Cognitive function after on or off pump coronary artery bypass grafting

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Abstract

Objective: To investigate cognitive outcome after on and off pump coronary artery bypass grafting. Methods: Seventy patients between 50 and 80 years with stable angina pectoris, ejection fraction >30%, serum creatinine <150 μmol/l, and lack of tight main stem stenosis were randomized to on or off pump coronary artery bypass grafting. Standardized neuropsychological tests evaluated attention, verbal and visuospatial short-term and working memory, verbal learning, delayed recall, visuo-motor speed, and aspects of executive functions. Levels of anxiety and depression were also investigated. Testing was performed before and at 1 week, 1 and 6 months after surgery. Results: There was no difference in cognitive impairment (defined as a 20% reduction in at least 20% of the tests) between groups. The incidence at 1 week post-operatively was 57% in the on pump group and 58% in the off pump group, after 1 month 30% and 12% and after 6 months 19% and 15%, respectively (p for interaction = 0.19). There was no difference between groups in anxiety (p = 0.18) or depression (p = 0.48).

Conclusions: This prospective, randomized study showed no differences in post-operative cognitive function after on pump compared to off pump coronary artery bypass grafting in low risk patients.

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Keywords: Coronary artery bypass grafting; Off pump; Cardiopulmonary bypass; Cognitive function

1. Introduction

Neurological deficits are important complications after coronary artery bypass grafting (CABG) with severe effects on health and quality of life. Stroke, transient ischemic attack and coma occur in 3% of the cases with a significant increase with age [1]. Cognitive dysfunction is more common, but more difficult to detect. Different studies report post-operative cognitive dysfunction in 3—50% of the patients [2], and a pooled analysis of six comparable studies showed a decline in 23% of the patients [2]. Different functions such as concentration, attention, memory and motor functions may be affected. Late cognitive decline, 5 years after CABG, has also been demonstrated [3,4], but these data are difficult to interpret due to lack of control groups.

There are several mechanisms for neurological damage. Manipulation of the aorta during cannulation and clamping may cause embolism and is an important cause of neurological injury [5]. A correlation between number of emboli and cognitive outcome has been reported [6]. Altered blood flow in the brain during perfusion and the systemic inflammatory reaction are other potential causes of damage [7]. As the patient population undergoing CABG gets older, neurological complications will increase [1].

Off pump coronary artery bypass grafting (OFFCAB) is now a well-established alternative to on pump CABG (ONCAB), although its exact role has not been defined. It can be performed on all coronary vessel territories with good early [8] and mid-term [9] results. OFFCAB is shown to cause less cerebral embolism [10], but it is highly controversial whether OFFCAB reduces cognitive dysfunction.

A few randomized studies concerning OFFCAB and cognitive function have been performed. One large-scale study [11] showed a minor improvement in cognitive function in OFFCAB patients 3 months post-operatively, which became negligible at 12 months. Lee et al. [12] also found a minor improvement in the OFFCAB group at 2 weeks and 1 year after surgery. Diegeler et al. [13] and Zamvar et al. [14] showed better cognitive outcome after OFFCAB, whereas Lloyd et al. [15] found no difference compared to ONCAB. In two of these studies only a minority of the patients had three vessel disease [11,15] and in one study the number of distal anastomoses was lower in the OFFCAB group [12].

The purpose of our study was to investigate the impact of cardiopulmonary bypass (CPB) on cognitive function after CABG in a prospective, randomized study. We hypothesized that in patients with multiple distal anastomoses cognitive dysfunction would be less following OFFCAB.
2. Materials and methods

2.1. Subjects

This study was approved by the Karolinska University Hospital Research Ethics Committee, and informed consent was obtained from all patients. Seventy-four patients admitted for elective CAGB were randomized to ONCAB or OFFCAB. Exclusion criteria were age under 50 or over 80 years, ejection fraction <30%, serum creatinine >150 μmol/l, tight main stem stenosis (>70%), redo operation, diffuse distal coronary artery disease and unstable angina. Revascularization of the circumflex artery territory and the number of bypasses planned were not exclusion criteria. All patients received pre-operatively acetylsalicylic acid until the day before surgery. Level of education was determined as following: low—junior high school completed (age 16); intermediate—senior high school completed (age 19); high—university completed. Four patients who had been randomized either withdrew from the study before surgery or they were excluded because there had to be a change of surgeons, and the ‘new’ surgeon wanted to perform ONCAB.

