

Cognitive Outcomes in Elderly High-Risk Patients After Off-Pump Versus Conventional Coronary Artery Bypass Grafting A Randomized Trial

Birte Ostergaard Jensen, MSc; Pia Hughes, PhD†; Lars S. Rasmussen, PhD;
Preben U. Pedersen, PhD; Daniel A. Steinbrüchel, DMSc

Background—It has been suggested that the risk of cerebral dysfunction is less with off-pump coronary artery bypass grafting (OPCAB) than with conventional coronary artery bypass grafting (CCAB). However, evidence for this statement is preliminary, and additional insight is needed.

Methods and Results—The study was a substudy of the randomized Best Bypass Surgery trial that compared OPCAB with CCAB treatment with respect to intraoperative and postoperative mortality and morbidity in patients with a moderate to high level of predicted preoperative risk. The outcome was cognitive function. A total of 120 elderly patients (mean age 76 years, SD 4.5 years) underwent psychometric testing before surgery and at a mean of 103 (SD 15) days postoperatively with a neuropsychological test battery that included 7 parameters from 4 tests. Cognitive dysfunction was defined as the occurrence of at least 2 of the 7 possible deficits. Secondary analysis was performed on the basis of the definition of a 20% decline in cognitive scores compared with baseline, and with *z* score analysis. Cognitive dysfunction was identified in 4 of the 54 patients (7.4%, 95% confidence interval [CI] 2.1% to 17.9%) in the OPCAB group and 5 of the 51 patients (9.8%, 95% CI 3.3% to 21.4%) in the CCAB group. We found no difference in incidence of cognitive dysfunction between the groups regardless of the definition applied.

Conclusions—In elderly high-risk patients, no significant difference was found in the incidence of cognitive dysfunction 3 months after either OPCAB or CCAB. (*Circulation*. 2006;113:2790-2795.)

Key Words: cardiopulmonary bypass ■ cerebrovascular disorders ■ coronary disease ■ brain complication
■ cognitive function

Coronary artery bypass grafting with the use of cardiopulmonary bypass (CPB) is one of the most common cardiovascular operations.¹ However, there is a substantial risk of procedure-related postoperative complications. In addition to the risk for mortality and an adverse effect on cardiac, pulmonary, and renal function, there is a risk of major (type 1) and minor (type 2) cerebral deficits, usually manifested as stroke or cognitive decline.² The reported incidence of postoperative stroke is ≈3% of the patients undergoing conventional coronary artery bypass grafting (CCAB).³

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Postoperative cognitive dysfunction is a condition characterized by impairment of memory or concentration, which is detected by neuropsychological testing and which presents

clinically with deficits in cognition and memory, representing a significant change from the patient's previous level of functioning.⁴ The incidence of this cognitive decline varies among different studies from 3% to 80% depending on how the deficit is defined, the test methods applied, the composition of the target population, and the study design.^{3,5,6} In a systematic review, the pooled analyses of 6 highly comparable studies yielded a proportion of 23% of patients with cognitive dysfunction 2 months after CCAB.⁷ Furthermore, neurocognitive deficit has been reported to affect up to 42% of patients 5 years after CCAB.⁵

It has been suggested that the risk of cerebral dysfunction is less pronounced with off-pump CABG (OPCAB).⁸⁻¹⁰ This is a procedure in which the distal graft anastomoses are performed on a beating heart without a heart and lung

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From the Department of Cardiothoracic Surgery, The Heart Center (B.O.J., P.H., P.U.P., D.A.S.); Department of Anesthesia, Center of Head and Orthopaedics (L.S.R.); and Copenhagen Trial Unit, Center for Clinical Intervention Research (P.H.), Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

†Deceased.

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Correspondence to Birte Ostergaard Jensen, MSc, Department of Cardiothoracic Surgery, The Heart Center, Copenhagen University Hospital, Section 9441, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail Birtej@rh.dk

