Cognitive outcomes in elderly high-risk patients 1 year after off-pump versus on-pump coronary artery bypass grafting. A randomized trial

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Abstract

Objective: Age is considered to be the strongest predictive factor of postoperative cognitive dysfunction (POCD) after cardiac surgery. Coronary artery bypass grafting (CABG) without the use of cardiopulmonary bypass is considered to be less harmful to the patient, especially in terms of neurological complications. Methods: The study was a sub-study of the randomized best bypass surgery trial that compares off-pump to on-pump treatment, with respect to peri- and postoperative morbidity in patients with a moderate to high-predicted preoperative risk. We investigated cognitive outcomes. A total of 120 elderly patients (mean age 76 years, SD 4.5 years) underwent cognitive testing before surgery, of which 90 patients (47 vs 43) were available for retesting at 1 year (mean 370 days) postoperatively, using a neuropsychological test battery that included seven parameters from four tests. POCD was defined as the occurrence of at least two deficits out of the seven possible scores. Secondary analysis was performed based on definition of 20% decline in cognitive scores compared to baseline, and using z-score analysis. Results: The incidence of POCD was 19% (95% CI 9—33) in the off-pump group and 9% (95% CI 3—22) in the on-pump group (p = 0.18). There were no significant differences in the incidence of cognitive decline between the off-pump and on-pump group regardless of the definition applied. Conclusions: We were unable to detect that CABG surgery without cardiopulmonary bypass was associated with significantly better cognitive outcome in elderly high-risk patients 1 year after the operation.

Keywords: Coronary artery bypass surgery; Off-pump; On-pump; Cognitive dysfunction

1. Introduction

Perioperative neurological injuries are among the most devastating complications of coronary artery bypass surgery (CABG) [1]. Postoperative cognitive dysfunction (POCD) is a condition characterized by impairment of memory or concentration, detected by neuropsychological testing and clinically presenting with deficits in cognition and memory, representing a significant change from a previous level of functioning [2]. Patients report that they are ‘just not the same’, involving problems with following directions, mental arithmetic and planning complex actions. Family members may also notice that a patient is more short-tempered, is less able to withstand frustration, and has wider mood changes [3]. The incidence varies between 3% and 80% depending on the test methods applied, the composition of the target population and study design [4]. Age is considered to be the strongest predictive factor of neurological and neuropsychological injury in cardiac surgery [5]. POCD after this type of surgery is supposed to be related to microembolization from the heart—lung machine or by manipulating the aortic root, and on the basis of the general inflammatory response. Other factors such as prolonged hypoperfusion during CABG or anesthesia, educational or occupational levels, and genetic factors may be important.

A recent meta-analysis indicated that cognitive dysfunction was reduced by 44% at 2—6 months after CABG, but the effect was not sustained beyond 12 months [6]. These studies up to now have mainly included low-risk patients less than 70 years of age with one or two vessel disease. We consecutively enrolled 120 patients from the randomized best bypass surgery (BBS) trial between July 2002 and December 2004. The effect of off-pump versus on-pump CABG on cognitive outcomes at 3 months has been reported previously [7], and did not differ significantly between the groups regardless of the definition of cognitive dysfunction applied. In the present study, we report the effect of CABG surgery with or without...
extracorporeal circulation on cognitive outcome at 1 year after surgery in the same patient population, with the hypothesis that the frequency of postoperative cognitive dysfunction is reduced after off-pump compared with on-pump CABG surgery.

2. Materials and methods

2.1. Design and participants

The local ethics committee approved the study, which is a sub-study of the randomized BBS trial that aims to compare off-pump to on-pump CABG treatment with respect to intraoperative and postoperative mortality and morbidity, in patients with a medium- to high-predicted preoperative risk. The design and methods of the BBS trial have been described in detail [8].

The definition of preoperative risk was based on the European system for cardiac operative risk evaluation (EuroSCORE), which is a method of calculating predicted operative mortality for patients undergoing cardiac surgery. The system consists of three variables related to patient factors, cardiac factors and operation factors which are applied to three risk groups (low, medium and high). Patients with a score \( \geq 6 \) belong to the high-risk group [9].

Inclusion criteria were: patients with known ischemic three vessel heart disease affecting one of the marginal coronary arteries scheduled for elective or sub-acute CABG at the Heart Center, Copenhagen University Hospital, who were \( \geq 55 \) years of age, and who had a EuroSCORE more than or equal to 5.

