESS water suppression. To compensate for volume size effects and magnetic field variances between subjects, the peak integrals of NAA and total Choline (tCho) were divided by the peak integral of creatine (Cr). Cognitive function was assessed with an extensive neuropsychological test battery. The between-group differences were tested using the Mann-Whitney U test. The relation between volume of white matter lesions and cognitive performance to brain metabolite ratios in both groups was explored using multivariable linear regression.

Results

Of the initial 138 patients randomly assigned to PCI and 142 to OPCAB 79 underwent MRS resulting in 69 successful spectra. There was no difference in brain metabolite concentrations between both treatment groups, median NAA/Cr ratios 1.84 (IQR 1.68-1.95) in the PCI and 1.81 (IQR 1.66-1.95) in the OPCAB group (MWU p=0.99) and median tCho/Cr ratios 1.13 (IQR 0.95-1.24) in the PCI and 1.10 (IQR 1.01-1.24) in the OPCAB group (MWU p=0.75). There was no difference between both groups in volume of white matter lesions nor any relation between brain metabolite ratios and volume of white matter lesions or overall cognitive performance.

Conclusions

NAA and tCho levels normalized to Cr cannot demonstrate a significant differences in brain integrity at long term follow-up between patients that have had OPCAB or PCI. We did not find a relation between volume of white matter lesions or overall cognitive performance and NAA and tCho levels normalized to Cr.

INTRODUCTION

Percutaneous coronary intervention (PCI) and off-pump coronary artery bypass grafting (OPCAB) are revascularization strategies on the beating heart that effectively relieve symptoms of angina pectoris.[1] Previously, we investigated the 7.5 years cognitive outcomes between both treatment strategies and found a trend towards better cognitive performance in favor of the OPCAB group.[2] This was unexpected, since we hypothesized that a reduced inflammatory response and no external manipulation of the aorta in the strictly endovascular approach would lead to cognitive protection in the long term. This result might be attributed to the better cardiac outcomes after OPCAB[1,3] and the higher rate of repeat revascularizations and diagnostic coronary angiographs in the PCI group.[4]

If this larger burden of repeated diagnostic coronary angiography and re-interventions in the PCI group indeed resulted in increased insults to the brain, does this show up in structural, neuroanatomical differences? Diffusion weighted magnetic resonance imaging (DWI) of the brain can distinguish between recent cerebral infarctions (hypointens DWI signal due to cell swelling and edema) and old cerebral infarctions (areas of gliosis). T2 weighted fluid attenuated inversion recovery (FLAIR) is sensitive to determine white matter lesions. Shortly after percutaneous coronary procedures DWI studies show new, silent ischemic lesions in 5 to 22% of the cases.[5] compared to 26 and 45% after conventional (on-pump) CABG surgery.[6] Less is known about silent ischemic lesions after OPCAB. Although embolic loads is significantly lower compared to conventional coronary artery bypass grafting (CABG),[7] evidence suggests a similar incidence of (silent) ischemic lesions in both procedures.[7,8] A study comparing OPCAB to conventional CABG showed no significant differences between groups in atrophy, subcortical white matter lesions, or acute infarctions at discharge and 7.5 year follow-up.[9] Very small emboli might go undetected on DWI, but still result in metabolic dysfunction. Subtle changes in brain integrity related to previous ischemic insults may be picked up by proton (hydrogen 1 [1H]) magnetic resonance spectroscopy that can non-invasive determine brain metabolites[10,11] like N-acetylaspartate (NAA), a biomarker of neuronal integrity and functionality,[12] which is decreased in neurodegenerative disease,[13-17] and choline(Cho), a biomarker of cellular proliferation.[12,18]

In this study, we have investigated brain integrity through detection of NAA and total Choline (tCho) in white matter using single voxel long TE 1H MRS at 1.5T and determination of volume of white matter lesions using T2 weighted FLAIR MRI19 in patients that have underwent either PCI with stent implantation or OPCAB . Secondary outcomes were the relation between NAA and tCho and neuropsychological test scores and white matter lesions.

MATERIALS AND METHODS

Design and patients

This was a sub-study within a larger, multicenter randomized clinical trial (trial registration number ClinicalTrials.gov: NCT 00975858).[2,20,21] Study subjects were 79 participants of the Octostent arm of the Octopus Study who were randomized to PCI with stent implantation or OPCAB. These patients were included in the Octopus Study if referred for PCI and both PCI and OPCAB were deemed technically feasible. The complete list of inclusion and exclusion criteria has been published elsewhere.[20] Patients were recruited in two centers in the Netherlands between 1998 and 2000. The primary objective of the Octopus study was to compare cardiac outcome at one year follow-up.20 After completion of the one year outcome, a long-term follow-up study was designed. The cerebral outcome measures assessed in this follow-up study were: overall cognitive performance, volume of white matter lesions on MRI scan and NAA and tCho levels on MRS. The long-term follow-up study adhered to the Helsinki declaration and was approved by the ethics committees of the participating centers. All patients gave additional written informed consent for the long-term follow-up study.

Magnetic Resonance Imaging

We used a 1.5-T Philips whole body imaging system (Philips Medical Systems, Best, The Netherlands). The MRI protocol consisted of transaxial T2-weighted (TR 2200ms/TE 100ms), T1-weighted (TR 234ms/ TE 2ms), inversion recovery (IR) (TR 2900ms/ TI xx/ TE 22ms) and FLAIR (TR 6000ms/ TI 2000ms/ TE 100ms) scans, performed with 38 slices of 4 mm slice thickness without slice gap, covering the entire brain, with a field of view of 230 x 230 mm and a 256 x 256 scan matrix. The volume of white matter lesions was measured with an automated probabilistic segmentation method, which has been described elsewhere.[22] Scans were read by an experienced neuroradiologist blinded to the clinical randomization and the neuropsychological data of the patient.

Magnetic Resonance Spectroscopy

A single voxel PRESS sequence with an echo time (TE) of 144ms and repetition time (TR) of 2s was used with CHESS water suppression to obtain the MR spectra. A relatively large volume pixel (voxel) was positioned in white matter (just above the ventricals in the left hemisphere) based on the MRI. Care was taken that the voxel included purely white matter, while maximizing the voxel size for each patient. Automatic pencil beam shimming (FASTERMAP) was performed followed by automated RF power adjustments for fine tuning the water suppression. Considering the relatively long TE, resonances of Creatine (Cr), Cho and NAA can be easily fitted by the software provided by the vendor of the MRI system (Philips). To compensate for volume size effects and magnetic field variances between subjects, the peak integrals of NAA and tCho were divided by the peak integral of Cr. Data quality was checked for the following parameters: signal to noise ratio more than 10, B0 shimming (line width) better than 0.1 ppm, and residual lipid signals less than 3 times the noise floor. See also Fig 1.

Cognitive assessment

At 7.5 year follow-up, cognitive status was assessed through a battery of nine neuropsychological tests yielding eleven a priori chosen test variables, which are described in detail in Appendix A. We applied the "core battery" of neuropsychological tests recommended in the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery,[23] supplemented with computerized tests from the CogHealth battery.[24] The total battery covers the cognitive domains of verbal memory, motor capacity, divided attention, reaction time, decision-making, working memory and learning. To obtain an overall score of cognitive performance, we first calculated a Z-score for each raw test score of each patient, by subtracting the total group mean

from the patient's individual score and dividing the residue by the group standard deviation. Scores of timed tasks were multiplied by -1, so that a higher Z-score always indicates better cognitive performance. Then, an overall Z-score was calculated as the mean of the Z-scores of the eleven test variables, and used as an overall composite cognitive outcome measure.[25]

Data acquisition

Each patient's general practitioner received a letter to inquire whether the patient was alive. When the general practitioner had confirmed that the patient was still alive, a consultant invited the patient over the telephone to participate in the follow-up study. In order to minimize patient burden and to maximize the completeness of cognitive follow-up, the neuropsychological tests were administered at the patient's home. Total test-time was 60 to 90 minutes, depending on the patient's speed of comprehension and execution.

Study outcomes

The primary study outcome was brain NAA, Cr and Cho ratios in both treatment groups at 7.5 years follow-up. Secondly, we investigated the relation between volume of white matter lesions and brain metabolite ratios and cognitive performance and brain metabolite ratios.

Statistical analysis

Continuous baseline variables were presented as mean or median values depending on distribution, and compared with the Student t test or Mann-Whitney U test, as appropriate. Binary data were presented as percentages and analyzed using the Pearson Chi-Square test or Fisher Exact test based on minimal cell count. The between-group difference (PCI versus OPCAB) of the primary outcomes (brain metabolite ratios) and volume of white matter lesions and overall cognitive performance were tested using the Mann-Whitney U test (MWU) and presented as medians with Interquartile Range (IQR). To explore the difference in the relation between volume of white matter lesions and brain metabolite ratios and the relation between cognitive performance and brain metabolite ratios in both groups we used multivariable linear regression. The analyses were performed using IBM SPSS version 21 (SPSS Inc). All reported p values were two-sided and a significance level of $p < 0.05$ was used.

Typical MR spectrum obtained from an 8cl volume in white matter of a patient indicated by the red box in the MRI insets. At the relatively long echo-time (144ms), resonances of NAA at 2.0ppm, creatine (Cr) at 3.0ppm and choline (Cho) are well resolved from macromolecules (simplified by the pink polynomial baseline). The signal integral of NAA, Cr and Cho can be determined (blue lines) using the software provided by the vendor of the MRI system. Note that despite the relatively low field strength of 1.5T, signal to noise ratio (SNR) is substantial, lipid artefacts are absent, and spectral resolution (magnetic field shimming) sufficient to distinguish Cr from Cho.

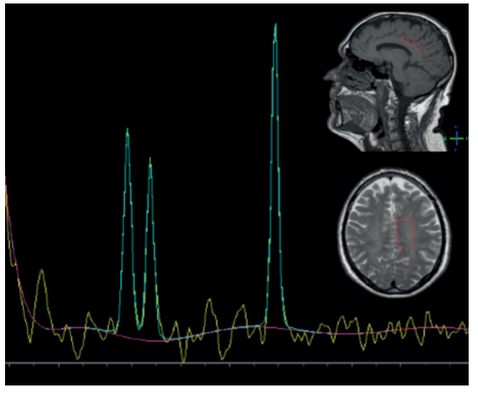

Fig 1. MR spectrum

RESULTS

Characteristics of the patients and completeness of follow-up

Initially a total of 138 patients were randomly assigned to PCI and 142 patients to OPCAB. Thirty-one patients (11%) had died (12 in the PCI and 19 in the OPCAB group). Of the patients available for long-term follow-up 79 agreed to undergo MRS at follow-up. Four datasets had to be excluded because substantial residual lipid signals were present. Another 2 had to be excluded because of poor B0 shimming, and 4 with insufficient suppression of water signals that obscured the fitting of the three metabolite signals. The flow of the patients through the trial is shown in Fig 2. The baseline characteristics of the 69 patients with successful spectra in the sub sample undergoing MRS are summarized in Table 1. The mean interval between index treatment and MRS was 7.7 ± 0.7 years after PCI and 7.9 ± 0.6 years after OPCAB (p=0.08).

Primary outcome

There was no difference in brain metabolite concentrations between both treatment groups. Median NAA/Cr ratios were 1.84 (IQR 1.68-1.95) in the PCI and 1.81 (IQR 1.66-1.95) in the OPCAB group (MWU p=0.99) and median tCho/Cr ratios were 1.13 (IQR 0.95-1.24) in the PCI and 1.10 (IQR 1.01-1.24) in the OPCAB group (MWU p=0.75).

Secondary outcome

The volume of white matter lesions was not significantly different between both groups (median 1.67 (IQR 1.08-6.63) in the PCI and median 1.59 (IQR 1.02-4.44) in the OPCAB group, p=0.48). The relation between volume of white matter lesions and brain metabolite ratios and the relation between cognitive performance and brain metabolite ratios are shown in Fig 3.1-4. Neither group showed a relation between brain metabolite ratios and volume of white matter lesions or overall cognitive performance.