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machine, aortic cross clamping, and cardioplegic arrest.¹¹ In an overview of 8 retrospective, nonrandomized observational studies, it was not possible to make any definitive conclusions regarding a significant difference in the incidence of stroke or transient ischemic attacks between OPCAB and CCAB surgery groups.¹² There are randomized trials available that examined the cerebroprotective effect of OPCAB versus CCAB surgery that showed inconsistent results.^{13–19} A newly updated and comprehensive meta-analysis of 37 randomized trials found no significant difference for neurocognitive dysfunction at 30 days and beyond 12 months, but a significant reduction was found at 2 to 6 months postoperatively.²⁰ However, the studies were conducted in younger patients, whereas neurocognitive decline is strongly age-dependent.²¹ Other known risk factors for adverse cerebral outcome are manipulation of an atherosclerotic aorta and CPB.²² It cannot be concluded that CPB is an independent risk factor for cerebral complications after CABG until large-scale, randomized studies with appropriate risk stratification are conducted.^{12,20,23} In particular, there is a need for randomized trials that include high-risk patients, eg, elderly patients with serious comorbidity, because this population might benefit the most by avoiding CPB.^{11,24} The aim of the present study was to evaluate the effect of OPCAB versus CCAB surgery on cognitive function at 3 months postoperatively compared with preoperatively in elderly high-risk patients (EuroSCORE [European system for cardiac operative risk evaluation] ≥ 5),²⁵ with the hypothesis that the degree and frequency of postoperative stroke and cognitive dysfunction are reduced after OPCAB compared with CCAB.

Methods

Participants

The local ethics committee approved the study. The study is a substudy of the randomized BBS (Best Bypass Surgery) trial that aims to compare OPCAB with CCAB treatment with respect to intraoperative and postoperative mortality and morbidity in patients with a moderate to high predicted preoperative risk. Patients with known ischemic 3-vessel heart disease affecting 1 of the marginal coronary arteries who were scheduled for elective or subacute CABG at the Heart Center, Copenhagen University Hospital who were ≥ 55 years of age and who had a EuroSCORE ≥ 5 were candidates for inclusion in the study. They were not admitted to the study if any of the following criteria were present: (1) previous heart surgery; (2) ejection fraction less than 30%; (3) unstable preoperative condition, ie, continuous infusion of inotropic drugs on the day of the operation; or (4) patient unable to give informed consent. For the present substudy, patients were recruited consecutively from the BBS trial between July 2002 and December 2004, but with the following additional exclusion criteria: (1) Mini Mental State Examination score below 24 points; (2) current severe psychiatric disease ie, depression, psychosis, or alcoholism (patients currently using either antipsychotic or antidepressant drugs or imbibing more than 5 drinks/units of alcohol per day within the last 3 months); (3) neuropsychological testing within the last year; (4) illiteracy; (5) poor comprehension of Danish; (6) severe visual or auditory disorder; or (7) unwillingness to return for follow-up.

After written informed consent about the BBS trial was obtained, the patients were centrally randomized to 1 of 2 groups by an external touchtone telephone voice-response system. The patients were stratified by the following characteristics: gender, age (55 to 65 years or >65 years), diabetes mellitus, and EuroSCORE (5 to 8 or >8). Patients were randomized in a 1:1 ratio to OPCAB or CCAB

surgery. The assessors of outcomes and the staff undertaking data analysis were blinded for allocation.

Intervention

In the OPCAB group, the revascularization procedure was performed on the beating heart with a stabilization of the target coronary arteries. When access to posterior coronary arteries was needed, a suction device lifted the heart. In case of suspicion of aortic calcification or plaque formation, the vein or radial grafts were anastomosed as T-grafts to the left internal mammary artery (LIMA) or a HeartString device (Guidant Corp, Santa Clara, Calif) was used to facilitate proximal graft-aortic anastomosis without clamping. In the CCAB group, the revascularization procedure was performed with the use of CPB in normothermia, an aortic cross clamp, and cold blood cardioplegic arrest. Patients with pronounced aortic calcifications were converted to OPCAB surgery, according to the BBS trial protocol. In case of macroscopically normal aorta, a side clamp was used for proximal anastomoses. When cross clamping revealed plaque formation, the proximal anastomoses were established before removal of the cross clamp. In both groups, the LIMA and saphenous vein grafts were composed of standard graft material. The same surgeons performed both procedures.

