Short-term and long-term neurocognitive outcome in on-pump versus off-pump CABG

Nathalie Stroobant, Guido Van Nooten, Yves Van Belleghem, Guy Vingerhoets

Abstract

Objective: Neuropsychological dysfunctions are considered to be important complications of coronary artery bypass graft surgery (CABG). We examined the frequency of neuropsychological abnormalities occurring in patients undergoing CABG with (on-pump) and without (off-pump) cardiopulmonary bypass. Methods: Neuropsychological assessment with seven cognitive tasks was performed one day before, 6–7 days after \((n = 49)\) and 6 months after \((n = 35)\) surgery. The subgroup undergoing on-pump surgery \((n = 30\) at 7 days and \(n = 22\) at 6 months) was demographically comparable to the off-pump subgroup. The on-pump group included more multiple vessel disease. Results: Repeated measures multivariate analysis of variance (using surgical group as a between-subjects factor) on the group data revealed no significant differences neither immediately after surgery nor at 6 months after surgery, compared with the preoperative performance. There were no significant differences between the on-pump and off-pump groups in post-operative neuropsychological performance soon after surgery. A significant difference was found between the two groups 6 months after surgery, with more favorable results for the off-pump group. Individual comparisons revealed that 59% of the patients of both groups undergoing CABG showed evidence of cognitive impairment soon after surgery. In 11% of the patients (all on-pump), the cognitive sequelae persisted at follow-up. Conclusion: This study showed no short-term difference between the on-pump and off-pump CABG groups. The long-term cognitive outcome revealed more favorable results for the off-pump group. Although a preference to operate multiple vessel disease with classical cardiopulmonary bypass (CPB) has to be considered, the present study shows evidence for a different pattern of early decline and late recovery of cognitive functions in patients undergoing CABG with and without CPB. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Coronary artery bypass grafting; Cognitive brain function; Neuropsychology; Cardiopulmonary bypass; Off-pump surgery

1. Introduction

Neuropsychological dysfunctions are considered to be important complications of coronary artery bypass graft surgery (CABG). Although the cause of this cerebral injury is unclear, a number of pathophysiologic features are frequently discussed in relation to conventional CABG using cardiopulmonary bypass (CPB). Focal dysregulation, caused by cerebral emboli, as well as diffuse cerebral ischemia, caused by hypoperfusion and the systemic inflammatory response of the body are implicated as possible causative factors [1,2]. As for the intraoperative cerebral microemboli, several studies using transcranial Doppler ultrasonography have reported a correlation between microemboli count and neuropsychological outcome [3–5]. Despite the continuing evolution in CPB techniques and management, limited advances have been made in terms of improving neuropsychological outcome after a bypass operation. Recently, the strategy of off-pump coronary artery bypass (OPCAB) has regained interest. As CPB is not performed during OPCAB, it is expected that this surgical procedure might allow patients to avoid some of the morbidity of CABG surgery. Evidence for the reduction of cerebral embolic load in OPCAB has already been described [6]. Nevertheless, recent studies examining the cerebroprotective effect of OPCAB procedures versus conventional CABG have yielded inconsistent results [7]. To investigate the current short-term and long-term impacts of CPB on neuropsychological functioning, we compared the post-operative acquired neuropsychological dysfunction 6 days and 6 months after the OPCAB procedure with the incidence of decline obtained from patients undergoing conventional CABG.
We hypothesized that if CPB is the cause of neuropsychological impairment over and above other intraoperative factors, the patients undergoing CABG without CPB could be expected to show better psychometric performance than patients undergoing CABG with CPB.

2. Materials and methods

After giving written informed consent, first-time CABG patients were neuropsychologically assessed. Exclusion criteria included carotid artery stenosis (as determined by Duplex B mode Doppler scan), emergency operation, cerebrovascular, neurological, or psychiatric disease, drug and/or alcohol addiction. The incidence of dementia and other neurological disturbances with associated cognitive impairment increases dramatically with advancing age. Therefore, we excluded patients >70 years.