2.2. Surgery and anesthesia

The patients were operated through median sternotomy by six different surgeons. All proximal anastomoses were performed by the use of a side-biting clamp. Protamine was administered at the end of the operation to fully reverse the heparin effect in both groups.

2.3. ONCAB

Heparin 300 IU/kg was given to obtain activated clotting time (ACT) over 480 s before start of CPB. The aorta was cannulated with a standard DLP cannula (Medtronic, Minneapolis, MN, USA) and a two-stage cannula was used in the right atrium for venous return. The CPB circuit consisted of tubings (Medtronic) without an arterial filter, primed with 1500—1800 ml Ringer’s acetate and 7500 IU heparin, a membrane oxygenator (Affinity NT, Medtronic) and a centrifugal pump (Biomedicus, Medtronic). CPB was conducted with a flow rate of 2.4 l/m2/min, alpha-stat acid—base management and a nasopharyngeal temperature of 34—35 °C. After aortic cross-clamping 700—1000 ml of antegrade cold blood cardioplegia was infused. During cross-clamping cardioplegia was given antegrade or retrogradely every 10—15 min. Rewarming was initiated when the last distal anastomosis was started and the patients were weaned from CPB when the nasopharyngeal temperature was above 36 °C.

2.4. OFFCAB

Heparin 150 IU/kg was initially given and ACT was kept above 300 s while the anastomoses were performed. The temperature in the operating room was 23 °C and a patient warming device (Warm Touch, Mallinckrodt Medical, Hazelwood, MO, USA).

Positioning of the heart was achieved by deep pericardial stay sutures or a suction device (Xpose CTS, Guidant, Indianapolis, IN, USA). One of the following stabilizers was used: OFFCAB multi use stabilizer (Guidant), CTS stabilizer Axicus or Ultima (Guidant) or Octopus II/III stabilizer (Medtronic). An intracoronary shunt was only used in a few cases when an anastomosis was performed on the main stem of the right coronary artery.

All patients were anesthetized according to clinical routine of the department. After pre-medication with morphine, anesthesia was induced with fentanyl, midazolam and propofol and muscular relaxation was achieved with pancuronium or atracurium. Volume-controlled ventilation with 40—50% O2 in air was performed. Anesthesia was maintained with intermittent fentanyl and isoflurane and continuous propofol was used as a supplement when needed. Mean arterial pressure was kept over 50 mmHg and norepinephrine was given if required.

All patients received 500 mg acetylsalicylic acid rectally on the evening the day of the operation and then 160 mg orally from the first post-operative day.

2.5. Neuropsychological assessment

The cognitive testing was performed in accordance with the ‘Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery’ [16]. A specially trained (and supervised by an experienced neuropsychologist, HN) research nurse administered a battery of standardized neuropsychological tests before surgery, 1 week, 1 month, and 6 months after surgery. At the pre-operative assessment the Vocabulary subtest of the WAIS-R (Table 1) was administered. This test was used as an index of pre-morbid cognitive function of each patient.

The tests were selected to represent attention, verbal and visuo-spatial short-term and working memory, verbal learning and delayed recall, visuo-motor speed, and aspects of executive functions (Table 1). There were seven test groups: Digit Span, Block Span, Trail-Making Test A—D, Digit-symbol, COWAT-FAS, Claeson-Dahl Verbal Learning Test and Claeson-Dahl Verbal Retention Test.

Table 1

<table>
<thead>
<tr>
<th>Neuropsychological function</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative functional level</td>
<td>Vocabulary (WAIS-R)</td>
<td>Wechsler (1981)</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>Claeson-Dahl Verbal Learning Test</td>
<td>Claeson et al. (1998)</td>
</tr>
<tr>
<td>Verbal retention</td>
<td>Claeson-Dahl Verbal Retention Test</td>
<td>Claeson et al. (1998)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Stat Form Y-1</td>
<td>Spielberger (1968)</td>
</tr>
<tr>
<td>Depression</td>
<td>Geriatric Depression Scale</td>
<td>Brink et al. (1982)</td>
</tr>
</tbody>
</table>
2.6. A brief description of the different tests