Neuropsychological Test Battery

The choice of the neuropsychological tests was made in accordance with the "Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery."^{26,27} Furthermore, specific cultures and language problems were taken into consideration.⁴ Normative data are available.²⁸ The test battery has been translated into Danish and validated previously for sensitivity among patients undergoing CCAB surgery.²⁹ High test-retest reliability coefficients have been obtained, and the learning effects are minimized because the test exists in 3 parallel versions.^{30,31} The battery comprised the following tests: The Mini Mental State Examination³² was used as a screening test for dementia after randomization and before inclusion in the study; the patient had to score at least 24 points out of a possible 30 points. The remaining tests were as follows: (A) Visual Verbal Learning test was used for assessment of memory that was based on a list of 15 words. The patients were asked to recall as many words as possible immediately upon viewing the list and after 15 to 25 minutes.³³ (B) The Concept Shifting Task consisted of 3 subtests that measure cognitive speed and flexibility.³⁴ Time to complete the test and the number of errors were registered. (C) The Stroop Color Word Interference Test measures attention and cognitive speed in simple and complex conditions.³⁵ Time and number of errors were registered. Finally, the Letter-Digit Coding (D) is a substitution exercise based on the Symbol Digit Substitution task in the Wechsler Adult Intelligence Scale.³⁶ Within 1 minute, as many fields as possible are completed. The number of correctly completed fields is recorded.

The sessions were done in a dedicated testing room, and only the patient and investigator were present. Each test was performed in a standardized way by the principal investigator, and parallel versions were applied.

Sample Size

We assumed a composite outcome incidence to be $\approx 50\%$ in the CCAB group during a 3- to 12-month period, with a possible reduction to 20% in the OPCAB group. To demonstrate a reduction in cognitive impairment from 50% to 20% (with a significance level of 0.05 and 80% power) would require 50 patients in each group.³⁷ With an expected 20% dropout rate, the total number of enrolled patients was 120.

Definitions and Data Analysis

Cognitive dysfunction was defined as the occurrence of at least 2 of 7 possible deficits (Table 1). The 7 possible deficits were 2 possible deficits in A, B, and C and 1 possible deficit in D. For the 2 error scores, a deficit was defined as ≥ 4 additional errors postoperatively compared with preoperatively out of 16 possible in B and ≥ 5

TABLE 1. Definition of Cognitive Dysfunction

Tests	Memory	Cognitive Speed, Attention, and Flexibility
A. Visual Verbal Learning	2 Deficits	
B. Concept Shifting Task		≥4 Errors and/or 1 deficit in time
C. Stroop Color Word Interference		≥5 Errors and/or 1 deficit in time
D. Letter-Digit Coding		1 deficit

additional errors postoperatively compared with preoperatively out of 40 possible in C. For the remaining 5 variables, a deficit was defined as a 40% postoperative deterioration in the neuropsychological test compared with preoperative tests results.

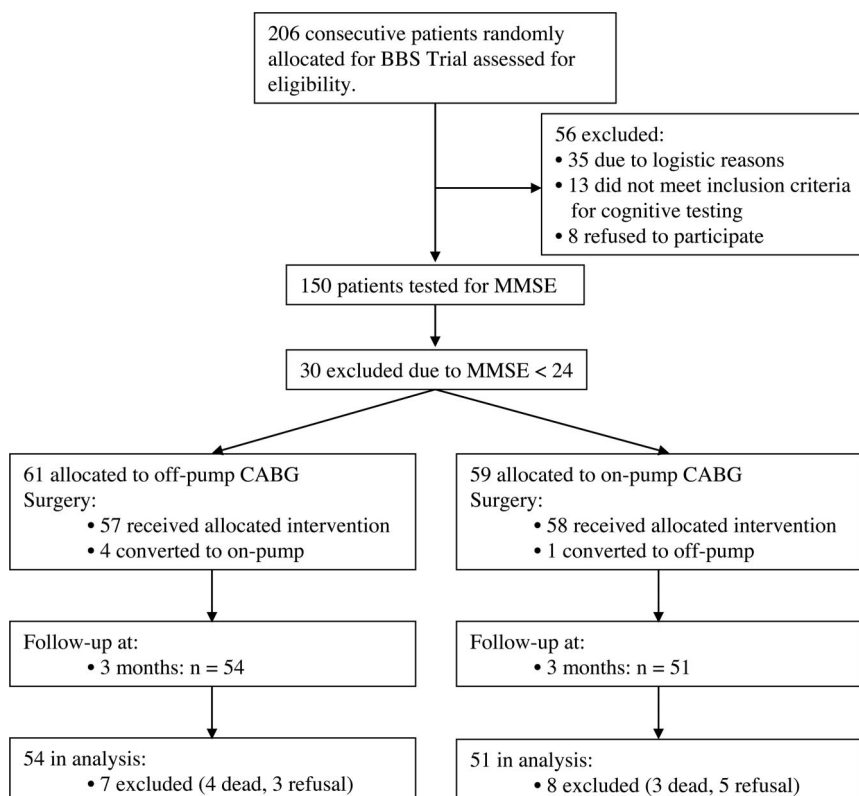
Secondary analysis was performed based on 2 other definitions of cognitive decline: (1) a 20% decline in cognitive scores compared with baseline³⁸ and (2) the ISPOCD (International Study of Post-Operative Cognitive Dysfunction) definition,²⁸ in which changes in the performance of 7 parameters from the result of the 4 tests were calculated. For each individual test outcome, the average learning effect was subtracted from these changes, and a *z* score was obtained after division by the SD from an age-matched healthy control group. When 2 of 7 *z* scores in individual tests or the combined *z* score were 1.96 or more, patients were defined as having cognitive dysfunction. (See Rasmussen et al³⁰ for details.) Differences in patient characteristics at baseline and frequency of cognitive dysfunction in the OPCAB and CCAB group were compared with χ^2 test and Fischer's exact test for categorical variables. Continuous data were compared with *t* test or Wilcoxon rank test as appropriate. Probability values less than 0.05 were considered statistically significant. All subjects were analyzed in the groups to which they were randomly allocated according to intention-to-treat analysis.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient Population and Allocation