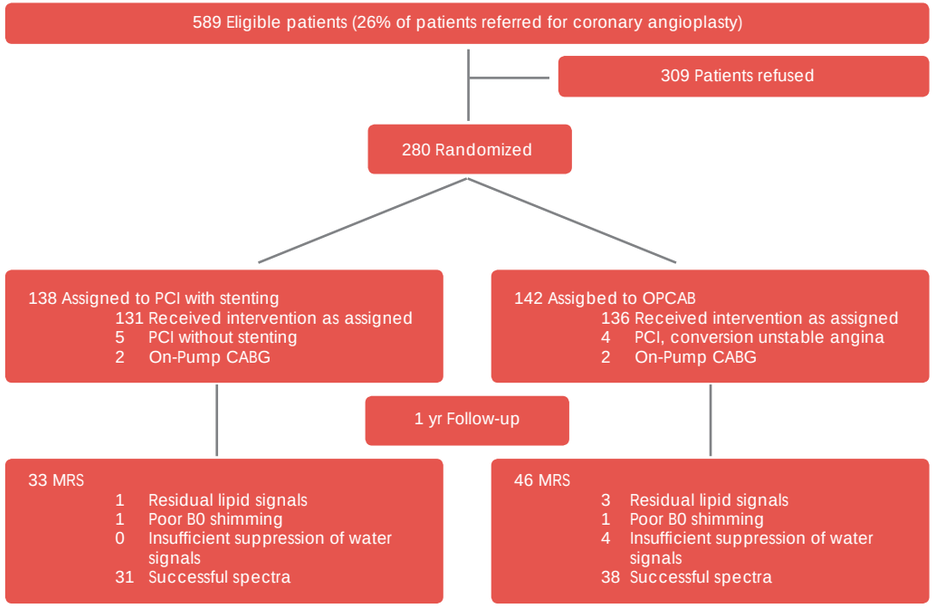

Fig 2. Flow of the patients

Variable*	PCI (n = 31)	OPCAB (n = 38)	P-value
Age mean (SD) year	67 (9)	64 (9)	0.12
Male sex (%)	22 (77)	29 (76)	0.62
Education mean (SD) score Ü	4.3 (1.5)	4.5 (1.3)	0.59
Previous conditions and risk factors			
Stroke or TIA (%)	3 (10)	3 (8)	1.00
Myocardial infarction (%)	7 (23)	8 (21)	0.88
Diabetes (%)	3 (10)	5 (13)	0.72
Hypertension (%)	10 (32)	15 (40)	0.54
Hypercholesterolemia (%)	19 (61)	27 (71)	0.39
Impaired LVF (%)	2 (7)	6 (16)	0.28
Multiple-vessel disease (%)	13 (42)	10 (26)	0.17
Smoking (%)	8 (26)	9 (24)	0.84

Table 1. Baseline characteristics
*Dichotomous data are presented as numbers with percentages in brackets.
†The level of education was classified according to Dutch norm data using the system of Verhage, ranging from 1 (no education) to 7 (university). PCI denotes percutaneous coronary intervention, OPCAB off-pump coronary bypass, SD standard deviation, TIA transient ischemic attack, LVF left ventricular function.

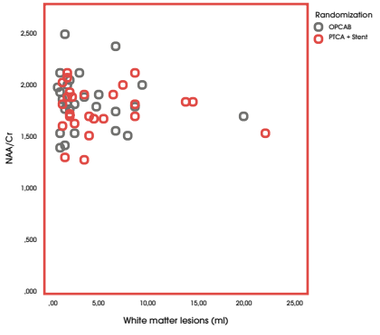

Fig 3.1: Relation between volume of white matter lesions and NAA/Cr ratio in both treatment groups

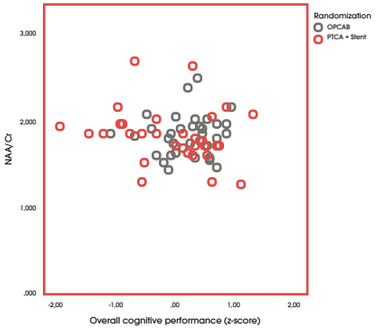

Fig 3.2: Relation between overall cognitive performance and NAA/Cr ratio in both treatment groups

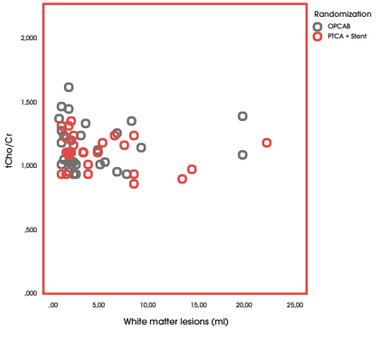

Fig 3.3: Relation between volume of white matter lesions and tCho/Cr ratio in both treatment groups

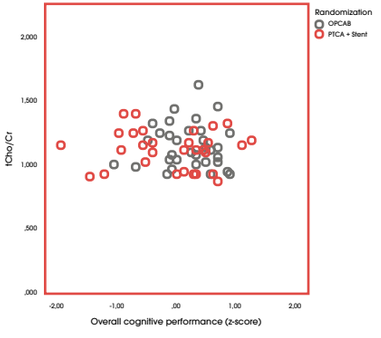

Fig 3.4: Relation between overall cognitive performance and tCho/Cr ratio in both treatment groups

DISCUSSION

We could successfully obtain tCho and NAA levels normalized to Cr in 87% of all patients using a standard commercially available MRS protocol at a field-strength of 1.5T. This enabled investigation of brain impairment in 69 patients that underwent OPCAB or PCI, approximately 7.5 years prior to the MRS exam. Differences in NAA/Cr or tCho/Cr between the two patient groups were less than the obtained standard deviation (SD) of about 10% of these ratios.

With the elderly population presenting for cardiac revascularization strategies and the improved survival rate following these procedures, postoperative quality of live and absence from neurologic morbidity become increasingly important as major outcomes. Although recent evidence suggests that the occurrence of delayed and late strokes are similar between conventional CABG, OPCAB and PCI, the incidence of early stroke is lower after techniques avoiding cardiopulmonary bypass and aortic manipulations, i.e. OPCAB and PCI.[26] However, avoiding manipulation of the aorta by using off-pump surgery instead of conventional CABG in the OctoStent study did not lead to better cognitive results.[27] In the follow-up of the other arm of the trial, comparing OPCAB and PCI, both techniques free of opening the aorta and with a comparable, lower risk of stroke we found a trend towards better cognitive performance in favor of the OPCAB group, which remained present after imputation of missing cognitive data.[28] In a multivariate model the difference was smaller and not statistically significant, supporting the hypothesis that demographic variables may have more influence on long-term cognitive outcome than revascularization strategy. We also found a non-significant difference in the volume of white matter lesions between the PCI and the OPCAB group with in general a larger lesion volume in the PCI group. A study of Bendszus et al using diffusion-weighted MRI and MRS to examine brain damage in the first 14 days after conventional CABG showed that focal ischemic lesions are more frequent than the apparent neurological complication rate, but that these lesions are not related to the diffuse postoperative encephalopathy.

They identified an association between postoperative impairment in neuropsychological test performance and metabolic neuronal disturbance (NAA/Cr) in the immediate postoperative period which disappeared with the recovery of both neuropsychological test performance and NAA/Cr at follow up.[29] In this long term follow-up study we did not find a correlation between cognitive test results and MR spectroscopy markers of brain tissue damage (NAA/Cr or tCho/Cr) or white matter lesions and spectroscopy results. In general with this MRI scan very long after the procedure there are alternative possibilities of brain tissue damage such as small and large artery disease in these patients with proven extra cranial vascular disease which may have hidden any potential effect of a difference between procedures. Furthermore, the absence of a relation between cognition and these global MRI markers of white matter integrity may indicate that in the future more attention should be paid to dedicated brain regions that affect certain functions including cognition. The absence of a correlation between volume of white matter lesions and MR spectroscopy may be explained by the relatively small volume of white matter lesions that is typically present also in patients with a larger burden of white matter lesions. In larger studies there are correlations found between white matter lesion load and cognition but the strength of this relation is typically weak.[30-32]

The standard deviation (SD) in high quality MRS is determined on the actual physiologic variance in metabolite levels as well as inverse related to the signal to noise ratio (SNR) that was obtained. The relatively low SD of Cho/Cr and NAA/Cr matches well to reports in literature even when obtained at higher fields.[33] While signal to noise ratio could have been improved at higher field strengths, none of our data had to be excluded because of low SNR. This may be due to our relatively large voxel size, since SNR scales linearly with its volume, but also to the limitation to only include the largest signals in MRS (i.e. Cho, Cr and NAA) rather than other metabolite compounds like glutamate, glutamine or GABA, which have lower SNR and are more difficult to detect and quantify. Therefore, the high SNR obtained in our study indicates that the obtained levels are dominated by brain metabolism rather than lack of SNR.

As a consequence of using a large TE, signal overlap from macromolecules that have fast transverse relaxation is minimized. Therefore, relatively simple, but standard available processing tools from the MRI system was used facilitating objective quantification of the signals. At short TE, more metabolite levels can be detected. However, the inherent signal overlap between all of these metabolite signals require more complex fitting algorithms (i.e. LC Model) to assess metabolite levels at short TE. Moreover, due to signal overlap that cannot be fully discriminated by using basis sets of spectral models, the results remain dependent on spectral resolution (B0 shimming), SNR, and macromolecular contribution to the signals.[†] In our study, we have used signal integrals of singlet peaks (less sensitive to B0 shimming) and used internal referencing to creatine levels (i.e. less sensitive to SNR). Though more robust to measurement variances, the long TE can bias the results if changes in creatine levels or relaxation times would be present between the groups.

Several limitations of our study should be mentioned. At the time of design of the trial no difference in cognitive outcome between off-pump CABG and PCI was expected and therefore no baseline imaging or neuropsychological assessment was performed before coronary intervention. It was not possible to quantify the change in cognitive performance over time in both groups or examine the course of metabolic disturbances over time, which affects what sort of conclusions can be drawn from the data. However, both groups came from a randomized controlled trial, enabling us to answer the cross-sectional question of whether one group has a better cognitive performance than the other 7.5 years after the randomization. Although the group of patients agreeing to MR imaging at follow-up, was a lot smaller than the original inclusion group, it is unlikely that patients refrained from imaging follow-up for different reasons in the PCI compared to the OPCAB group, but it is possible that the follow-up sample is more vital than the total group at baseline. This is one of the few studies that used a substantial sample size for follow up with MRS after treatment. In contrast to recent literature, we have used a relatively simple MRS sequence at a routine MRI system used for high throughput patient scanning. Apart from voxel positioning, all methods were fully automated including magnetic field shimming, therefore the additional scan time needed for the MRS exam was only 5 minutes. In combination with fully automated data processing, our data is operator independent, hence facilitated this double blinded study in investigating neuronal NAA and choline levels 7.5 years after PCI or OPCAB treatment.

Conclusion

NAA and tCho levels normalized to Cr cannot demonstrate significant differences in brain integrity at long term follow-up between patients that have had OPCAB or PCI. We did not find a relation between volume of white matter lesions or overall cognitive performance and NAA and tCho levels normalized to Cr.

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Chapter 5

Intraoperative dexamethasone and delirium after cardiac surgery: a randomized clinical trial

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M.M.J. van Eijk, J.W. Devlin, D. van Dijk

Anesthesia & Analgesie 2014; 119:1046–52

ABSTRACT

Background

Delirium is common after cardiac surgery, and may be partly related to the systemic inflammatory response triggered by the surgery and the use of cardiopulmonary bypass. We hypothesized that intraoperative, high dose dexamethasone, an agent with potent anti-inflammatory effects, administration would reduce the incidence of delirium at any time point during the first 4 postoperative days after cardiac surgery.

Methods

This is a single-center substudy within a larger, multicenter placebo controlled randomized clinical trial, the Dexamethasone for Cardiac Surgery (DECS) trial that randomized patients ≥ 18 years, undergoing cardiac surgery with cardiopulmonary bypass, to receive, in a double-blind fashion, either dexamethasone 1 mg/kg or placebo at the induction of anesthesia. Over the first 4 postoperative days, we compared between groups the incidence of delirium (based on the Confusion Assessment Method (CAM)-ICU, or after ICU discharge, by the CAM, accompanied by chart review), restraint use, and administered haloperidol, benzodiazepines, and opioids. Data were analyzed according to the intention to treat principle. The proportion of patients with delirium in the dexamethasone versus the placebo group was compared using the odds ratio (OR) with a 95% Confidence Interval (CI). The proportion also was compared using logistic regression to adjust for common baseline variables that might confound the presence of delirium between the 2 groups.

Results

Of 768 eligible patients, 737 subjects (96.0%) had complete data. The incidence of delirium was similar between the dexamethasone (14.2%) and placebo (14.9%) groups (crude OR = 0.95, 95% CI = 0.63-1.43; adjusted OR = 0.85, 95% CI = 0.55-1.31). Among patients who developed delirium, the median (interquartile range) duration of delirium was similar between the dexamethasone and placebo groups (2 [1-3] versus 2 [1-2] days, respectively, p = 0.45; WMWodds 0.98, 95% CI 0.83-1.17). Restraint use and the administration of haloperidol, benzodiazepines, and opioids were also similar between the 2 groups.

Conclusions

The intraoperative administration of dexamethasone did not reduce the incidence or duration of delirium in the first 4 days after cardiac surgery.

INTRODUCTION

Delirium, defined by an acute change in consciousness, attention, cognition, and perception caused by a general medical condition,[1] occurs in up to 52% of patients undergoing cardiac surgery.[2-4] Patients who develop delirium have an increased risk of death,[5] prolonged hospitalization and long-term cognitive impairment.[6,7] While the precise mechanisms of delirium after cardiac surgery are not fully elucidated, the profound inflammatory response associated with the surgery and the use of cardiopulmonary bypass (CPB) remains a key potential instigating factor. This inflammatory response,[8] along with an increased embolic load, are postulated to increase blood-brain-barrier permeability, leading to neuroinflammation and potentially cerebral edema, possibly causing postoperative delirium and cognitive decline[9-11] The role of the hypothalamic-pituitary axis and serum cortisol in the pathogenesis of postoperative delirium is controversial.[12-16] While postoperative serum cortisol concentrations are higher in patients who develop delirium,[12,14,16] this association has not been consistently found,[12] and it remains unclear if this relationship is causally related to delirium, or simply a marker of the inflammatory stress response that develops during surgery.[14-16]

The inflammatory response during and after cardiac surgery can be suppressed with the administration of high-dose corticosteroids.[17] It has been hypothesized that this reduces neuroinflammation and cerebral edema, and therefore may prevent the development of postoperative delirium. One small controlled study indeed suggested that postoperative administration of dexamethasone was associated with a reduced delirium prevalence.[18] It could also be argued, however, that dexamethasone increases the risk of delirium because delirium is a known complication of long-term and/or high dose treatment with corticosteroids.[19] It remains currently unknown whether dexamethasone will increase or decrease the incidence of postoperative delirium.