Exclusion criteria were: 1. previous heart surgery; 2. ejection fraction less than 30%; 3. unstable preoperative condition i.e., continuous infusion of inotropics on the day of the operation; or 4. patient unable to give informed consent. Additional exclusion criteria for the present sub-study were: 1. mini mental state examination score below 24 points; 2. current severe psychiatric disease i.e., depression, psychosis or alcoholism (patients currently using either antipsychotics or antidepressant drugs or imbibing more than five 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 to follow-up. After written informed consent about the BBS trial was obtained, the patients were centrally randomized to one of two groups by an external press button telephone voice response system. The patients were stratified by the following characteristics: gender, age (55—65 years; \( \geq 65 \) years), diabetes mellitus and EuroSCORE (5–8 or \( \geq 8 \)). Patients were randomized in a 1:1 ratio to off-pump or on-pump CABG surgery. The assessors of outcomes and the staff undertaking data analysis were not aware of the allocation.

3. Treatment procedures

In the off-pump group, the revascularization procedure was performed on beating heart with 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, CA) was used to facilitate proximal graft-aortic anastomosis without clamping. In the on-pump group, the revascularization procedure was performed with the use of cardiopulmonary bypass in normothermia, aortic cross-clamping, and cold blood cardiopulmic arrest in all patients. Patients with pronounced aortic calcifications were converted to off-pump 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 standard graft material. The same surgeons performed both procedures.

4. Outcome measures

The primary outcome of this study was cognitive dysfunction at 12 months after surgery. The patients underwent a battery of five neuropsychological tests before and 3 and 12 months after operation. The sessions were done in a dedicated test room, only the patient and investigator were present. Each test was performed in a standardized way by the principal investigator and parallel versions were applied.

The choice of the neuropsychological tests was in accordance with the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery [10]. Furthermore specific cultures and language problems were taken into consideration [2]. Normative data are available [11]. The test battery has been translated into Danish and previously validated for sensitivity among patients undergoing CABG surgery. High test—retest reliability coefficients are obtained and the learning effect was minimized because the tests exist in three parallel versions [12]. The battery comprises the following tests: mini mental state examination as a screening test for dementia after randomization and before inclusion in the study. The patient had to score at least 24 point out of 30 possible points. (A) Visual verbal learning test used for assessment of memory based on a list of 15 words. The patient was asked to recall as many words as possible, immediate and delayed recall after 15—25 min. (B) Concept shifting test consists of three subtests that measure cognitive speed and flexibility. Time and number of errors were registered. (C) Stroop color word interference test measures attention and cognitive speed, in simple and complex conditions. Time and number of errors were registered. (D) The letter-digit coding is a substitution exercise based upon the symbol digit substitution task in the Wechsler adult intelligence scale. Within one minute as many fields as possible are completed. The number of correctly completed fields was recorded.

Cognitive dysfunction was defined as the occurrence of at least two of seven possible deficits. The seven possible deficits were two possible deficits in A, B, and C and one possible deficit in D. For the two error scores, a deficit was
defined as ≥4 additional errors postoperatively compared to preoperatively out of 16 possible in B and ≥5 additional errors postoperatively compared to preoperatively out of 40 possible in C. For the remaining five variables, a deficit was defined as 40% postoperative deterioration in the neuropsychological test compared with preoperative tests results.

Secondary analysis was performed based on two other definitions of cognitive decline: 1. a 20% decline in at least two cognitive scores compared with baseline [13] and 2. the ISPOCD (International Study of Post-Operative Cognitive Dysfunction), definition [11] in which changes in the performance of seven parameters from the results of the four 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, based on data obtained on a 3-month test interval. When two out of seven 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 al. [12] for details).

5. Sample size and data analysis

The sample size calculation was based on the assumptions of the outcome incidence to be about 50% in the on-pump group during a 3—12 months period, with a possible reduction to 20% in the off-pump group. To demonstrate a reduction in cognitive impairment from 50% to 20% (with a significance level of 0.05 and a 80% power) would require 50 patients in each group. With an expected 20% drop out the total number of enrolled patients was 120.

Differences in patient characteristics at baseline and frequency of cognitive dysfunction in the off-pump and on-pump group were compared with chi-squared test and Fischer’s exact test for categorical variables. Continuous data were compared using unpaired t-test or Mann—Whitney U 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 access to all of the data in the study and take full responsibility for the integrity of the work as a whole. All authors have read and agree to the manuscript as written.

6. Results

Between July 2002 and December 2004, 206 consecutive patients from the BBS trial were evaluated for eligibility in the present study. At 12-month follow-up cognitive outcomes could be determined in 47 patients in the off-pump group and 43 patients in the on-pump group. Eight patients had died, 21 refused to participate and 1 patient was not able to complete neuropsychologic testing due to cognitive limitations. Flow of patients through the study is shown in Fig. 1. 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. The mean EuroSCORE for all patients was 6.6 (Table 1). There were no significant differences in demographic and clinical characteristics of patients who did not complete 12 months follow-up compared to those who completed. In addition, there were no significant differences in the baseline characteristic between on- and off-pump patients who did not complete 12-month follow-up.