Between July 2002 and December 2004, 206 consecutive patients included in the BBS trial were evaluated for eligibility in the present study. In total, 13 patients did not meet criteria for cognitive testing because of severe visual (3 patients) or auditory (1 patient) disorders, neuropsychological testing within the last year (1 patient), more than 5 drinks/units of alcohol per day (1 patient), current severe psychiatric disease (1 patient), poor comprehension of Danish (4 patients), and unwillingness to return to follow-up (3 patients). Furthermore, 30 of the eligible patients were excluded due to having a Mini Mental State Examination score less than 24. Logistic reasons were responsible for the exclusion of 35 patients, eg, the staff who were responsible for data collection had vacation or a day off, patients were not available for baseline testing because of inclusion late in the evening or just before surgery, or patients lived so far away from the hospital that follow-up was impossible. Therefore, 120 patients were included in the present study. At 3 months, cognitive outcomes could be determined in 54 patients in the OPCAB group and 51 in the CCAB group. Seven patients had died, and 8 patients refused to participate in further cognitive tests (Figure). At baseline, there were no significant differences between the groups regarding age, sex, comorbidity, smoking habits, and basic school education; however, in the OPCAB group, the level of education was higher. Twenty-four percent of the patients had a EuroSCORE of 5 (12 OPCAB and 17 CCAB patients). The mean EuroSCORE for all patients was 6.68. Patients in the OPCAB group were on average 1 year older than those in the CCAB group and



Flow of patients through the trial. MMSE indicates Mini Mental State Examination.

TABLE 2. Baseline Characteristics of Patients According to Surgery Procedure

Variable	OPCAB (n=61)	CCAB (n=59)
Age, mean (SD), y	76 (4.8)	75 (4.2)
Sex, female, n (%)	26 (43)	22 (37)
Comorbidity, n (%)		
Predisposition for IHD <55 y of age	18 (31)	12 (20)
Diabetes	11 (18)	11 (19)
Hypertension	40 (66)	33 (56)
Previous myocardial infarction	42 (69)	46 (78)
Previous neurological complications*	12 (20)	15 (25)
History of atrial fibrillation	3 (5)	6 (10)
Ejection fraction, mean (SD)	49.8 (8.9)	48.6 (8.3)
EuroSCORE, mean (SD)	6.8 (1.6)	6.6 (1.6)
Current smoker, n (%)	10 (16)	12 (20)
Former smoker, n (%)	37 (61)	34 (58)
Basic school, n (%)		
7 y or less	31 (51)	34 (58)
8 to 9 y	16 (26)	18 (31)
10 y	9 (15)	5 (9)
High school	5 (8)	2 (3)
Education, n (%)		
None	17 (28)	30 (51)
Vocational	35 (57)	28 (48)
University	9 (15)	1 (2)

IHD indicates ischemic heart disease.