All patients were potential candidates for off-pump surgery except in case of unstable angina, severe left main stenosis (>90%) or anatomical inaccessibility. In multiple vessel disease, complete revascularization especially in the region of the distal circumflex or right coronary artery using the off-pump technique necessitates important prolonged tilting of the heart sometimes leading to hazardous hemodynamic instability. As a consequence, more patients with multiple distal anastomoses in the region of the circumflex and right coronary were selected to be included in the on-pump group. However, since the beginning of the study, the types of stabilizers used have improved considerably, thus broadening the indications for off-pump surgery. At the moment, the ratio off/off-pump CABG has been reversed to 60/40% in favor of the off-pump group.

2.1. Procedure

We first tested the patients 1 day before surgery. The early post-operative session took place on the 6th or 7th post-operative day, which is approximately 1 or 2 days before hospital discharge. We invited the patients for a follow-up assessment 6 months after surgery. All patients were alert and medically and pharmaceutically stable at the time of the neuropsychological examinations. One patient died before the early post-operative examination (due to a cerebrovascular accident) and was not further included in the study. One other patient died before the late post-operative examination (sudden death). Both patients had undergone on-pump surgery. For the other patients we observed no in-hospital psychiatric complications, and none of the patients suffered from post-operative neurological complications such as transient ischemic attacks or strokes. We inventorized the preoperative factors such as hypertension, hyperlipidemia, insulin-dependent diabetes, history of regular smoking, prior myocardial infarction, and ejection fraction.

2.2. Anesthesia and surgical procedures

Anesthesia was induced and maintained with benzodiazepines, propofol and opioids.

For the conventional CABG, all patients underwent a midline sternotomy. Cardiopulmonary bypass with moderate hypothermia was achieved by cannulation of the ascending aorta, venous cannulation through the right atrium into the inferior caval vein. After cross-clamping of the ascending aorta, antegrade crystalloid cardioplegia was given to preserve the myocardial function during surgery. Roller pumps and membrane oxygenator were used for cardiopulmonary bypass. The proximal anastomosis of the veins or free arterial grafts were anastomosed to the ascending aorta during reperfusion during one single aortic cross-clamp.

For the off-pump CABG, midline sternotomy was performed in all patients. The Octopus II system (Medtronic Inc, Minneapolis, MN, USA) was used in all patients to stabilize the suture site. Under normothermia, venous or free arterial grafts were first of all anastomosed (with partial cross-clamping) to the ascending aorta before tilting the heart, allowing immediate restoration of blood flow to the distal target coronary after distal coronary anastomosis.

We inventorized peri- and post-operative factors like number of grafts per patient, number of affected vessels, operation time, and length-of-stay in the intensive care unit.

2.3. Neuropsychological assessment

One examiner (N.S.) administered a battery of seven standardized neuropsychological tests 1 day before, 7 days after \( (n = 49, \text{ with } n = 30 \text{ on-pump}) \) and 6 months after \( (n = 35, \text{ with } n = 22 \text{ on-pump}) \) surgery. On the moment of the first assessment, it was unknown whether an on-pump or off-pump strategy would be used. The tests were selected to sample a broad range of cognitive abilities and included measures of attention and concentration, verbal and non-verbal memory, language, visuospatial functions, executive functions, motor and psychomotor speed. To reduce test–retest effects, we used alternate test versions for most tests. The tests used in the study are listed below.

1. The Rey auditory verbal learning test (AVLT) assesses verbal memory. The measure retained is the total number of words immediately recalled over the first five trials.
2. The trail-making test (TMT Part B) assesses speed for visual search, attention and mental flexibility. The time taken to complete is the measure taken.
3. The grooved pegboard test (GPT) measures finger and hand dexterity. The sum of the time taken to complete the left and right placements of all pegs is the measure taken.
4. The block taps test (TAPS) assesses non-verbal immediate memory and attention. The number of errors is the measure retained.
5. The line bisection test (LBT) assesses unilateral visual
inattention. Total deviation from the true centre is the measure taken.

6. The controlled oral word association test (COWAT, orthographic categories) assesses word fluency. The total number of words (with four given letters) is the measure retained.

7. Judgement of line orientation (JLO) examines the ability to estimate angular relationships between line segments. The measure retained is the correct number of answers. Tests (1), (2), and (3) constitute the core neuropsychological battery as recommended by the Statement of Consensus on assessment of neurobehavioral outcomes after cardiac surgery [8].