‘Digit Span’ is a test of verbal short-term memory, where the subject is read series of digits and then requested to repeat them in the same order. ‘Block Span’ is a spatial short-term memory test, where the subject has to repeat back series of positions of blocks on a board, by pointing at them in the correct order. In the ‘Trail Making Test’ the subject is supposed to draw a line through numbered circles as fast as possible, in numerical order, and then by alternating between numbered and lettered circles (1—A—2—B— and so on). In the ‘Digit Symbol Test’ digits are represented by symbols in a code, and the subject is supposed to replace the digits with the symbols in a worksheet as fast as possible. ‘COWAT-FAS’ is a test of verbal fluency requesting the subject to say as many words as possible beginning with a certain letter within a time limit. The ‘Claeson-Dahl Verbal Learning Test’ is a standardized list-learning task with up to 10 presentations, and in ‘Claeson-Dahl Verbal Retention Test’ the subject is asked to recall the 10 words after 30 min.

2.7. Statistics

The present study was primarily designed to investigate cognitive dysfunction and was not powered to investigate clinical outcome. The time courses within and between groups were analyzed with general linear mixed models (SAS, SAS Institute Inc., Cary, NC, USA). Logistic regression (SAS) was used to determine differences in cognitive impairment. For between group analysis of operative and post-operative clinical data Fisher’s exact p-test and Mann–Whitney U-test were used. Data in the text is presented as mean with 95% confidence intervals or number of patients (percentage). ONCAB, on pump; OFFCAB, off pump coronary artery bypass surgery; level of education, see Section 2.

3. Results

3.1. Patient characteristics and operative data

There were no major inter-group differences in baseline characteristics (Table 2). The number of distal anastomoses and grafting of the different coronary artery territories were similar in the two groups (Table 3). One patient in the OFFCAB group had a history of stroke with no deficit. There were no strokes or transient ischemic attacks during the hospital stay or during the follow up period. No patient had convulsions or delirium during the hospital stay. One patient in the ONCAB group developed mediastinitis and another ONCAB patient was readmitted to the intensive care unit and treated with ventilator due to pneumonia.

3.2. Conversion to on pump and missing data

Three patients had to be converted from OFFCAB to ONCAB because of technical difficulties to perform the anastomoses. They were treated as OFFCAB patients in the study according to ‘intention to treat’. Testing at 1 week was not completed by four patients (two ONCAB, two OFFCAB, due to post-operative complications), at 1 month by five patients (three ONCAB, two OFFCAB) and at 6 months by
eight patients (five ONCAB, three OFFCAB). Reasons for not completing the tests at 1 and 6 months were: moved out of the region 2, declined testing 5 and cancer diagnosis 1.

3.3. Neuropsychological performance and cognitive impairment

In the Vocabulary subtest (from the WAIS-R, used as an index of pre-operative cognitive function) OFFCAB patients tended to perform better 13.2 (12.3—14.2) versus 12.2 (11.3—13.0) (p = 0.09). The rest of the pre-operative test results were within normal range for this patient category. Detailed results for the different tests are shown in Table 4.

Cognitive impairment was defined as a 20% reduction in at least 20% (that is two) of the main seven variables [17]. At 1 week post-operatively the incidence was 57% in the ONCAB group and 58% in the OFFCAB group, at 1 month 30% and 12% and at 6 months 19% and 15%, respectively (p for interaction 0.19, p for time <0.001). Because p for the interaction was not significant, we did not continue with post hoc analysis.

4. Discussion

This prospective, randomized study did not show any significant difference between ONCAB and OFFCAB in low risk patients regarding cognitive function up to 6 months post-operatively. In both groups a decline in cognitive function was observed in almost 60% of the patients at 1 week after surgery, with a remaining dysfunction in nearly 20% of the patients after 6 months. The incidence of dysfunction at 1 month (30% and 12% in ON- and OFFCAB, respectively) suggests that a clinical important difference might exist in the advantage of OFFCAB. However, our study may not have sufficient power to show a difference.