*Includes stroke and transient ischemic attack.

comprised slightly fewer men (Table 2). Perioperatively, the mean length of operation was 159 (SD 40) minutes in the OPCAB group and 152 (SD 30) minutes in the CCAB group. In the OPCAB group, the nontouch aorta technique (proximal T grafting plus right internal mammary artery) was used in 6 of 57 patients, the HeartString technique in 3 of 57, and a side clamp in the remaining 48 patients. In the CCAB group, proximal T grafting was used in 3 of 58, the 1-clamp technique in 5 of 58, and a side clamp in the remaining 50 patients. Four of 61 patients allocated to OPCAB were converted to on-pump CABG. One of the patients was converted during the OPCAB procedure owing to hemodynamic instability. Three procedures were performed as on-pump cases because the surgeon considered that the operation could not be performed successfully as an OPCAB procedure in his hands. One of the 59 patients allocated to CCAB was converted to OPCAB owing to severe calcification.

Duration of CPB in the CCAB group was 60 (SD 19) minutes, with 36 (SD 13) minutes of cross-clamp time. The incidence of postoperative atrial fibrillation was 57% (95% confidence interval [CI] 43.2% to 69.4%) in the OPCAB group and 55% (95% CI 41.5% to 68.3%) in the CCAB group. Postoperatively (in-hospital incidence), 1 nonfatal stroke was seen in the OPCAB group and 1 in the CCAB group.

Cognitive Outcome

The mean interval between operation and 3-month follow-up was 100 (SD 11) days in the OPCAB group and 106 (SD 18)

days in the CCAB group ($P=0.07$). When we applied our definition of at least 2 of 7 possible deficits compared with baseline, 7.4% (95% CI 2.1% to 17.9%) of the patients in the OPCAB group and 9.8% (95% CI 3.3% to 21.4%) in the CCAB group had cognitive dysfunction ($P=0.7$).

When we used the definition of a 20% decline in cognitive scores compared with baseline, the incidence of cognitive decline at 3 months was 20.4% (95% CI 10.6% to 33.5%) of the patients in the OPCAB group and 23.5% (95% CI 12.8% to 37.5%) in the CCAB group ($P=0.8$). When cognitive dysfunction was defined according to a z score ≥ 1.96 , 26.0% (95% CI 15.0% to 39.7%) of the patients in the OPCAB group and 21.6% (95% CI 11.3% to 35.3%) in the CCAB group had cognitive dysfunction ($P=0.7$). There was no significant difference in the incidence of neurocognitive decline between the 2 groups regardless of the definition applied.

Discussion

Our objective was to evaluate the effect of OPCAB versus CCAB on cognitive function in elderly high-risk patients at 3 months postoperatively. To the best of our knowledge, this is the first randomized study focusing on that specific topic. In addition, the present study is characterized by a high degree of internal validity in terms of accounting for patient selection, and a large number of the patients were available for 3-month follow-up, because only 8 of 120 refused to participate. The sample-size calculation was based on achieving a 60% reduction in cognitive decline at 3 months. The risk of type 2 error is important, and a more modest reduction cannot be excluded, but detection of a small difference would need to be investigated in a larger randomized study. The detection of a difference between 7% and 10% would require approximately 3000 patients if a type 2 error of 20% is accepted.

It is remarkable that 30 (20%) of 150 eligible patients were excluded because their Mini Mental State Examination score was <24 (Figure). One explanation could be related to patient characteristics, including age, with associated arteriosclerosis that might be manifested in arteries other than the coronaries. The groups were similar with regard to demographic characteristics. The difference in education is considered incidental (Table 2). The high incidence of atrial fibrillation did not differ significantly between the groups and can therefore be precluded as a confounder in terms of thromboembolic events.

We found no difference between the 2 groups with regard to incidence of cognitive dysfunction and stroke. It was anticipated, however, that at 3 months, outcome would have been significantly improved in favor of the OPCAB technique. It is remarkable that in the present study, the 9.8% to 23.5% variation in incidence of cognitive decline in the CCAB group (Table 3), depending on the definition used, is consistent with the previous reported incidence, from uncontrolled studies, of 4% to 47% in younger patients (mean age 55 to 70 years) 2 months after the operation,⁷ because advanced age is the least controversial demographic risk factor for cognitive decline.^{5,39} Moreover, the lack of benefit from avoiding CPB was not expected, because the use of CPB is generally regarded as the main cause of cognitive decline, and its effects are anticipated to be even more notable in older patients with more comorbidity.^{40,41} Three other randomized