In the recent multicenter, randomized study, the Dexamethasone for Cardiac Surgery (DECS) trial, intraoperative administration of high dose dexamethasone (1mg/kg) of bodyweight was associated with less delirium.[20] However, in that study, the presence of delirium was defined by the postoperative use of an antipsychotic medication(s), rather than based on delirium screening using a validated instrument, and thus it is likely that delirium was underrecognized.[21,22]
The objective of the present study was to investigate in detail whether the intraoperative administration of high-dose dexamethasone to patients undergoing cardiac surgery affects the incidence of postoperative delirium during the first four postoperative days. We hypothesized that dexamethasone administration would reduce the incidence of delirium at any time point during the first four postoperative days.

METHODS

Study Design and Participants

The Medical Ethics Committee of the University Medical Center Utrecht approved this study and written informed consent was obtained from all patients. This was a single-center substudy within a larger, multicenter placebo controlled randomized clinical trial, the Dexamethasone for Cardiac Surgery (DECS) trial that was registered in ClinicalTrials.gov (NCT00293592). The design of the DECS trial has been published in detail elsewhere.[20] Briefly, patients 18 years or older undergoing cardiac surgery with cardiopulmonary bypass at the University Medical Center Utrecht were randomized, in a double-blind fashion, to receive a single 1mg/kg intravenous injection of dexamethasone (maximum100 mg), or placebo at the time of induction of anesthesia. Specifics regarding the randomization, allocation, and implementation of the interventions are described in detail in the DECS trial.[20] We excluded patients who required emergency surgery, those who were scheduled for a procedure using an off-pump technique, and patients with a life expectancy $\leq$ 6 months.

Delirium Assessment

The primary study outcome was the presence of delirium on any of the first four postoperative days. Patients were assessed for delirium seven days a week at a fixed point in time as much as possible by trained research personnel using a previously validated method.[23] Briefly, during ICU admission, delirium was assessed daily by a research nurse using the Confusion Assessment Method (CAM) adapted for the ICU (CAM-ICU),[24] and a chart review over the previous 24 hours which included the results of twice daily CAM-ICU assessments conducted by the bedside nurse, and notation of administration of haloperidol. Patients found to have a Richmond Agitation Sedation Scale (RASS)[25] score of -4 or -5 were deemed to be unarousable and were not evaluated for delirium.[26] Patients transferred to the ward were evaluated on a daily basis for the presence of delirium by trained research personnel using the CAM.[27] Like the ICU evaluations, each patient's record over the prior 24 period was reviewed to identify key words suggestive of delirium (e.g., confused, agitated, drowsiness, disorientated, delirious) and the administration of antipsychotic therapy.2[8]

Secondary Outcomes

Restraint use, episodes of patient-initiated device removal (e.g., self-extubation), and the amount of administered benzodiazepines, opioids, and haloperidol were recorded for each postoperative assessment day. Duration of delirium was also considered a secondary study outcome. All benzodiazepine use was converted in diazepam equivalents[29] where 1 mg of diazepam was equivalent to: 1.5 mg midazolam, 4 mg oxazepam, 0.2 mg lorazepam, 2 mg temazepam,1.3 mg zopiclone, 0.8 mg clonazepam, 30 and 1 mg zolpidem.[30] All opioid use was converted in morphine equivalents[31,32] where 1mg IV morphine was deemed equivalent to: 10 mcg IV fentanyl, 1.5 mg oral oxycodone, 15 mg oral tramadol, and 1.5 mg oral piritramide. Demographic, clinical and surgical data was obtained from the DECS trial database.[20]

Statistical Analysis

Given the assumption that the prevalence of delirium in cardiac surgery patients is 16%, that a clinically significant decrease in the incidence of delirium with the use of dexmethasone use would be 50%, and 90% power, and a two-sided significance level of 5%, we estimated that 345 patients would be required in each group to detect a reduction in delirium from 16% to 8%. Data were analyzed according to the intention to treat principle. The proportion of patients with delirium in the dexamethasone versus the placebo group was compared using the odds ratio (OR) with a 95% confidence interval (CI). The proportion also was compared using logistic regression.

We performed logistic regression analysis to adjust for common baseline variables that might confound the presence of delirium between the two groups: age, gender, valve surgery, history of stroke (see secondary digital content). Additional sensitivity analyses were conducted in which deceased patients were assigned to have delirium. Normally distributed continuous data were presented as means with a 95% CI, and compared using a Student's test. Skewed data were presented as medians with interquartile ranges (IQR) and analyzed with a Mann-Whitney test and WMWodds with accompanying 95% confidence interval.[33,34] Binary data were presented as percentages and analyzed using the Pearson Chi-Square test. The analyses were performed using SPSS software, version 15 (SPSS Inc, Chicago, Ill). All reported p-values were two-sided and a significance level of $p < 0.05$ was used.

RESULTS

Among the 768 patients enrolled patients in the DECS trial at the University Medical Center Utrecht between June 2009 and November 2011, complete data for this study could be obtained for 737 patients (96.0%, Figure 1). Baseline demographic, clinical, and surgical factors were similar between the dexamethasone (n=367) and placebo (n=370) groups (Table 1).
The incidence of delirium over the first four postoperative days was comparable between the dexamethasone and placebo groups (14.2% [n=52] versus 14.9% [n=55]; crude OR 0.95, 95% CI 0.63-1.43, p= 0.79). After adjusting for the potential confounders described above, the incidence of delirium remained similar between the two groups (adjusted OR 0.85, 95% CI 0.55-1.31, p= 0.45). The proportion of patients in each group who had delirium on each of the four postoperative days was also similar (Figure 2). Among patients who developed delirium, the median (IQR) number of delirium days did not differ between the dexamethasone and placebo groups (2 [1-3] versus 2 [1-2]; Mann-Whitney U p= 0.45, WMWodds 0.98, 95% CI 0.83-1.17). A sensitivity analysis, where any patient who died during the four day postoperative period was assigned to have delirium, did not change these findings.

The daily amount of administered haloperidol, benzodiazepines, and opioids was similar between the two groups on each of the four assessment days (Table 2). The proportion of patients who received ≥ 1 dose of haloperidol over the course of the 4 day assessment period did not differ either between the dexamethasone (9.3%, n=34) and placebo (8.9%, n=33) groups (p= 0.87). Further, restraint use and incidence of patient-initiated device removal were similar between the two groups (Table 3). In addition, we found a comparable proportion of patients who experienced deep sedation or coma (RASS of -4 or -5) over the assessment period in the dexamethasone (2.4%) and placebo (3.4%) groups (p= 0.36).

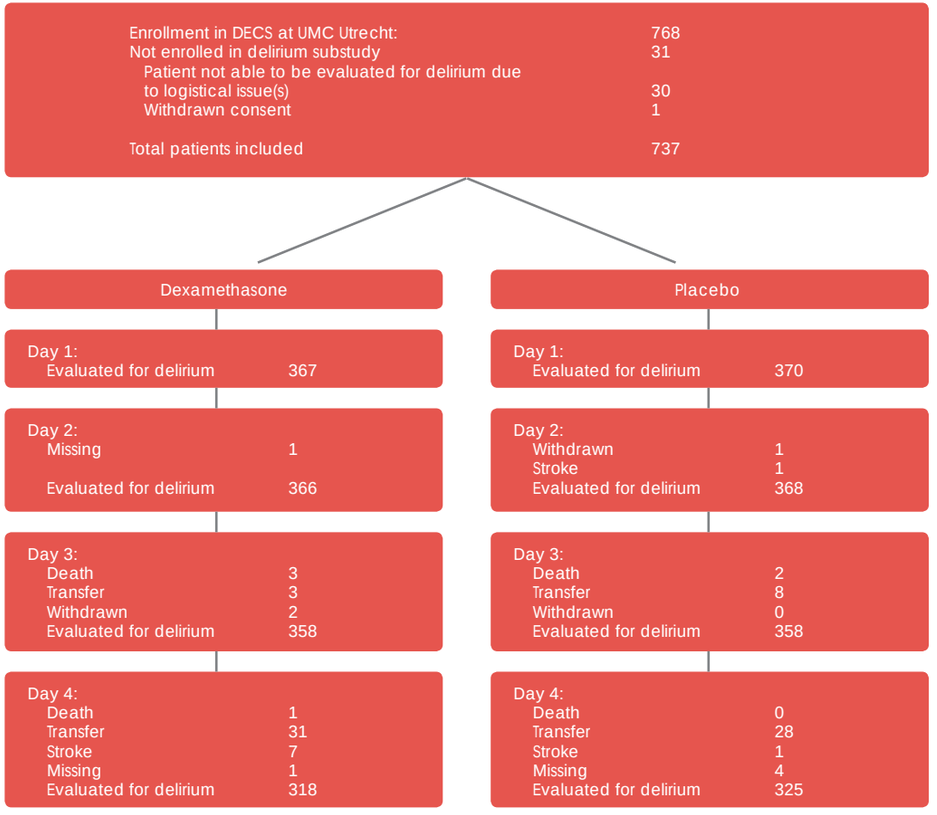

Figure 1. Flow of the patients
DECS trial patients at University Medical Center Utrecht eligible for the delirium substudy and flow of patients evaluated for delirium on each of the four study days. Missing: missing delirium data; Withdrawn: withdrawn from the DECS study; Stroke: new stroke; Death: death on the study day; Transfer: discharge from the University Medical Center Utrecht.

	Dexamethasone (N=367)	Placebo (N=370)
Male sex [a]	70 (255)	69 (225)
Age (years) [b]	67 (12)	66 (12)
Weight (kg) [b]	81 (14)	81 (15)
Hypertension [a]	54 (199)	58 (216)
Diabetes mellitus [a]	20 (72)	18 (68)
COPD requiring treatment [a]	14 (51)	11 (40)
Previous stroke [a]	13 (48)	9 (32)
Peripheral vascular disease [a]	10 (35)	8 (28)
Recent myocardial infarction [d]	7 (27)	9 (32)
Serum creatinine (µmol/l) [b]	99 (37)	100 (40)
EuroScore [b,f]	5.2 (2.9)	4.9 (2.8)
Left ventricular function [e]		
Moderate	23 (85)	25 (91)
Poor	4 (14)	4 (16)
Type of surgery [a]		
Isolated CABG	35 (127)	38 (141)
Valve surgery	62 (227)	57 (211)
Time to extubation (hours) [c]	8 (5-10)	8 (6-11)
Cardiopulmonary bypass time (mins) [c]	105 (55-116)	103 (75-152)
Cross-clamp time (mins) [c]	76 (56-117)	76 (55-116)
Repeat surgery [a]	7 (24)	6 (21)

Table 1. Demographic, clinical and surgical characteristics of the dexamethasone and placebo groups
Data are shown as [a] percentages (number of patients), [b] mean (standard deviation), or [c] median (interquartile range). [d] Definition of myocardial infarction: the presence of new Q waves or a new left bundle branch block on the electrocardiogram, combined with a biomarker (creatine kinase–MB or troponin) elevation of more than 5 times the upper reference limit. [e] Definition of left ventricular function classes: moderate, ejection fraction of 30% to 50%; poor, ejection fraction of less than 30%. [f] Higher EuroScores present increased risk of perioperative mortality.[42] Abbreviations: COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting.

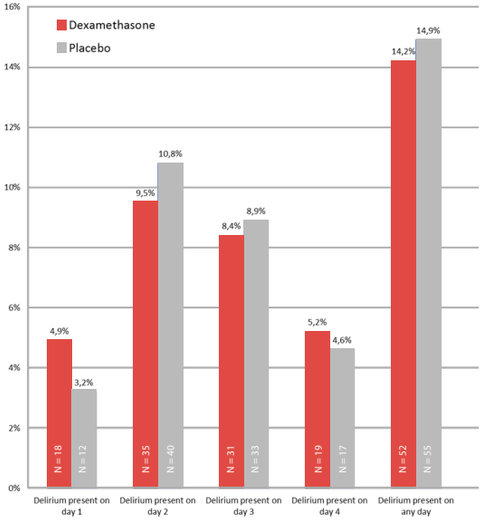

Figure 2. Proportion of patients with delirium on each postoperative study evaluation day
DECS trial patients at University Medical Center Utrecht eligible for the delirium substudy and flow of patients evaluated for delirium on each of the four study days. Missing: missing delirium data; Withdrawn: withdrawn from the DECS study; Stroke: new stroke; Death: death on the study day; Transfer: discharge from the University Medical Center Utrecht.