6.1. Cognitive outcome

The mean interval between operation and 12-month follow-up was 371 (SD 13) days in the off-pump group and 369 (SD 14) days in the on-pump group. An improvement in intrasubject scores was seen in both groups for several cognitive domains (Table 2). In the concept shifting test there was a decline in time and number of errors in both groups and in Stroop color word interference test there was a decline in time in the off-pump group.

From Table 3 it appears that when we applied our definition of at least two of seven possible deficits compared with baseline, the incidence of POCD was 19% (95% CI 9.2—33.3) in the off-pump group and 9% (95% CI 2.6—22.1) in the on-pump group. When we used the definition of a 20% decline in cognitive scores the incidence was 13% (95% CI 4.8—25.7%) versus 12% (95% CI 3.9—25.1%), and when POCD was defined according to a z-score ≥1.96, 30% (95% CI 17.3—44.9%) of the patients in the off-pump group and 28% (95% CI 15.3—43.7%) in the on-pump group had cognitive dysfunction. Of the four patients who were converted to on-pump surgery one had cognitive dysfunction at 3-month follow-up and one had cognitive dysfunction at 12-month follow-up according to our definition of at least two of seven possible deficits compared...
smoker, blood pressure (mmHg), letter-digit coding, score 21.4 (6.4) 22.3 (6.4) 20.5 (5.6) 21.5 (6.1)
stroop color word test, number of errors in part 3 2.6 (3.2) 2.4 (3.7) 3.0 (4.2) 1.7 (2.6)
stroop color word test, time for part 3 (s) 64.8 (18.7) 65.2 (20.6) 72.1 (27.7) 66.7 (21.2)
concept shifting test, number of errors in part C 1.8 (2.7) 2.2 (2.5) 0.9 (1.7) 1.8 (2.5)
concept shifting test, time for part C (s) 61.7 (24.9) 66.7 (27.0) 63.6 (23.4) 64.4 (25.1)
visual verbal learning, cumulated recall, number of words 21.9 (4.8) 23.8 (4.7) 21.8 (5.6) 22.8 (4.5)

Table 2
Baseline characteristics of patients who were available for 12 months follow-up according to surgery procedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Off-pump CABG (n = 47)</th>
<th>On-pump CABG (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>75.5 (5.1)</td>
<td>75.0 (4.2)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>29 (62)</td>
<td>26 (60)</td>
</tr>
<tr>
<td>Basic school, n (%)</td>
<td>7 years or less</td>
<td>23 (49)</td>
</tr>
<tr>
<td></td>
<td>8—9 years</td>
<td>14 (30)</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>7 (15)</td>
</tr>
<tr>
<td></td>
<td>High school</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td>None</td>
<td>11 (23)</td>
</tr>
<tr>
<td></td>
<td>Vocational</td>
<td>29 (62)</td>
</tr>
<tr>
<td></td>
<td>University</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Comorbidity, n (%)</td>
<td>12 (26)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Predisposition for</td>
<td>IHD &lt;55 years of age</td>
<td>32 (68)</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>8 (17)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>32 (68)</td>
</tr>
<tr>
<td></td>
<td>Previous neurological eventa</td>
<td>9 (19)</td>
</tr>
<tr>
<td></td>
<td>History of atrial fibrillation</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>Current smoker</td>
<td>9 (19)</td>
</tr>
<tr>
<td></td>
<td>Former smoker</td>
<td>30 (64)</td>
</tr>
<tr>
<td>Blood pressure (mmHg), mean (SD)</td>
<td>Systolic</td>
<td>142 (26)</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>72 (11)</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction, mean (SD)</td>
<td>50.4 (8.7)</td>
</tr>
<tr>
<td></td>
<td>EuroSCORE, mean (SD)</td>
<td>6.8 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>27 (5.0)</td>
</tr>
<tr>
<td>IHD: ischemic heart disease.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| a Includes stroke and transient ischemic attack.

with baseline. There were no significant differences in the incidence of neurocognitive decline between the two groups regardless of the definition applied.

7. Discussion

Although an increasing number of patients with advanced age and other risk factors for neurocognitive injuries are being referred for CABG, this study is the first randomized trial investigating the effect of avoiding the heart–lung machine on cognitive function 1 year after surgery in that specific patient population. Using three different definitions of cognitive dysfunction, we found no significant difference in late cognitive performance between the groups. This is remarkable because the effect of using cardiopulmonary bypass is generally regarded as the main cause of cognitive decline and anticipated to be even more noticeable in older patients with more comorbidity [14]. The present results are, however, in line with other randomized studies of late cognitive outcome in younger patients with less advanced coronary artery disease and lower preoperative risk [15–17].