There have only been a few randomized studies on neuropsychological function comparing ON- and OFFCAB. Our study is both in concordance and in opposition with these. Lee et al. [12] found a better cognitive performance in the OFFCAB group in one of the seven cognitive tests (the Rey Auditory Verbal Learning Test) at 2 weeks and 1 year after surgery, but no difference in general cognitive decline (defined as a 20% impairment in 20% of the tests). However, the number of grafts was fewer in the OFFCAB group. Lloyd

### Table 4

<table>
<thead>
<tr>
<th>Test</th>
<th>Domain</th>
<th>ONCAB</th>
<th>1 week</th>
<th>1 month</th>
<th>6 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit Span forward</td>
<td>Verbal short-term and working memory (h)</td>
<td>OFFCAB</td>
<td>7.4 (6.8—8.0)</td>
<td>6.7 (6.3—7.1)</td>
<td>7.5 (7.1—8.0)</td>
<td>7.2 (6.8—7.6)</td>
</tr>
<tr>
<td>Block Span forward</td>
<td>Visuo-spatial short-term and working memory (h)</td>
<td>OFFCAB</td>
<td>6.2 (5.6—6.7)</td>
<td>5.0 (4.5—5.6)</td>
<td>6.3 (5.8—6.8)</td>
<td>6.7 (6.2—7.3)</td>
</tr>
<tr>
<td>Block Span backward</td>
<td>Visuo-spatial short-term and working memory (h)</td>
<td>OFFCAB</td>
<td>7.2 (6.6—7.8)</td>
<td>6.7 (6.1—7.2)</td>
<td>7.4 (6.9—7.9)</td>
<td>7.1 (6.6—7.7)</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>Visuo-motor speed (l)</td>
<td>ONCAB</td>
<td>104 (86—122)</td>
<td>100 (93—107)</td>
<td>81 (76—86)</td>
<td>83 (74—92)</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>Shifting capacity (l)</td>
<td>OFFCAB</td>
<td>82 (72—92)</td>
<td>102 (95—110)</td>
<td>88 (82—94)</td>
<td>84 (80—87)</td>
</tr>
<tr>
<td>Trail Making Test C</td>
<td>Visuo-motor speed (l)</td>
<td>ONCAB</td>
<td>59 (49—69)</td>
<td>66 (53—79)</td>
<td>59 (52—66)</td>
<td>61 (53—68)</td>
</tr>
<tr>
<td>Trail Making Test D</td>
<td>Visuo-motor speed (l)</td>
<td>OFFCAB</td>
<td>54 (44—64)</td>
<td>57 (52—62)</td>
<td>48 (45—51)</td>
<td>48 (44—52)</td>
</tr>
<tr>
<td>Digit Symbol 90 seconds</td>
<td>Motor speed (h)</td>
<td>ONCAB</td>
<td>56 (4.1—5.8)</td>
<td>6.3 (5.7—6.8)</td>
<td>6.1 (5.4—6.6)</td>
<td>6.0 (5.4—6.5)</td>
</tr>
<tr>
<td>Digit Symbol free recall</td>
<td>Incidental learning (h)</td>
<td>OFFCAB</td>
<td>5.6 (4.8—6.4)</td>
<td>5.7 (5.1—6.3)</td>
<td>6.4 (5.8—7.1)</td>
<td>5.7 (5.2—6.2)</td>
</tr>
<tr>
<td>COWAT-FAS</td>
<td>Verbal fluency (h)</td>
<td>ONCAB</td>
<td>7.1 (6.6—7.6)</td>
<td>7.7 (7.3—8.0)</td>
<td>7.6 (7.3—7.7)</td>
<td>7.7 (7.3—7.7)</td>
</tr>
<tr>
<td>Claeson-Dahl</td>
<td>Verbal learning (l)</td>
<td>OFFCAB</td>
<td>151 (129—172)</td>
<td>190 (171—209)</td>
<td>154 (136—173)</td>
<td>148 (132—165)</td>
</tr>
<tr>
<td>Claeson-Dahl</td>
<td>Verbal retention (h)</td>
<td>ONCAB</td>
<td>66 (59—73)</td>
<td>49 (43—55)</td>
<td>52 (47—58)</td>
<td>61 (55—67)</td>
</tr>
<tr>
<td>Stat Form Y1</td>
<td>Anxiety (h)</td>
<td>OFFCAB</td>
<td>66 (62—70)</td>
<td>69 (66—72)</td>
<td>71 (68—75)</td>
<td>68 (64—73)</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>Depression (h)</td>
<td>ONCAB</td>
<td>24 (22—25)</td>
<td>25 (24—26)</td>
<td>23 (22—25)</td>
<td>24 (22—26)</td>
</tr>
</tbody>
</table>

Data presented as mean with 95% confidence intervals. p, interaction between groups over time. For references on the different tests, see Table 1. (h), a higher value is a better result (for example a high score in anxiety means low level of anxiety); (l), a lower value is a better result.