	Dexamethasone		Placebo		p-value [a]
Haloperidol (mg)	n	median (IQR)[b]	n	median (IQR)[b]	
Day 1	8	2.3 (1.0-4.8)	8	1.5 (1.0-4.5)	0.74
Day 2	23	3.0 (1.0-4.0)	22	2.0 (1.0-5.0)	0.42
Day 3	40	2.0 (1.0-3.0)	22	2.0 (1.0-4.0)	0.61
Day 4	14	2.0 (1.0-3.0)	14	2.0 (1.0-3.0)	0.58
Benzodiazepines (as diazepam equivalents, mg)					
Day 1	116	3.3 (1.7-6.7)	131	3.3 (2.0-6.7)	0.52
Day 2	101	5.0 (2.5-5.0)	118	5.0 (2.5-7.5)	0.66
Day 3	104	5.0 (2.5-5.0)	113	5.0 (2.5-5.0)	0.45
Day 4	95	5.0 (2.5-5.0)	101	5.0 (2.5-5.0)	0.64
Opioids (as morphine equivalents, mg)					
Day 1	289	16.0 (7.0-22.0)	303	15.0 (7.0-23.0)	0.96
Day 2	183	6.7 (3.3-10.0)	219	6.7 (3.3-10.0)	0.60
Day 3	135	5.0 (3.3-10)	135	6.7 (3.3-10.0)	0.51
Day4	64	6.7 (3.3-10.0)	72	4.2 (3.3-10.0)	0.61

Table 2. Use of haloperiodol, benzodiazepines, or opioids on each study day
[a] Mann-Whitney test;
[b] Median (interquartile range) dose calculated over users;
n, number of patients.

	Dexamethasone	Placebo (n=367)	p-value (n=370)
Restrain use, % (n) [a]	2.5 (9)	1.9 (7)	0.60
Patient-initiated device removal, % (n) [a]	2.5 (8)	3.1 (10)	0.66
Duration of ICU stay, hours [b]	23 (20-24)	22 (20-24)	0.98

Table 3. Clinical outcomes between the dexamethasone and placebo groups
[a] Occurrence on one or more days during the four-day postoperative evaluation period;
[b] Median (interquartile range);
n, number of patients.

DISCUSSION

In this randomized clinical trial in 737 cardiac surgical patients we did not find a difference in the incidence and duration of delirium over the first four postoperative days between patients who received a high dose of intraoperative dexamethasone and those who received placebo, despite controlling for other factors that could have affected delirium incidence. Sensitivity analyses in which deceased patients were assigned to have delirium, did not change our findings.
Previous reports on the incidence of delirium in cardiac surgery vary widely ranging from 3-50%.[2-4,7,16,21,22] The incidence found in this study corresponds closely to a similar, large trial that reported an incidence of 11.9% in 1528 cardiac patients.[22] The incidence of postoperative delirium in our Utrecht cohort (14.5%) was higher than in the overall DECS study population (10.4%).[20] This most likely results from different methods to detect delirium between the two cohorts. In Utrecht, delirium was evaluated in detail on a daily basis by trained research personnel. By contrast, patients at the other centers were not screened for delirium using a formalized procedure. Instead, delirium was deemed to have occurred based on a retrospective review of the patient's record and documentation of antipsychotic use in discharge letters. The results of our study support earlier observations that failure to use a validated delirium screening will miss delirium that is present. [21,22]
Compared to other assessment methods for delirium in the ICU, the CAM-ICU shows good validity and sensitivity in a research setting[35] and is proven to be superior to diagnosis by critical care physicians alone.[21] However, it might not comprise the fluctuating nature of the disease. To overcome these, we based our definition of delirium also on inspection of the medical records and prescription of antipsychotics.

The anti-inflammatory effects of dexamethasone may lead to a number of potential beneficial effects in patients undergoing cardiac surgery, including potential decrease of cerebral edema and neuroinflammation, improved pulmonary gas exchange, and the reduced need for postoperative inotropic support.[17] We hypothesized that dexamethasone would reduce the occurrence of delirium, either directly through its anti-inflammatory effect, or indirectly through faster post-surgical recovery that would reduce the risk for delirium. Although there is some evidence that inflammation is an important mechanism for postoperative cognitive dysfunction,[10] the results of our investigation suggest that other, not yet identified, factors might play a greater role in the development of delirium in this population, explaining also why (pre)treatment with other agents with anti-inflammatory properties like statins[36] and haloperidol[37,38] does not seem to lower the incidence of postoperative delirium.

Our study has several strengths including its large sample size compared to other studies investigating delirium, the detailed method that was used to identify delirium, and the use of multivariate models to adjust for possible confounding. Potential limitations are, firstly, that the assessment for delirium was limited to the first four postoperative days. While it is possible that patients may have developed delirium after four days, previous studies suggest that the vast majority of delirium in this population is clinically apparent over the first three postoperative days. The number of patients with later-onset delirium, who may have been missed in the current study, is therefore likely very small.[9,39-41] Secondly, we may also have missed delirium in patients who were transferred before the fourth postoperative day. It is however unlikely that this will have influenced our findings, as the number of patients who were transferred before the fourth day was low and similar between the two study groups. Thirdly, we did not collect data on some potential risk factors for delirium, including pre-operative cognitive status, education level,sensory impairment and history of psychiatric disease. Although these factors may be relatively rare in a population undergoing elective cardiac surgery, we cannot exclude that there may have been a disbalance between the two study groups, despite the randomized, controlled design of the trial. Finally, to obtain full workday and weekend coverage on delirium assessments,[7] individual observers were involved in this study whom were thoroughly trained by 2 staff members (AJCS & MMJvE). Despite this extensive training, inter-individual differences in assessment may have occurred.

In conclusion, the administration of a single intraoperative injection of high-dose dexamethasone did not influence the incidence or duration of delirium in the first four days after cardiac surgery.

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Chapter 6

The association between delirium and cognitive change after cardiac surgery

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Submitted

ABSTRACT

Background

Previous studies are inconsistent whether postoperative delirium (POD) is a risk factor for postoperative cognitive decline (POCD), and it is only partly clear which factors predispose to POD. We aimed to investigate the relationship between POD and POCD after cardiac surgery. We also assessed the relation between pre-operative cognitive domain scores and POD.

Methods

POD was assessed with the Confusion Assessment Method (Intensive Care Unit) accompanied by chart review. Cognitive function was assessed pre-operatively, one month and one year after elective cardiac surgery with an extensive neuropsychological test battery. Cognitive change was calculated using the Reliable Change Index (RCI). Multiple linear regression was used to adjust for confounding.

Results

Of the 184 patients who completed baseline assessment, 23 (12.5%) developed POD. At one month, patients with POD had more severe decline in cognitive performance (median composite RCI -1.00, IQR -1.67 to 0.28) than non-delirious patients (RCI -0.04, IQR -0.70 to 0.63, p=0.02). At one year, both groups showed on average cognitive improvement compared to baseline (POD patients median composite RCI 0.25, IQR -0.42 to 1.31 versus non-POD patients RCI 0.92, IQR 0.18 to 1.53; p=0.08). Correction for differences in age and level of education did not change the results. Furthermore, patients who later developed POD performed less than patients without POD on the preoperative Trailmaking test part A (p=0.03).

Conclusion

POD is independently associated with cognitive decline one month after surgery, but cognitive performance generally recovers in a year. Patients with a predisposition to POD can be identified pre-operatively by lower attention.

INTRODUCTION

Transient (lasting up to a few months) postoperative cognitive decline (POCD) and postoperative delirium (POD) are relatively common complications after surgery. Cardiac surgery patients are at high risk for both conditions as they are relatively old, and often have multiple comorbidities, including hypertension, diabetes and previous ischemic stroke.[1-5] Impaired pre-operative overall cognitive function and low level of education[2] increase both the risk of POD and POCD, but the predisposing cognitive profile for both conditions has not been fully elucidated yet. There is limited information on the predictive value of impairment in specific cognitive domains.
There is inconsistency in the literature whether POD increases the risk of POCD.[6] Two recent studies demonstrated an association between POD and subsequent POCD in elderly patients undergoing orthopaedic surgery[7] and cardiac surgery.[8] Both studies used the Mini-Mental State Examination (MMSE) as a global measure of cognitive function.[9] There is, however, long-standing consensus that a battery of neuropsychological tests is required to reliably detect POCD after cardiac surgery.[10] Furthermore, it is currently unclear how postoperative cognitive function evolves over time with respect to the magnitude of the change, changes in overall cognitive function and changes in different cognitive domains.

The primary aim of this study was to examine the relationship between POD and POCD at one month after cardiac surgery, assessed with a battery of neuropsychological tests and based on a comparison with preoperative neuropsychological test performance. Secondarily, we examined whether POD is associated with POCD at one year, whether POD differentially affects specific cognitive domain scores over time and which preoperative cognitive profile predisposes cardiac surgery patients to develop POD.

METHODS

Study Design and Participants

For this cohort study, we used data from the Dexamethasone for Cardiac Surgery (DECS) trial registered in ClinicalTrials.gov (NCT00293592).[11] This multicentre, double-blind, placebo-controlled trial randomized 4494 patients aged 18 years or older undergoing cardiac surgery with cardiopulmonary bypass to a single high dose of 1mg kg-1 intravenous injection of dexamethasone with a maximum of 100 mg, or placebo at the time of induction of anaesthesia. The use of intraoperative dexamethasone did not reduce the 30-day incidence of major adverse events, a composite of death, myocardial infarction (MI), stroke, renal failure, or respiratory failure, compared with placebo. The study design and the primary results have been described in detail previously.[11] From 768 patients enrolled in the DECS trial between June 2009 and November 2011 at the University Medical Center Utrecht data on delirium were obtained. Between August 2010 and October 2011 patients recruited at the UMC Utrecht were invited to undergo additional assessment of their cognitive performance. These patients were included in the present cohort to evaluate the association between postoperative delirium and POCD. Additional exclusion criteria for this substudy were evident mental illness or significantly impaired vision, hearing, or motor skills (e.g., hemiplegia). Dexamethasone appeared to have no effect on POD and POCD.[12,13] Data on demographics, clinical, and surgical characteristics were prospectively collected in the DECS trial database.11 The Medical Ethics Committee of the University Medical Centre Utrecht approved this study and written informed consent was obtained from all patients. Patients who provided written informed consent but were unable to complete the baseline neuropsychological assessment were excluded.
To define true cognitive decline beyond natural variation in test performance, we recruited a group of volunteers with documented coronary artery or valve pathology, but without scheduled surgery from the cardiology outpatient clinic as control subjects. In this group, the same neuropsychological test battery and protocol was used by the same investigators as the trial participants, assessing cognition twice with an interval of one month.[13]

Delirium Assessment

Delirium was assessed by trained research personnel using a previously validated method.[14] This included daily assessment by a research nurse using the Confusion Assessment Method (CAM) adapted for the ICU (CAM-ICU)[15] in the ICU setting, the CAM[16] when the patient was transferred to the ward, a chart review over the previous 24 hours to identify key words suggestive of delirium (e.g., confused, agitated, drowsiness, disorientated, delirious),[17] the results of twice daily CAM(-ICU) assessments conducted by the bedside nurse, and the administration of antipsychotic medication. If any of these indicators were present, the patient was scored as delirious. Patients that were deemed to be unarousable as determined by a Richmond Agitation Sedation Scale (RASS)[18] score of -4 or -5 were not evaluated for delirium.[19] Patients were assessed on the first four postoperative days at a fixed point during the day whenever possible.

Neuropsychological Assessment

Cognitive function was assessed one day before surgery (baseline), at one month after cardiac surgery, and at one year follow-up. If possible, patients were assessed in the hospital by trained research personnel. In order to maximize the completeness of cognitive follow-up, patients who were unable to come to the hospital for follow-up were offered the option to have the neuropsychological tests administered at their home. Total test-time was approximately 30 to 40 minutes, depending on the patient's speed of comprehension and execution.
The following tests[20] were administered: Corsi Block-Tapping Task (spatial memory), Rey Auditory Verbal Learning (immediate recall (short term verbal memory) and delayed recall (intermediate term verbal memory)), Grooved Pegboard (motor skills), Trailmaking test (part A (attention) and B (executive function)), Digit Span forward and backward (Wechsler Adult Intelligence Scale - Revised) (verbal memory) (see Appendix A).

To obtain an overall score of baseline cognitive performance, we first calculated a Z-score for each raw test score of each patient, by subtracting the total group mean from the patient's individual score and dividing the residue by the group standard deviation. In timed tasks, scores were inverted so that a higher Z-score always indicates better cognitive performance. Then, an overall Z-score was calculated as the mean of the Z-scores of the 8 test variables, and used as a baseline composite cognitive outcome measure. To control for natural variation and practice effects in cognitive test performance during follow-up, we used the Jacobson and Truax' Reliable Change Index (RCI).[21] This approach yields a z-score for every individual test by subtracting from the follow-up score the baseline test score and the mean change on that test in the control group and dividing the result by the SD of the change in the control group. In timed tasks, RCI values were inverted as described above. For the composite RCI, the sum of the Z-scores of the different tests was divided by the standard deviation of this sum in the control group.[13] Psychometric test scores from the control group are presented in Appendix B.

Study outcomes

The primary study outcome was change in cognitive performance from baseline to one month after surgery. Secondly, cognitive performance was assessed at one year. In addition, we assessed the influence of POD on individual cognitive test scores at one month and one year postoperatively. Finally, the association between preoperative cognitive test performance and the occurrence of POD was investigated.