TABLE 3. Incidence of Cognitive Dysfunction

Definition	OPCAB, % (n=54)	CCAB, % (n=51)	P, OPCAB vs CCAB
2 Deficits out of 7 possible (95% CI)	7.4 (2.1–17.9)	9.8 (3.3–21.4)	0.74
20% Decline in cognitive scores (95% CI)	20.4 (10.6–33.5)	23.5 (12.8–37.5)	0.81
z Score ≥ 1.96 (95% CI)	26.0 (15.0–39.7)	21.6 (11.3–35.3)	0.65

studies that included younger, low-risk patients found no significant difference in cognitive function after 2.5 months¹⁷ or 3 months^{16,19} with OPCAB versus CCAB. In contrast, Zamvar et al⁴² found significantly greater deterioration in cognitive scores in the on-pump group after 10 weeks using a battery of 9 neuropsychometric tests. Cognitive dysfunction was defined as deterioration of 1 SD from the baseline score of all patients. Recently, in a longitudinal study, 140 patients undergoing CCAB were compared with a control group of 92 demographically and medically similar nonsurgical patients with coronary artery disease who underwent cardiac catheterization with or without an angioplasty procedure.^{43,44} No significant differences in cognitive outcomes were found between the groups at 3 months or at 1- or 3-year follow-up, which suggests that the previously reported early postoperative cognitive decline after CABG tended to be resolved before the 3-month examination.

Two retrospective observational studies examined patients with EuroSCORES >5 and found no benefit from OPCAB surgery related to the incidence of stroke.^{45,46} A meta-analysis of 9 nonrandomized observational studies, which included 4475 elderly patients aged 70 years or older, 1253 of whom underwent OPCAB and 3222 of whom underwent CCAB, showed that the OPCAB technique was associated with a significantly lower incidence of stroke than the CCAB technique.⁴⁷ Because of the limited design of the studies included in the meta-analyses, and inconsistency with the results of the present study, further prospective randomized trials of sufficient size are required before a final conclusion can be drawn with regard to whether there is a cerebroprotective benefit from avoiding CPB in elderly high-risk patients.

The reasons for the limited differences in cognitive outcome between the treatment groups observed in the present study may be explained in several ways. When one examines the literature, the crucial step of finding a significant neurocognitive deficit is in determining the definition itself. The definition of a significant deficit varies, and the lower the threshold of “deficit” is determined to be, the more patients there will be who have a deficit. This level is arbitrary from research group to research group and varies from a deterioration of 1 SD in 1 or more tests, a deterioration of 20% or 25% in at least 1 or 2 tests, to the use of a standardized z score or composite z score.^{29,30} The definition of cognitive dysfunction in the present study was more restrictive than the “20% criterion” and the definition with the z score. In the analyses of the test results from the present study, the evaluation of cognitive function was based on differences between preoperative and postoperative performance. Therefore, the association between early and late cognitive outcome could be

explained by regression toward the mean,⁴⁸ because generally, the use of scores favors patients with poor preoperative performance because of the “protective” effect of low baseline performance.³⁰ On the other hand, the ISPOCD test battery is in accordance with the “Statements of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery”²⁶ and has been tested for sensitivity in elderly patients undergoing CCAB.²⁹ The error scores were considered and learning effects taken into account by the inclusion of a control group of healthy volunteers.

Another explanation involves the short-term follow-up in the present study, because it has been suggested that improved cognitive outcome with an OPCAB procedure may only become clear in the long term. van Dijk et al¹⁹ found an increasing incidence of cognitive decline from 3 to 12 months, and Newman et al⁵ found cognitive decline in 24% of patients 6 months after CCAB, which increased to 42% after 5 years.

A final explanation might be that the OPCAB technique is a new source of cognitive dysfunction caused by decreased cerebral perfusion pressure during episodes of elevated central venous pressure and corresponding decreased arterial blood pressure, in connection with dislocation of the heart during surgical exposure of the posterior cardiac wall.⁴⁹ The influence of systemic mean arterial pressure during CPB and neurological outcome has been the subject of considerable debate. Commonly, a mean arterial pressure of 50 to 60 mm Hg when the patient is undergoing CPB is regarded as safe to avoid neurological complications, which corresponds to current guidelines at our institution.

In conclusion, the results of this randomized trial in 120 selected high-risk elderly patients suggest that patients who undergo CABG surgery without CPB have no improvement in cognitive outcomes at 3 months compared with patients who undergo a CCAB procedure.

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Disclosures

None.

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