*a Post hoc analysis showed no difference at any time point, but a difference in trends.
et al. [15] detected no difference in cognitive function at 12 weeks follow up. Patients in this study had mainly one- and two-vessel disease. Diegeler et al. [13] found less cognitive decline (Syndrom Kurtz Test was used) in OFFCAB patients 7 days after surgery, but the patients were not followed any further. Zamvar et al. [14] showed a lower incidence of cognitive decline in OFFCAB patients at 1 and 10 weeks post-operatively. As in our study, the Diegeler et al. [13] and Zamvar et al. [14] studies had mainly patients with three-vessel disease and equal number of distal anastomoses. A recently published randomized study with 60 mainly three-vessel disease patients in each group showed no difference in cognitive function at 3 and 12 months post-operatively [18].

The largest study published so far [11] involved 142 ONCAB and 139 OFFCAB patients. They found no difference between groups in the number of patients with cognitive decline at 3 (29.2% in ONCAB and 21.1% in OFFCAB patients, \( p = 0.15 \)) and 12 months (33.6% vs 30.8%, \( p = 0.7 \)). As in our study there was no difference in cognitive decline between groups, but in the van Dijk study patients did not improve over time despite being low risk patients with mainly one- and two-vessel disease. Thus, compared to other randomized studies, our study included patients with mainly three-vessel disease who were followed with extensive cognitive testing over 6 months.

In all of the above-mentioned randomized studies, as in our study, mainly low risk patients were included with exclusion criteria such as recent myocardial infarction [11,14,15], poor ventricular function [11,15], reoperation [11,12,14,15], previous cerebrovascular lesion [13—15], renal dysfunction [12—15] and emergency operation [11,13,14]. Due to selection of patients important differences might have gone undetected. In our study only low risk patients for cerebral post-operative dysfunction were included with no patients above 80 years of age. Elderly patients are at high risk for neurological complications [1,3] and an observational study [19] has demonstrated a reduced stroke incidence in OFFCAB compared to ONCAB octogenarian patients.

There are other possible reasons for the lack of difference between groups. Other factors than CPB and aortic cannulation are potential causes of the cognitive dysfunction after CABG, as stress caused by surgical trauma, anesthesia, hypothermia, hospitalization, and changed cerebral blood flow. A study by Rasmussen et al. [20] showed that 14% of the patients had cognitive decline 3 months after major non-cardiac surgery regardless if they received regional or general anesthesia. In another study by the same group [21] on younger patients, 40–60 years, 19% had neuropsychological impairment 1 week after major abdominal or orthopedic surgery with general anesthesia compared with 4% in an age-matched control group (\( p < 0.001 \)).

We used a side-biting clamp for the central anastomoses and clamping of the aorta is associated with embolization [22], which may be associated with neuropsychological deficit [6]. The randomized studies mentioned above have all been conducted with a side-biting clamp. In a study by Lev-Ran et al. [23], the incidence of neurological complications decreased when using the no aortic touch technique in OFFCAB patients. However, Calafiore et al. [24] showed in a retrospective study that use of a side-biting clamp in OFFCAB provides the same risk for transient ischemic attack and stroke as in patients in whom CPB, aortic cannulation, and cross-clamping were used. On the other hand a study by Bowles et al. [10] demonstrated fewer micro emboli in OFFCAB patients when a side-biting clamp was used, compared to ONCAB.

Low cardiac output during suturing of distal anastomoses in OFFCAB might affect cognitive function post-operatively. In the Calafiore study [24], low output syndrome was identified as a strong risk factor for stroke and transient ischemic attack in both ON- and OFFCAB. It is possible that this also affects cognitive function. Changes in cerebral cortical oxygenation had been demonstrated during OFFCAB [25].

There are some limits with our study: The testing was not blinded to the examiner. Differences might have gone undetected due to a limited study population. Power analysis showed that 57 patients in each group would be needed (with the observed differences) to detect a 20% difference in cognitive dysfunction.

In conclusion this prospective, randomized study, conducted on low risk patients did not show any important difference in cognitive outcome between ONCAB and OFFCAB patients up to 6 months post-operatively.

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