Statistical analysis

The sample size of this cohort study was determined by the available number of 184 patients within the DECS trial in whom both the presence of postoperative delirium and cognitive functioning were prospectively measured. Continuous baseline variables were presented as mean or median values depending on distribution, and compared with the Student t test or Mann-Whitney U test, as appropriate. Binary data were presented as percentages and analysed using the Pearson Chi-Square test or Fisher Exact test based on minimal cell count. Categorical data were compared using an analysis of variance (ANOVA). For the primary outcome (change in cognitive performance at one month as represented by the continuous, composite RCI values), we tested the between-group difference (POD versus no POD) using the Mann-Whitney U test. Linear regression analyses was performed to study the association between POD and change in cognitive performance at one month and at one year, adjusting for randomization to dexamethasone or placebo, age, and level of education. To study the association between pre-operative cognitive tests and POD we tested the between-group difference (POD versus no POD) using logistic regression analysis and adjusted for the same co-variables. The analyses were performed using IBM SPSS version 21 (SPSS Inc). All reported p values were two-sided and a significance level of $p < 0.05$ was used.

RESULTS

Between August 2010 and October 2011, 184 patients underwent the neuropsychological preoperative baseline assessment, of whom 176 (95.7%) completed the one month follow-up and 146 (79.3%) the one year follow-up. Of the 184 patients who completed the baseline assessment, 23 (12.5%) patients developed delirium during their postoperative hospital stay. In the POD group 1 patient died (5%) between the 1 month and 1 year follow-up and 1 refused follow-up (5%), total lost to follow-up was 9%. In the group without POD 3 patients (2%) died and 25 (17%) refused follow-up, therefore, total lost to follow-up was 18%. Figure 1 shows the enrolment flowchart and loss to follow-up. Baseline demographic, clinical, and surgical characteristics of the 176 patients who completed the one month follow-up are presented in Table 1. Patients who developed POD were significantly older, had more often peripheral vascular disease and had a higher EuroScore compared to non-delirious patients. Incidence of delirium and baseline characteristics, except for serum creatinine and left ventricular function, were comparable between the group of patients with complete follow-up and the group without 1 year follow-up (data not shown).

Change in cognitive performance at one month

At one month, both patient groups showed a negative change in cognitive performance, based on the composite RCI. The decrease in performance was significantly more in patients who had been delirious compared to those without delirium (median composite RCI -1.00, IQR -1.67 to 0.28 versus -0.04, IQR -0.70 to 0.63; p=0.02). The unadjusted β was -0.99 (95% CI -1.59 to -0.39, p<0.01). Adjusting for the possible confounders mentioned above with multiple linear regression resulted in a β of -0.91 (95% CI -1.53 to -0.28, p<0.01).

Change in cognitive performance at one year

At one year follow-up, positive median composite RCI scores were found, indicating improved performance compared to pre-operative baseline in both groups. The median composite RCI score was less positive in patients who had POD (median composite RCI 0.25, IQR -0.42 to 1.31) than in patients without POD (0.92, IQR 0.18 to 1.53; p=0.08) suggesting less improved scores in the POD group, but this difference was not statistically significant. Multivariable regression analysis did not change the results (unadjusted β = -0.58, 95% CI -1.13 to -0.03, adjusted β = -0.40, 95% CI -0.98 to 0.18; p=0.17).

POD and postoperative scores on individual neuropsychological tests

The raw neuropsychological test results at one month and one year and the adjusted changes from baseline are presented in Table 2 and 3. Change from baseline in the Grooved Pegboard and the Trailmaking test part B significantly differed between delirious and non-delirious patients at both time points. In the POD group persistent decline was seen on the Grooved Pegboard and initially more severe decline recovering to minimal decline was seen at the Trailmaking test part B compared to improved performance on both tests in the non-delirious group.

Pre-operative cognitive assessment and POD

As shown in Table 4, consistently lower scores in the delirious group versus the non-delirious group were observed, but except for the Trailmaking test part A, these differences did not reach statistical significance after adjusting for potential confounders.

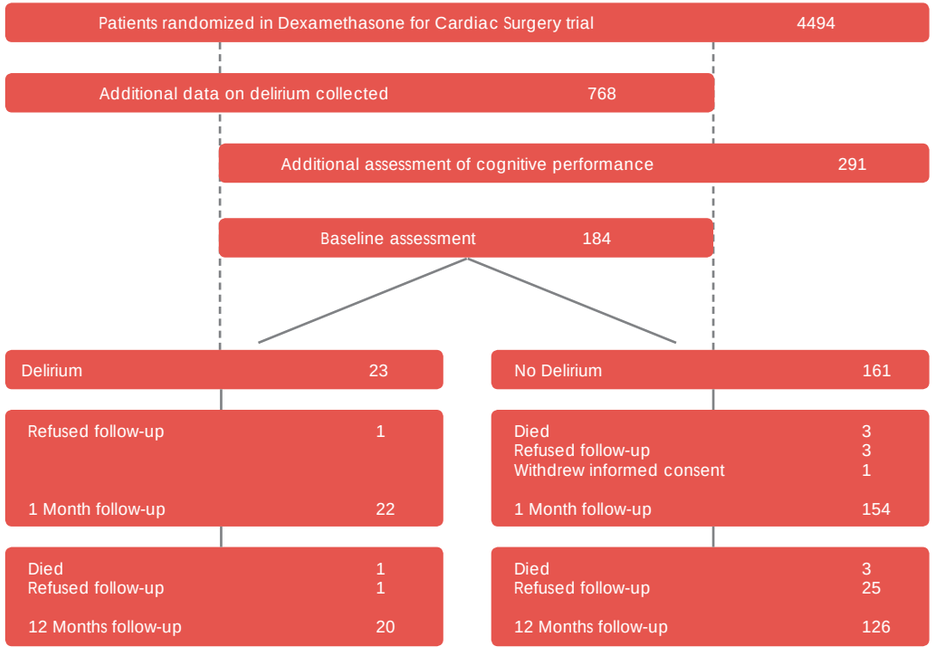

Figure 1. Flow of patients through the trial

Characteristic	Delirious (n=22)	Non-Delirious (n=154)	p-value
Male sex[a]	12 (54.5)	115 (74.7)	0.05~
Age (years)[b]	78.1 (74.6 - 82.7)	65.5 (57.0 - 72.2)	<0.01*
Weight (kg)[b]	74.0 (63.0 - 84.0)	80.0 (71.0 - 90.0)	0.03*
Education[b,c]	5 (3 - 6)	5 (4 - 6)	0.81
Hypertension[a]	14 (63.6)	83 (53.9)	0.39~
Diabetes mellitus[a]	4 (18.2)	24 (15.6)	0.76 ^
COPD requiring treatment[a]	6 (27.3)	19 (12.3)	0.10 ^
Previous stroke[a]	3 (13.6)	9 (5.8)	0.18 ^
Peripheral vascular disease[a]	7 (31.8)	17 (11.0)	0.02 ^ *
Recent myocardial infarction[a,d]	0 (0.0)	9 (5.8)	0.60 ^
Serum creatinine (μmol/l)[b]	87.5 (78.0 - 109.3)	91.5 (80.0 - 105.3)	0.64
EuroScore[b,e]	8.0 (6.0 - 9.3)	4.0 (2.0 - 7.0)	<0.01*
Left ventricular function[f]			0.35`
Moderate	2 (9.1)	32 (20.8)	
Poor	1 (4.5)	3 (1.9)	
Treatment Dexamethasone[a]	8 (36.4)	75 (48.7)	0.36~
Type of surgery[a]			
Isolated CABG	2 (9.1)	41 (26.6)	0.07~
Valve surgery	17 (77.3)	103 (66.9)	0.33~
Time to extubation (hrs)[b]	8.0 (6.8 - 12.3)	7.0 (6.0 - 10.0)	0.14
Cardiopulm.bypass time (min)[b]	121.5 (89.5 - 154.5)	103 (77.0 - 152.5)	0.18
Cross-clamp time (min)[b]	92.0 (71.0 - 123.3)	78.0 (59.0 - 120.0)	0.17
Repeat surgery[a]	3 (13.6)	14 (9.1)	0.45 ^

Table 1. Demographic, clinical and surgical characteristics
Data are shown as [a] number of patients (percentages), or [b] median (interquartile range).
[c] The level of education was classified according to Dutch norm data using the system of Verhage, ranging from 1 (no education) to 7 (university). [d] Definition of myocardial infarction: the presence of new Q waves or a new left bundle branch block on the electrocardiogram, combined with a biomarker (creatine kinase–MB or troponin) elevation of more than 5 times the upper reference limit. [e] Higher EuroScores present increased risk of perioperative mortality.[22] [f] Definition of left ventricular function classes: moderate, ejection fraction of 30% to 50%; poor, ejection fraction of less than 30%.
Abbreviations: COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting.
~Pearson Chi-Square, ^Fisher Exact Test, `ANOVA, *Statistically significant

	Delirious (n=154)		Not Delirious (n=22)		
Test	z-score	raw score	z-score	raw score	p-value
Corsi Blocks (total score)	-0.04 (-0.57 - +0.36)	30 (23 - 36)	-0.59 (-0.93- +0.30)	40 (35 - 54)	0.06
RAVL (IR)	+0.26 (-0.55 - +0.91)	34 (27 - 43)	+0.09 (-0.63 - +1.23)	43 (34 - 50)	0.55
RAVL (DR)	+0.15 (-0.61 - +0.53)	5 (4 - 7)	+0.15 (-0.71 - +0.24)	8 (5 - 11)	0.93
Grooved Pegboard[a] (s)	+0.08 (-0.41 - +0.71)	105 (92 - 176)	-0.76 (-1.7 - +0.57)	81 (69 - 96)	0.01*
Trailmaking test A[a] (s)	+0.05 (-0.41 - +0.35)	48 (35 - 66)	-0.03 (-0.95 - +0.89)	34 (26 - 44)	0.11
Trailmaking test B[a] (s)	-0.06 (-0.45 - +0.28)	84 (65 - 168)	-0.67 (-1.96 - +0.26)	58 (40 - 86)	<0.01*
WAIS Digit Span (span)	-0.12 (-1.08 - +0.83)	5 (5 - 6)	-0.12 (-1.08 - -0.12)	5 (5 - 7)	0.32
WAIS Digit Span (total)	-0.43 (-1.32 - +0.46)	13 (11 - 14)	-0.42 (-1.32 - +0.46)	14 (12 - 16)	0.83

Table 2. Raw neuropsychological test results at 1 month and change from baseline (z-score)
Abbreviations: WAIS, Wechsler Adult Intelligence Scale. Positive values indicate improvement, and negative values indicate decline in test performance. aln timed tasks, lower scores reflect better performance. RCI values of these variables were inverted so that positive RCI values always indicate improvement and negative RCI values indicate decline in test performance. *Statistically significant. P-values are for the adjusted z scores and were calculated with multiple linear regression analysis.

	Delirious (n=126)		Not Delirious (n=20)		
Test	z-score	raw score	z-score	raw score	p-value
Corsi Blocks (total score)	+0.64 (0.00 - +1.04)	40 (35 - 42)	+0.29 (-0.28 - +0.87)	54 (40 - 60)	0.30
RAVL (IR)	+0.65 (0.00 - +1.62)	34 (27 - 43)	+0.81 (-0.32 - +1.13)	46 (35 - 54)	0.81
RAVL (DR)	+0.76 (0.00 - +1.14)	7 (5 - 10)	+0.76 (0.00 - +1.14)	9 (6 - 12)	0.44
Grooved Pegboard[a] (s)	0.21 (-0.28 - 0.63)	99 (88 - 148)	-0.56 (-1.05 - 0.21)	77 (65 - 92)	<0.01*
Trailmaking test A[a] (s)	-0.08 (-0.32 - +0.38)	46 (34 - 63)	-0.04 (-0.58 - +0.83)	35 (28 - 47)	0.97
Trailmaking test B[a] (s)	+0.17 (-0.17 - +0.66)	86 (55 - 152)	-0.06 (-0.96 - +0.59)	51 (36 - 73)	0.03*
WAIS Digit Span (span)	0.00 (-0.96 - 0.96)	5 (5 - 6)	0.00 (-0.96 - +0.72)	6 (5 - 7)	0.95
WAIS Digit Span (total)	0.44 (-0.44 - +1.33)	14 (12 - 15)	0.00 (-0.44 - +1.33)	15 (13 - 18)	0.56

Table 3. Raw neuropsychological test results at 1 year and change from baseline (z-score)
Abbreviations: WAIS, Wechsler Adult Intelligence Scale.Positive values indicate improvement, and negative values indicate decline in test performance. aln timed tasks, lower scores reflect better performance. RCI values of these variables were inverted so that positive RCI values always indicate improvement and negative RCI values indicate decline in test performance. *Statistically significant. P-values are for the adjusted z scores and were calculated with multiple linear regression analysis.

Test	Delirious (n=22)	Not Delirious (n=154)	unadj OR (95%CI)	adj OR (95% CI)
Corsi Blocks (total score)	33 (24-42)	40 (30-48)	0.97 (0.94-1.01)	0.99 (0.95-1.03)
RAVL (IR)	34 (26-37)	39 (32-47)	0.94 (0.89-0.98)*	0.98 (0.92-1.04)
RAVL (DR)	5 (3-7)	7 (5-10)	0.76(0.64-0.90)*	0.85 (0.70-1.04)
Grooved Pegboard[a] (s)	102 (86-158)	85 (72-102)	1.02 (1.01-1.03)*	1.01 (0.99-1.02)
Trailmaking test A[a] (s)	52 (39-60)	37 (28-47)	1.06 (1.03-1.09)*	1.04 (1.00-1.09)*
Trailmaking test B[a] (s)	90 (53-113)	61 (41-90)	1.01 (1.00-1.02)*	1.00 (0.99-1.02)
WAIS Digit Span (span)	6 (5-6)	6 (5-7)	0.85 (0.60-1.22)	0.76 (0.45-1.15)
WAIS Digit Span (total)	13 (11-15)	14 (11-17)	0.93 (0.89-1.05)	0.90 (0.78-1.04)

Table 4. Neuropsychological test results at baseline
Abbreviations: WAIS, Wechsler Adult Intelligence Scale; adj OR, adjusted odds ratio; CI, confidence interval.
aln timed tasks, lower scores reflect better performance. *Statistically significant.