In our study, POCD tended to be less common in the on-pump group. This could be further affirmative to the suggestions that many other factors such as inflammatory processes including sternotomy, heparin administration and hemodynamic variations may be responsible for cognitive dysfunction during surgery [18]. Moreover, in a recent study with 50 elderly (more than 65 years of age) cardiac surgery patients, no relationship between occurrence of new ischemic changes, demonstrated by diffusion-weighted magnetic resonance imaging, and postoperative cognitive deficits was found [19]. A comparison of CABG with percutaneous coronary intervention failed to show a considerable difference in cognitive decline in patients undergoing cardiac revascularization [20]. A nonrandomized study included three groups of cardiac patients (on-pump; off-pump; non-surgical) and a group of healthy controls with no cardiac risk factors. At baseline patients with coronary artery disease had lower cognitive test scores than the healthy controls, but there were no difference in cognitive performance between the surgical and non-surgical groups over a 1-year period [21]. Therefore it also seems possible that patient characteristics, including atherosclerosis, are more relevant than the type of intervention in prediction of neurocognitive injury in patients with severe coronary artery disease [22].

The present study has several limitations, including single center design, and 30 patients were lost to follow-up (25%) of which 8 was due to mortality. The presence of cognitive impairment might be responsible for some

Table 3
Cognitive dysfunction 12 months after either on-pump or off-pump CABG surgery

<table>
<thead>
<tr>
<th>Definition of POCD</th>
<th>Off-pump CABG (N = 47)</th>
<th>On-pump CABG (N = 43)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 deficits out of 7 possible</td>
<td>9 (19.2%)</td>
<td>4 (9.3%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Deterioration of 20% in 2 tests</td>
<td>6 (12.8%)</td>
<td>5 (11.6%)</td>
<td>0.87</td>
</tr>
<tr>
<td>z-score ≥ 1.96</td>
<td>14 (29.8%)</td>
<td>12 (27.9%)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

 p = chi-square test.

performance between the groups. This is remarkable because the effect of using cardiopulmonary bypass is generally regarded as the main cause of cognitive decline and anticipated to be even more noticeable in older patients with more comorbidity [14]. The present results are, however, in line with other randomized studies of late cognitive outcome in younger patients with less advanced coronary artery disease and lower preoperative risk [15–17].

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The present study has several limitations, including single center design, and 30 patients were lost to follow-up (25%) of which 8 was due to mortality. The presence of cognitive impairment might be responsible for some
refusals, but only one patient in both groups had cognitive dysfunction at both 3 and 12 months. The dropout rate was almost identical across the groups and baseline characteristics of the remaining patients did not differ significantly from those of the patients who completed cognitive tests. Therefore, no relationship seems plausible between cognitive dysfunction and loss to follow-up in our study. The 30% versus 28% incidence of cognitive decline in the off-pump and on-pump group, respectively, when the z-score definition was used, is consistent with the previously reported incidence of 31% in the off-pump group and 34% in the on-pump group, from a larger randomized trial in younger low-risk patients 1 year after the operation [15]. On the other hand, in a secondary analysis of their data, Keizer and colleagues found a much lower proportion of cognitive decline (12% after 12 months) indicating that the incidence of cognitive decline in younger low-risk patients after CABG surgery has previously been highly overestimated [23]. It has been pointed out that the variability in performance during repeated neuropsychological testing can only be taken into consideration by using a control group [12]. Recently, a larger study [24] comprising 204 CABG patients (mean age 68.8 years) and 90 age- and gender-matched healthy controls assessed the sensitivity and specificity of three commonly used statistical definitions of postoperative cognitive dysfunction. They demonstrated that the definition using a z-score was superior in sensitivity and specificity compared to the definitions of 20% decline in 20% of the tasks and 1 SD deviation decline on two or more tasks. These findings indicate that using the z-score definition for secondary analysis contributes to a further verification of the results from our study. Therefore, the incidence of cognitive dysfunction at 19% in the off-pump group and 9% in the on-pump group can be considered as a minimum. The detection of a difference between 19% and 9% would require approximately 400 patients if a type 2 error of 20% is accepted. Hence, there is a need for larger multi-center trials in order to verify whether or not there is a difference in cognitive function between elderly high-risk patients undergoing off-pump and on-pump surgery. It must also be taken into account that an inability to detect a difference between groups can be related to limitations in the neuropsychological test battery and a different result may have been obtained with other tests which could be more sensitive. Our battery has specifically been compiled to be used in elderly surgical patients, and a postoperative deterioration was found in all considered seven test variables after non-cardiac surgery with most deterioration in tests thought to assess attention and cognitive speed [25]. We therefore believe that the test battery has a reasonable sensitivity but we cannot exclude that impairment in some specific cognitive domains have been overlooked. Future research should determine which cognitive domains are particular vulnerable, and if the pattern of deterioration is different between on-pump and off-pump surgery.

In conclusion, we were unable to detect whether CABG surgery without cardiopulmonary bypass was associated with significantly better cognitive outcome in elderly high-risk patients 1 year after the operation.

Acknowledgments

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