DISCUSSION

We assessed the relationship between POD and POCD at one month after cardiac surgery and found that patients with POD had a greater decline in cognitive performance than those without POD. However, at one year, patients with and without POD showed an improved cognitive performance compared to pre-operative baseline cognitive levels, without a statistically significant difference between the two groups. Adjustment for differences in age and level of education did not change the results.

These findings are in line with previous research, indicating that POD is an independent risk factor for POCD in the immediate postoperative trajectory.[6-8] Previous studies on cognitive function assessed after a longer duration of follow-up were less consistent.[6-8] Cognitive functioning on average recovers in the first year after cardiac surgery, and then it assumes a downward trajectory over time. This long-term decrement of cognitive function is similar for patient with and without POCD early after surgery.[4,23,24] This pattern of long-term cognitive decline is similar to the trajectory of older adults in general, regardless of whether or not they undergo heart surgery, especially if they have risk factors for cognitive decline like vascular disease. In our study, we observed over the course of one year, on average, an improvement in cognitive performance compared to baseline in patients with and without POD.

The relation between POD and POCD is complex and not fully elucidated yet. Both entities share many risk factors such as increasing age, low level of education and underlying co-morbidities, [1-5,8] and might be viewed as two expressions of the same underlying process of pre-existing decreased cognitive reserve,25 as opposed to other evidence supporting a more independent, possibly causal, relation between delirium and cognitive impairment.[7,8,21] A causal relation could have important clinical implications, as delirium would then be one of the few modifiable risk factors for POCD opening up possibilities for prevention. The magnitude of the influence of delirium as an independent risk factor for POCD is difficult to determine. Previous research in the field of POCD has already shown that cognitive function may recover over time.[6,8] Delirium might influence the speed and extent of recovery. In the present study, both groups showed, on average, cognitive improvement compared to baseline scores, but this effect was less pronounced in the delirious group. Furthermore, we did find consistent differences between both groups on the Grooved Pegboard and Trailmaking test part B indicating that suffering from a delirium might influence especially fine motor skills and executive functions. In this study we found lower baseline scores on all but the WAIS digit span tests for the group that later on develops delirium. After adjusting for the difference in age and education between both groups, the Trailmaking test part A remained discriminative between both groups, which might indicate that impaired attention at baseline might predispose to development of delirium. Earlier studies on dysfunction in specific cognitive domains predictive for the development of delirium did show an association with impairment in executive functions tested with the trailmaking test part B[26] and with more complex executive function tasks[27] which we were unable to find in the present study.

Our study had several strengths. We used a well-validated rigorous method of delirium detection, combining the results of standardized observations by research personnel with data available from standard clinical patient care.[14] This allowed us to capture the fluctuating nature of the condition. Seven days/week staff availability enabled us to minimize missing observations and ensure complete follow-up. For logistic reasons we limited our observation period to the first four postoperative days. Being a tertiary centre, a significant part of the patient population with uncomplicated recovery returned to their referring centres within a week after the surgery. This approach might have missed delirium that developed later in the postoperative trajectory. The impact of this limitation is likely to be small, because previous studies showed that the vast majority of delirium in this population is clinically apparent during the first 3 postoperative days.[28,29] Our study population was relatively young compared to other research in the field, which may have resulted in a relatively low incidence of POD

Research on POCD has been hampered by the lack of consensus on strict definitions for POCD based on neuropsychological test methods.[25] We chose a combination of neuropsychological tests, covering a broad range of cognitive domains vulnerable for postoperative change, including the core battery recommended by the 1995 consensus statement.[10] We present a continuous outcome to avoid arbitrary dichotomization and were able to show improvement in performance. Furthermore, we corrected for learning effects and natural fluctuation in test results by comparing our patients to a non-surgical control group with similar characteristics.[21] Loss to follow-up was low, especially at one month with a follow-up rate of 95.7%.

Our study has some limitations. The primary study outcome and focus in our analysis was change in cognitive performance from baseline to one month after surgery. Results from the other analyses should be interpreted as hypothesis-generating. Overcorrection for learning might have occurred by using a control group with no intervention, which might not have been exposed to the same amount of psychological stress and/or depression at baseline, which is known to exist in cardiac surgery patients in the period prior to their intervention. We did not collect data on subjective patient outcomes and the experienced burden of impairment. Therefore we can make no statements about the clinical impact of the cognitive decline that we measured with our neuropsychological test battery. We believe that in general at 1 month follow up, patients are still recovering from their cardiac surgery and the clinical relevance of POCD at this follow-up moment might be limited. Like many other studies, our study suggests that perioperative factors might affect cognitive performance in the first months after surgery, but not at long term. Including subjective assessments of postoperative cognitive change at different time points in future research might generate valuable information on clinical impact of the cognitive decline.

In conclusion, this study showed that POD is independently associated with cognitive decline one month after surgery, but cognitive performance generally recovers in the year following the operation, except for the specific cognitive domains motor skills and executive function. Patients with a predisposition to POD are characterized by lower performance in attention.

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CONCLUSION

GENERAL DISCUSSION

In this thesis we provided an overview of cerebral outcomes after cardiac surgery, we investigated the influence of different cardiac revascularization strategies on post-operative cognitive performance, assessed the effect of an anti-inflammatory pharmacologic intervention on cerebral outcomes after cardiac surgery, and we investigated the association of delirium with cognitive decline in the postoperative setting.

Although postoperative cognitive decline (POCD) has been the subject of extensive research during the last two decades, many questions still remain unanswered. It is undisputed that both cardiac and non-cardiac surgery can result in POCD. After both major and minor surgical procedures conducted under sedation, regional or general anesthesia, a period of lower cognitive performance may occur.[1-3] Cardiac surgery and specific orthopedic procedures were often selected for research in this field, because of an assumed high incidence of POCD. Even within these domains the incidence and prevalence of POCD reported in literature varies widely.[4] Among the most cited causes for this extreme variability in the reported incidences are the lack of a uniform definition of 'decline', the use of different batteries of cognitive tests, (in some studies) the lack of parallel control groups not undergoing surgery, populations with very different risk profiles and the timing of the testing.[4] In this thesis we encountered each of these issues and have tried to deal with them in various ways.

Defining cognitive decline

Postoperative cognitive decline is generally defined as a decrease in individual post-operative performance, as compared with the pre-operative scores, on a series of neuropsychological tests. Previously accepted definitions included: (i) one standard deviation decrease in test performance in 20% of the tests; and (ii) 20% decrease in test performance in 20% of the tests. Keizer et al. showed that taking the natural variability in test performance into account, the incidence of POCD was reduced dramatically.[5,6] Controlling for natural variation and also practice effects reduces misclassification. This can be achieved with the Reliable Change Index (RCI), first described by Jacobson and Truax,[7] that compares change in cognitive test performance of patients to the variation in performance in a control group, thus better presenting the real decline in test performance of the patients. In this thesis we aimed to be as strict as possible in our definition of decline to avoid reporting spuriously high incidences of POCD. In chapter 2, cognitive decline was defined as a composite reliable change (RC) score equal to or less than -1.96 or an RC equal to or less than -1.96 in two or more main variables. As additional measures to correct for practice effects, 6 of the 10 tests were also administered 2 weeks before baseline assessment and, wherever possible, parallel forms of the tests were used in the consecutive assessments. In chapter 6 we used the same RC score, but chose to present continuous outcomes of cognitive performance to avoid the arbitrariness of dichotomization and enable us to also show improvement in performance compared to baseline. In contrast to chapter 2 where the control group was composed of healthy volunteers, the control group in chapter 6 consisted of age- and sex-matched volunteers recruited at the cardiology outpatient clinic who had documented coronary artery or valve pathology.[8] Although harder to obtain, we felt that a control group matched on the most important clinical risk factors for the outcome other than the intervention, would even more precisely reflect the natural fluctuation in test performance in this population that cannot be attributed to surgery. When the OctoStent arm of the Octopus study was designed, evaluation of long-term cognitive outcomes was not considered, because at the time percutaneous interventions were not considered to be associated with POCD. As a result, data regarding baseline neurocognitive status was not available for OctoStent patients and a RC score could not be calculated. This can be seen as a limitation for the studies reported in chapters 3 and 4, because it is not possible to quantify the change in cognitive performance over time in both groups, let alone to assess the occurrence of individual cognitive decline. However, it still offers the possibility to answer the cross-sectional question of whether one group has a better long–term cognitive performance than the other, because the randomized design has resulted in an even distribution of baseline characteristics over the two groups. In addition, baseline testing immediately prior to cardiac surgery or PCA has been criticized and even discouraged,[9] because shortly before an operation anxiety and depression levels are high, which might result in unreliable (low) baseline test scores. However, baseline testing is recommended in the consensus statement, and in my opinion when given the opportunity one should always include this whenever possible. To be able to give some estimate of decline in chapter 3, we compared individual patient data against available normative values of the different tests.

Cognitive test batteries

Cognitive decline in the postoperative period is documented in several domains of cognitive functioning including (short-term) memory, psychomotor capabilities (fine motor skills), concentration, and speed of information processing.[10] The multifocal nature of cerebral lesions caused by microemboli, hypoperfusion or perioperative inflammation precludes the use of one single test to detect postoperative neurobehavioral dysfunction. The 1995 consensus statement by a group of experts from various disciplines proposed a minimal core battery of four neuropsychological tests to provide a basis for rational comparison across clinical outcome studies and eventually allow combination of study results by meta-analysis.[11] The four selected tests were chosen based on their sensitivity and reliability, effort required and time taken to perform the test, the degree to which learning may occur, availability of parallel forms and the overall balance of the cognitive domains assessed in the battery. The consensus group recommended that beside the core battery consisting of the Rey auditory verbal learning test, Trail-making A, Trail-making B and Grooved pegboard, additional tests could be added as deemed appropriate. We adhered to the consensus statement in choosing our test battery. In chapter 2 we added tests to assess speed and capacity of working memory, visuospatial capacity, selective and sustained attention, and information processing. In chapter 3 and 4 we used a slightly different subset of tests, supplementing the core battery with computerized tests from the CogHealth battery,[12] in anticipation of the development of an internet-based test battery that we planned on implementing. When it proved not feasible to implement the internet-based testing procedures within the time frame of this thesis research, for the study reported in chapter 6 we chose to supplement the core battery with the Corsi block-tapping task for assessment of spatial memory and the digit span forward and backward from the Wechsler adult intelligence scale (revised) for verbal memory. Although comparability between studies remains an issue, the limited core battery does provide a solid basis for cognitive assessment and leaves room for extension as one sees fit in the designated research population. Extending the core battery, although it might improve comparability across more domains, would probably diminish its use, since we already observed a considerable mental strain on patients completing the present test battery. Any further extension targeted at a specific area of interest might then prove to be too exhaustive for the patients and could even adversely affect test performance.

Study populations

The studies presented in this thesis were embedded within two large clinical trials, the Octopus study and the DECS trial. The Octopus study consisted of two separate multicenter randomized clinical trials, one comparing coronary artery bypass grafting on the beating heart (off-pump

CABG, using the Octopus Method) to conventional coronary artery bypass using cardiopulmonary bypass (CPB) (OctoPump trial); the other trial comparing percutaneous coronary intervention (PCI) with intracoronary stent implantation to off-pump CABG (OctoStent Trial). Patients included in the latter trial had coronary lesions that were technically suitable for both angioplasty and off-pump CABG.[13] This group was on average around 60 years old, predominantly male (around 70%) and had a variable profile of one or more co-morbidities (baseline tables chapter 2,3 and 4). The DECS trial randomized patients aged 18 years or older who were scheduled for any type of elective or urgent cardiac surgical procedure requiring CPB to high-dose intravenous dexamethasone or placebo.[14] These patients were on average 6 years older than the Octopus population, showed the same gender distribution and varied slightly in the percentage of co-morbidities.[14] Compared to similar studies in the same period[15] our population showed a relatively low incidence of delirium and cognitive decline. The low incidence might be partly related to issues raised in the previous paragraphs, and partly explained by the fact that our population, despite the indication for surgery, was relatively young and had a low incidence of previous stroke. The low incidence resulted in less statistical power than comparable studies of the same size. However, our study population reflects the general patient population presenting for surgery in our center, ensuring clinical applicability of our results.

Cognitive trajectories

The timing of testing can influence the observed incidence of POCD, because even the young and relatively healthy patients are likely to experience some decline in the immediate postoperative period. The clinical significance and practical impact of this initial (first weeks after surgery) deterioration when patients are bedridden, receiving medication with sedative side-effects or even purposely sedated, is likely limited and much less important than subtle decline months later when the patient is expected to have recovered and resumed his tasks of everyday life. As stated before, baseline measurements are highly recommended. These provide a starting point for intra individual comparison with postoperative scores and can reveal pre-existing cognitive impairment which is known to increase the risk of POCD.[16] Some authors even state that longitudinal assessment of preoperative cognitive trajectories (i.e., more than one preoperative cognitive assessment) might be superior to identify patients on a downward slope that might reflect pre-existing cognitive vulnerability.[4] However, this is often precluded by the urgent - or at least pressing - indication for surgery. In the postoperative period patients show in general an initial steep decline within the first days to weeks after surgery, with a gradual recovery over the course of a year. Various studies show that from 1 year after surgery onward the prevalence of POCD increases again.[17-19] However, without a parallel non-surgical control group it is impossible to know if this must be attributed to the surgery or to natural aging effects and other unrelated factors. In chapter 2, as part of the OctoPump trial, cognitive assessment was performed pre-operatively, at discharge and at 3 months, 12 months and 5 years postoperatively. For the long-term follow-up of the OctoStent trial, reported in chapters 3 and 4, which was initiated after the findings of the OctoPump trial had been reported, we only assessed patients' cognitive performance 7.5 years postoperatively. In the DECS trial, chapter 6, patients were assessed at baseline, at one month and one year postoperatively. We feel that the sequence of follow-up tests conducted in chapter 2 provided the most reliable insight in the postoperative cognitive trajectory, but also placed more demands on patient compliance and research costs. The overall approach of early (hospital discharge, one month), but not direct (within days after the procedure), follow-up combined with medium- to long-term follow-up gave us insight in the cognitive trajectory of patients within the time frame that it is most likely to be subject to change due to the effects of the intervention, perioperative challenges and the recovery process, without our findings being clouded by high initial decline rates due to quickly resolving factors in the immediate (first days) postoperative period.

Delirium

A clinical entity closely related to POCD is postoperative delirium (POD). This neurocognitive disorder is defined by a disturbance in level of awareness and reduced ability to direct, focus, sustain, and shift attention, and a change in cognition not accounted for by a preexisting neurocognitive disorder, caused by an underlying general medical condition and develops over a short period of time with a tendency to fluctuate in severity during the course of a day.[20] When occurring in the postoperative period this is specified as POD. Many pathophysiological mechanisms for the development of delirium have been described, with a complex interplay of preexisting predisposing and perioperative precipitating factors. Possible pathophysiologic explanations may stem from neurotransmitter disturbances, increased activity of the limbic-hypothalamic-pituitary-adrenal axis caused by physical stress due to the surgical trauma and neuroinflammation.[21] POD is related to POCD in various ways; both entities may have a common etiology, sharing many risk factors for their development, but could also be causally interrelated, with the occurrence of early postoperative delirium suggested to be an independent risk factor for the development of subsequent POCD. Like POCD, there is not a uniform method by which delirium is assessed in the research setting. In our studies we tried to be as thorough as possible, minimizing the chance of missing a diagnosis of POD, which can be especially challenging for the more subtle 'hypoactive' form of delirium. Our method[22] included frequent assessments with a standardized screening tool,[23,24] chart review and documentation of the use of haloperidol, the most commonly used pharmacological agent to treat delirium clinically. Patients with coma for example because of deep sedation (defined as Richmond Agitation Sedation Scale[25] score of −4 or −5), were excluded from the analysis, to avoid misclassification of delirium.

Etiology and Risk factors

One of the main challenges in the field of postoperative cognitive research is the fact that there is not a single underlying cause or mechanism that can fully explain the occurrence of postoperative decline. Although the multifactorial nature of the etiology is widely accepted, the differential impact of various underlying causes on the resulting pathology is likely to differ per procedure and per individual patient. Identifying preoperative, intraoperative and postoperative risk factors can help to identify high risk patients and/or high risk procedures. Strategies to reduce the risk of POD and POCD are still urgently needed. In this thesis we explored two strategies aiming to reduce per-operative insult to the brain: (1) the use of a less invasive revascularization strategy in the Octostent trial and (2) suppression of the systemic inflammatory response to surgery by high-dose dexamethasone in the DECS trial. As expected, we were unable to find a single intervention preventing all postoperative delirium or cognitive dysfunction. Off-pump CABG resulted in a slightly more favorable cognitive performance, but the difference was subtle and lost statistical significance once we corrected for confounding variables. Concurrent imaging results did not show a difference in brain metabolite levels or a correlation to volume of white matter lesions. The use of high-dose corticosteroids did not result in a decreased incidence of POD. Throughout this thesis the influence of various demographic characteristics and perioperative risk factors prevailed over the effect of the interventions. Within the two trials we examined two specific risk factors for the occurrence of POCD: (1) the possible protective effect of a favorable vascular profile, the presence of coronary collaterals, and (2) the detrimental effect of POD. We did show significant differences between the comparison groups in these both studies (chapter 2 and 6). Finally, we examined the preoperative cognitive profile related to the development of POCD and found that patients with a predisposition to POD are characterized by lower preoperative performance in tests assessing attention. The most important conclusion supported by this thesis might be that the multifactorial etiology of POCD and the large influence of individual patient characteristics will necessitate careful risk assessment in the individual patient and most likely a multimodal approach to prevention and therapy.

Future perspectives

Although we achieved quite a substantial long-term follow-up rate, longitudinal analysis of cognitive function will be much easier when testing could be done in a less time and resource consuming manner. Current methods include well standardized, frequently used 'paper and pencil' tests or sometimes computerized test batteries, but most of these require the physical presence of a trained observer. For individual, diagnostic purposes observation of the patient during testing can yield invaluable additive diagnostic information and diminishes errors in test conduction. Besides, in the clinical and research setting, optimal psychometric circumstances demand the test environment to be as standardized as possible with distracting factors reduced to a minimum. In order to fulfil these criteria patients must travel to the research facility, where a psychologist or test assistant should be available for the duration of the test. Especially in the field of cardiac surgery, where highly specialized complex care is usually organized in expertise centers, even in a small country like the Netherlands this results in substantial travel demands, which are not conducive for frequent repeated testing. Of more concern is that this induces selection bias by selective testing of the more mobile segment of the studied population. One solution would be to develop a validated comprehensive suite of internet-based tests that patients can perform repeatedly in the comfort of their own at home. Such solutions are likely to become available in the near future, because internet-access is no longer a limiting factor and even the majority of older patients now has basic computer skills. Although in some aspects internet-based testing will never be able to compete with meticulous conventional testing by a clinical neuropsychologist in the clinical setting, I believe that it will provide great opportunities for future research. Larger numbers of patients can be tested, in a much more 'patient friendly' and less expensive way. The increase in the number of measurements will compensate for the presumed loss of accuracy, provided that the limitations of these methods are dealt with appropriately. The benefits of an easily administered, well-constructed test battery covering a range of domains might prove to be more accurate in detecting subtle changes in cognition or change restricted to very distinct domains than crude - but still frequently used - measurements such as the mini mental state examination (MMSE).

Internet-based testing might also prove to be useful in further exploration of the pre-operative cognitive profile. In this thesis we consistently found that demographic variables play an important role. The at-risk population is, as expected, older with lower levels of education, and hampered by more co-morbidities, together resulting in a more frail profile with less cognitive reserve. In chapter 6 we found evidence of a predisposing cognitive profile. Repeated pre-operative testing with a broad test battery including various cognitive domains will give a more detailed insight in this profile and in the cognitive trajectory a patient is on and might identify specific brain areas at risk. Long term follow-up shows in general after the initial insult a gradual recovery over the course of a year. In chapter 6 we demonstrated that this recovery can develop to the level of actual improvement compared to baseline, even in patients who experienced postoperative delirium (a potential second insult to the brain). Longer follow-up has shown a second period of decline after the first year. Due to the lack of baseline testing we cannot confirm this with our data from the first part of this thesis (chapter 3 and 4), but a possible explanation for the better results in the groups with a superior vascular profile (chapter 2) and a revascularization method with less chance of repeat interventions (chapter 3) suggest that over a longer period of time, decline due to natural aging might be aggravated by repeated cardiovascular insults. More intense, longitudinal testing would give valuable insight in the changes in cognitive performance in this period and in potential insults that might present themselves in the postoperative period.

Chapter 6 strengthens the evidence that postoperative delirium is associated with lower postoperative cognitive performance. Given the emerging evidence for cerebral inflammation as a possible causal factor in the development of both POD and POCD, we had hoped to prevent the occurrence delirium by suppressing the systemic inflammatory response with high dose steroids, but such an effect could not be demonstrated (chapter 5). Delirium is postulated as one of the few modifiable risk factors for development of POCD. Although this hypothesis might well be true, further reduction in the incidence of POD might prove difficult to achieve, since clinicians are already increasingly aware of the potential harmful effects of delirium and in all delirium trials, preventive measures and treatment of active delirium were already in place according to good clinical practice. There is undoubtedly still considerable practice variation, and more attention to prevention might further reduce delirium incidence but it is unlikely that the problems of POD and POCD can be completely eliminated. Delirium could prove to be one of the cerebral symptoms of generalized severe illness expressed in elderly patients with decreased cognitive reserve. POCD, in contrast, while most often transient (typically 3 months in younger patients)[26] but with slower recovery in older patients, can also be permanent, especially when it is the end-result of subtle multifocal ischemic cerebral injury. Extending our study design with measurements of delirium severity and duration might provide answers to these fundamental questions related to the causal mechanisms between delirium and POCD. Although we were not able to show a difference in brain metabolism and white matter lesion volume at 7.5 years follow-up (chapter 4) between two revascularization techniques or find an association between those parameters and clinical proven cognitive decline, imaging has evolved since and non-invasive techniques might prove to be of added value in identifying organic substrate of cognitive symptoms. Especially when targeted at an interval around observed change in cognition or provoking events.

An important issue to consider is the clinical impact of the observed changes in cognitive performance. Did patients or their family actually suffer from this decline or was it merely a 'research finding'? Previous research has shown that persistent and severe POCD can certainly negatively influence patients' lives, forestall return to work, impede normal activities of daily life and affect interpersonal relations. This was not the focus of our research and in order to be able to give substantiated answers to these questions we believe that they should be examined using methods designed for these specific questions, including the meticulous recording of patient-centered cognitive outcomes over time, which we hope to include in our future research.

Conclusions

Since the start of the first trials reported in this thesis, many advances have been made in revascularization techniques and perioperative care, all contributing to better survival and improved quality of life. These advances, also increasingly allow frail patients, with a high a priori chance of POD and POCD, to undergo complex and extensive cardiac surgical procedures.27,28 The work presented in this thesis contributes to a better understanding of the complex, multifactorial etiology of these burdensome complications of cardiac interventions and their interaction in the postoperative trajectory. We found a protective effect of the presence of cardiac collaterals on cognitive outcome and a harmful effect of occurrence postoperative delirium on the development of cognitive decline and the extent of recovery from decline in the first year after surgery. At 7.5 years follow-up, off-pump CABG patients had a similar or perhaps slightly better cognitive performance compared with PCI patients and magnetic resonance spectroscopy did not demonstrate significant alteration differences in brain integrity. Demographic variables are more important determinants of long-term cognitive outcome than mode of revascularization. The intraoperative administration of dexamethasone does not reduce the incidence or duration of delirium in the first 4 days after cardiac surgery. Future research will hopefully complete our understanding of the pathologic substrate of postoperative delirium and cognitive decline so that in patients at risk preventive strategies can be implemented.

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Chapter 7.2

Summary

SUMMARY

In this thesis we present a series of studies on cerebral outcomes after cardiac surgery: we investigated the influence of different cardiac revascularization strategies on post-operative cognitive performance, assessed the effect of an anti-inflammatory pharmacologic intervention on cerebral outcomes after cardiac surgery, and we investigated the interaction between delirium and postoperative cognitive decline in the postoperative setting.

Postoperative cognitive dysfunction (POCD) is a decline in cognitive performance relative to preoperative levels. Although cognitive function can be assessed using neuropsychological tests, reliable diagnosis of POCD appears to be difficult. Test selection, definition of decline, analyses of correlated data and the way missing data due to lost to follow-up is dealt with can strongly influence the results of a study. Therefore, the true incidence of POCD is currently still unknown. Severe POCD, which is apparent even without neuropsychological testing, is reported most frequently after cardiac surgery and hip-replacement surgery. Many perioperative risk factors related to POCD have been identified. They most likely play a variable role in different patients and different procedures.

Cerebral injury after cardiac surgery has been attributed to insufficient brain perfusion and embolism due to multiple causes during the procedure. In the heart, the presence of coronary collaterals increases myocardial viability following infarction and favors long-term cardiac outcome in patients undergoing percutaneous cardiac interventions (PCI) and off-pump coronary artery bypass grafting (OPCAB). We therefore hypothesized in chapter 2 that a sufficiently developed intracranial collateral blood supply, which might develop according to the same principles as cardiac collaterals, might reduce cerebral injury by protecting watershed areas that are most susceptible to infarction, and by limiting the size of an ischemic area following embolic vessel occlusion. Furthermore, coronary collaterals preserve myocardial function, and consequently lead to a better cardiac output, which will most likely improve end-organ perfusion, and thus cerebral blood flow. We found that in patients undergoing first-time conventional coronary artery bypass grafting (CABG) surgery, presence of coronary collaterals is associated with a decreased risk of cognitive decline at both 3 and 12 months of follow-up. Moreover, a trend remained present at 5 years. Preoperative differences in the cardiac vascular condition may therefore predict cognitive outcome in patients undergoing CABG surgery.

Emboli arise from cardiopulmonary bypass (CPB), and from external manipulation of the ascending aorta during conventional CABG surgery, and from internal manipulation of the aorta by coronary catheters during PCI. In chapter 3 we investigated whether a revascularization strategy avoiding these embolic risks, off-pump CABG, would result in a better postoperative cognitive performance compared to PCI. We found that at 7.5 years follow-up, off-pump CABG patients had a similar or perhaps even better cognitive performance compared with PCI patients. Correction for known risk factors through a multivariable analysis attenuated this difference, supporting the hypothesis that demographic variables may have more influence on long-term cognitive outcome than the mode of revascularization.

PCI is less invasive than CABG, but is not associated with better long-term cognitive outcomes. A possible explanation might be the higher rate of repeat revascularization and diagnostic coronary angiographs in PCI patients. In chapter 4 we investigated brain integrity with magnetic resonance spectroscopy, determining the brain metabolites N-acetylaspartate (NAA), a biomarker of neuronal integrity and functionality, and choline (Cho), a biomarker of cellular proliferation, in white matter

and the volume of white matter lesions using diffusion weighted magnetic resonance imaging (DW-MRI). NAA and Cho levels normalized to creatine did not demonstrate a significant alteration in brain integrity at long term follow-up between patients that have had OPCAB or PCI. We did not find a relation between volume of white matter lesions or overall cognitive performance and NAA and Cho levels normalized to creatine. This might be explained by alternative possibilities of brain tissue damage such as small and large artery disease, which may have hidden any potential effect of a difference between procedures found by MRI at this long time interval. Furthermore, the absence of a relation between cognition and these global MRI markers of white matter integrity may indicate that in the future more attention should be paid to dedicated brain regions that affect certain cognitive domains.

The inflammatory response during and after cardiac surgery can be suppressed with the administration of high-dose corticosteroids. It has been hypothesized that this reduces neuroinflammation and cerebral edema and thereby may prevent the development of postoperative delirium (POD). On the other hand is delirium a presumed complication of long term and/or high-dose treatment with corticosteroids. In chapter 5 we investigated in a randomized design in detail whether the intraoperative administration of high dose dexamethasone to patients undergoing cardiac surgery affected the incidence of POD during the first 4 postoperative days. We found no influence on the incidence or duration of delirium in the first 4 days after cardiac surgery. Previous studies were inconsistent whether POD is a risk factor for POCD, and it is only partly clear which factors predispose to POD. In chapter 6 we aimed to investigate the relationship between POD and POCD after cardiac surgery and assessed the relation between pre-operative cognitive domain scores and POD. We found that patients with POD had a greater decline in cognitive performance one month after surgery than those without POD. However, at one year, both patients with and without POD showed an improved cognitive performance compared to pre-operative baseline cognitive levels, without a statistically significant difference between the two groups. Patients with a predisposition to POD were characterized by lower performance on tests assessing attention.

Chapter 7.3

Nederlandse samenvatting
Dutch summary

NEDERLANDSE SAMENVATTING

Postoperatieve cognitieve disfunctie (POCD) is een bekend, maar slecht gedefinieerd begrip. In algemene bewoordingen komt het neer op achteruitgang in cognitief functioneren na het ondergaan van een operatie, ten opzichte van preoperatief niveau. Het spectrum van vermogens die gevat worden onder cognitie is breed en omvat onder andere de domeinen leren, geheugen, perceptie, aandacht, uitvoerende functies en abstract denken. Hoewel cognitieve functies onderzocht kunnen worden met een breed scala aan neuropsychologische tests, is het betrouwbaar stellen van de diagnose POCD lastig. Het gebruik van een wisselende samenstelling van neuropsychologische tests, verschillende analyse methodes en definities van POCD en uitval van participanten in een longitudinaal onderzoek voor het einde van de studieperiode kunnen de studie resultaten sterk beïnvloeden. Deze factoren maken dat de ware incidentie van POCD nog steeds niet bekend is.

Ernstig cognitief disfunctioneren, welke zonder aanvullend onderzoek evident is, wordt het meest gezien na hartchirurgie en heupchirurgie. Oorspronkelijk werd postoperatieve cerebrale schade na hartchirurgie voor een groot deel toegeschreven aan de gevolgen van het gebruik van de hartlongmachine. Om die reden hebben we in hoofdstuk 2, 3 en 4 patiënten vervolgd, die geïncludeerd waren in de Octopus trial, waarin conventionele bypass chirurgie, 'on-pump coronary artery bypass grafting' (CABG), werd vergeleken met chirurgie op het kloppende hart zonder gebruik van hartlongmachine (de zogenaamde 'off-pump CABG' (OPCAB)) en percutane coronaire interventie (PCI), een puur endovasculaire techniek, ook wel bekend als 'dotteren'.

Naast het gebruik van de hartlongmachine zijn er verschillende perioperatieve risicofactoren voor het ontwikkelen van POCD geïdentificeerd, waaronder gevorderde leeftijd, aanwezigheid van co-morbiditeit, preoperatief verminderd cognitief functioneren, duur en aard van de ingreep en het ontwikkelen van postoperatieve complicaties. Waarschijnlijk spelen deze risicofactoren bij de verschillende patiënten en procedures in wisselende mate een rol.

Als oorzaak voor het ontstaan van cerebrale schade na hartchirurgie werd gedacht aan verminderde hersenperfusie door een slechtere hemodynamische status of cerebrale ischemie ten gevolge van embolieën van verschillende origine (lucht, vet, stolsels), die vrijkomen gedurende de procedure. In het hart zorgt de aanwezigheid van collateralen voor een betere perfusie van het myocard na een infarct en verbeteren collateralen de lange termijn cardiale uitkomsten in patiënten die een PCI of OPCAB chirurgie ondergaan. In hoofdstuk 2 onderzochten wij daarom of patiënten met cardiale collateralen een betere cognitieve uitkomst hadden dan patiënten zonder collateralen. Deze vraag baseerden wij op de hypothese dat enerzijds de beschermende functie van cardiale collateralen op het myocard weefsel zou kunnen leiden tot een beter hartminuutvolume en zodoende een betere eindorgaan perfusie zou kunnen waarborgen en anderzijds dat cerebrale collateralen zich volgens hetzelfde mechanisme zouden kunnen ontwikkelen als cardiale collateralen, waarbij in deze patiëntengroep de cerebrale schade beperkter zou kunnen blijven door bescherming van de waterscheidingsgebieden, die het meest vatbaar zijn voor infarcering en door vermindering van de grootte van een ischemisch gebied na embolische vaatocclusie. We vonden dat in patiënten die voor het eerst een bypass operatie van de coronair arteriën ondergingen de aanwezigheid van coronaire collateralen geassocieerd is met een verminderd risico op cognitieve achteruitgang zowel bij 3 als bij 12 maanden vervolgonderzoek. Deze trend bleef zichtbaar 5 jaar na de operatie, maar het effect was statistisch niet meer significant. Preoperatieve verschillen in cardiale vascularisatie zijn daarom mogelijk

voorspellend voor cognitieve uitkomsten in het eerste jaar na de operatie in patiënten die een coronaire bypass operatie ondergaan.

Tijdens openhartchirurgie kunnen verschillende type embolieën ontstaan door peroperatief gebruik van de hartlongmachine, door manipulatie van de aorta ascendens tijdens canulatie en door het plaatsen van klemmen door de operateur. Echter ook bij manipulatie van de aorta van binnen uit zoals bij PCI kunnen embolieën ontstaan. Wij onderzochten in hoofdstuk 3 of een revascularisatie strategie zonder deze embolische risico's, de off-pump cardiochirurgische techniek, tot betere postoperatieve cognitieve uitkomsten zou leiden dan PCI. Zeven en een half jaar na de ingreep vonden we in OPCAB patiënten gelijkwaardige tot betere cognitieve uitkomsten vergeleken met PCI patiënten. Correctie voor bekende risicofactoren door middel van multivariabele analyse verminderde de grootte van het verschil, suggererend dat demografische variabelen een grotere invloed hebben op lange termijn cognitieve uitkomsten dan de wijze van re-vascularisatie.
PCI is minder invasief dan coronaire bypass chirurgie, maar is niet geassocieerd met betere lange termijn cognitieve uitkomsten. Een mogelijke verklaring hiervoor zou het hogere aantal post procedurele re-interventies en diagnostische angiografieën in PCI patiënten kunnen zijn. In dit kader onderzochten we in hoofdstuk 4 de brein integriteit met magnetische resonantie spectroscopie (MRS), een techniek waarmee de lokale concentratie van verschillende hersen metabolieten gemeten kan worden. Hierbij keken we specifiek naar N-acetylaspartate (NAA), een biomarker voor neuronale integriteit en functionaliteit, en choline (Cho), een biomarker voor cel proliferatie, beiden genormaliseerd tegen creatine. Daarnaast maten we het volume van witte stof afwijkingen door middel van diffusie gewogen magnetische resonantie imaging (DW-MRI). Bij vervolgonderzoek 7.5 jaar na de procedure vonden wij geen verschil in NAA en Cho levels genormaliseerd tegen creatine tussen patiënten die een OPCAB operatie of PCI hadden ondergaan. Ook vonden we geen relatie tussen volume van witte stof afwijkingen of cognitief functioneren en NAA en Cho levels genormaliseerd tegen creatine. Een verklaring hiervoor kan zijn dat bij deze lange termijn van follow-up andere oorzaken van hersenweefselschade een rol gespeeld hebben, waardoor een effect van de operatie niet meer meetbaar is. De afwezigheid van een relatie tussen cognitie en deze globale indicatoren van witte stof integriteit zou een reden kunnen zijn om in de toekomst gerichter naar specifieke hersengebieden te kijken die bij de verschillende cognitieve functies betrokken zijn.

De inflammatoire reactie die zich manifesteert tijdens en na cardiale chirurgie kan onderdrukt worden door het toedienen van hoog gedoseerde corticosteroïden. Dit zou door vermindering van neuroinflammatie en hersenoedeem het ontwikkelen van postoperatief delier (POD) mogelijk kunnen voorkomen. Het ontwikkelen van een delirium is echter juist een bekende complicatie van hoog gedoseerd of langdurig gebruik van steroïden. In hoofdstuk 5 hebben we in een gerandomiseerde studie in detail gekeken of de intra-operatieve toediening van hoog gedoseerde dexamethason aan patiënten, die hartchirurgie ondergingen de incidentie van postoperatief delier in de eerste 4 dagen na chirurgie beïnvloedde. We vonden geen relatie tussen gebruik van corticosteroïden en de incidentie of duur van delirium in de eerste 4 dagen na hartchirurgie.

Er zijn aanwijzingen uit eerdere studies dat het doormaken van een POD de kans op het ontwikkelen van POCD vergroot, maar de resultaten zijn niet eenduidig. Ook is het slechts ten dele duidelijk welke preoperatieve risicofactoren predisponeren voor het ontwikkelen van een postoperatief delier. In de studie beschreven in hoofdstuk 6 was ons doel om de relatie tussen een POD en POCD na hartchirurgie te onderzoeken en de relatie tussen preoperatieve cognitieve domein scores en postoperatief delirium vast te stellen. We zagen dat patiënten die postoperatief delirant geweest waren een grotere achteruitgang in cognitief functioneren hadden 1 maand na de operatie dan de groep patiënten zonder delirium. Echter, na 1 jaar, scoorden zowel patiënten met als zonder een delirium beter op de neuropsychologische testbatterij dan preoperatief en was het verschil tussen beide groepen niet meer statistisch significant. De patiënten die een POD doormaakten, werden gekenmerkt door een preoperatief lagere score op tests die naar aandacht keken.

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DANKWOORD

Dankwoord

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About the author

Curriculum Vitae

Curriculum Vitae

Anne-Mette Charlotte Sauër

Anne-Mette Charlotte Sauër was born on October 16th 1981 in the Hague, the Netherlands. After graduating from secondary school (Gymnasium Haganum, the Hague), she studied one year at the University of St. Andrews, Scotland, where she took courses in psychology, mathematics, biology and management. In 2001 she started medical training at the University of Groningen. During her study she took part in the junior scientific masterclass. She did her internships in the Deventer Ziekenhuis. After completion of her research internship at the anesthesiology department in the University Medical Center Utrecht under supervision of prof. Cor Kalkman, MD, she graduated in 2007.

Under the supervision of prof. Diederik van Dijk, MD and prof. Cor Kalkman, MD she started her research on cerebral outcomes after cardiac surgery. In June 2009 she combined this with the start of her clinical residency under supervision of prof. Knape, MD and Reinier Hoff, MD. PhD. In 2013 she completed her postgraduate master in Clinical Epidemiology at the University of Utrecht.

As a resident she was chair of the residents association of the UMCU, Vereniging voor Academici in Opleiding (VAO), and a board member of the Dutch anesthesiology residents association, Commissie Assistent-geneeskundige Anesthesiologie (CAGA).
Anne-Mette is married to Gijs Bloemsma and they have two wonderful sons, Thijs and Philip.

List of publications

List of publications

1 Dieleman JM, Sauër AC, Klijn C, Nathoe HM, Moons KG, Kalkman CJ, Kappelle J, Van Dijk D. Presence of coronary collaterals is associated with a decreased incidence of cognitive decline after coronary artery bypass surgery. Eur J Cardiothorac Surg. 2009 Jan;35(1):48-53

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