2.4. Data analysis

Statistical analysis was undertaken using the SPSS for Windows statistical software package (version 9.0). Normally, distributed data (ratio–scale) were compared with independent t-tests. If the data were not normally distributed, the non-parametric Mann–Whitney test was used. Nominal data were analyzed with Chi square statistics if all expected cell frequencies were greater or equal to five.

3. Results

From the 49 patients fully assessed before surgery and 6 days after surgery, 30 (61%) were operated with CPB and 19 (39%) without CPB. In the CPB group, 93% underwent total aortic and partial aortic clamping. In the non-CPB group, 89% underwent partial aortic clamping. Table 1 shows demographic, pre-, peri-, and post-operative variables in CPB patients and non-CPB patients. Significant differences were found for the IQ estimate, the number of grafts, the number of affected vessels, and the operation time, which was always higher/longer for the on-pump group. Due to the significant difference in the estimated intelligence between the two groups (due to outliers), IQ was included as a

Table 1
Patient characteristics (demographical, pre-, peri- and post-operative variables)a

<table>
<thead>
<tr>
<th></th>
<th>CPB (n = 30)</th>
<th>Without CPB (n = 19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>58 ± 8</td>
<td>60 ± 7</td>
<td>0.46</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>87</td>
<td>95</td>
<td>0.64</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11 ± 3</td>
<td>10 ± 2</td>
<td>0.86</td>
</tr>
<tr>
<td>IQ estimate (NLV)</td>
<td>95 ± 10</td>
<td>86 ± 11</td>
<td>&lt;0.005**</td>
</tr>
<tr>
<td>Preoperative risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>47</td>
<td>68</td>
<td>0.14</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>63</td>
<td>53</td>
<td>0.46</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>27</td>
<td>42</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>67</td>
<td>90</td>
<td>0.10</td>
</tr>
<tr>
<td>Prior myocardial infarction (%)</td>
<td>30</td>
<td>26</td>
<td>0.78</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>68 ± 14</td>
<td>71 ± 21</td>
<td>0.54</td>
</tr>
<tr>
<td>Peri- and post-operative factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n grafts/patient (mean)</td>
<td>4 ± 0.9</td>
<td>3 ± 0.9</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>n grafts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (%)</td>
<td>0</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>2 (%)</td>
<td>0</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>3 (%)</td>
<td>33.3</td>
<td>42.1</td>
<td></td>
</tr>
<tr>
<td>4 (%)</td>
<td>40</td>
<td>31.6</td>
<td></td>
</tr>
<tr>
<td>5 (%)</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6 (%)</td>
<td>6.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Affected vessels (mean)</td>
<td>2.9 ± 0.4</td>
<td>2.2 ± 0.8</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>195 ± 40</td>
<td>171 ± 38</td>
<td>0.03**</td>
</tr>
<tr>
<td>Intubation time (h)</td>
<td>11.1 ± 4.8</td>
<td>9.1 ± 2.8 (n = 18)</td>
<td>0.11</td>
</tr>
<tr>
<td>Stay in intensive care unit (h)</td>
<td>36 ± 19 (n = 29)</td>
<td>33 ± 17 (n = 18)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

a Data given as mean and standard deviation, unless otherwise indicated. IQ, Intelligence quotient; NLV, Nederlandse Leestest voor Volwassenen.

*P-value, significant on 0.05 level.

**P-value, significant on 0.01 level.
covariate for further analyses on the cognitive data to correct for the between-group difference. Thirty-five of the 49 patients (71%) were available for 6-month follow-up assessment.

Table 2 shows the different measurements (pre-, early and late post-operative) for the two groups. Two analyses of variance (using surgical technique as a between-subjects factor and IQ as covariate and with normally distributed data (as shown by Kolmogorov–Smirnov tests) (MANCOVA) on the group data revealed no significant differences immediately after surgery (MANCOVA1) nor at 6 months after surgery (MANCOVA2) compared with the preoperative performance. There were no significant differences between the on-pump and the off-pump groups in post-operative neuropsychological assessment soon after surgery. However, a significant difference between the two surgical groups in late post-operative neuropsychological performance was noticed 6 months after surgery ($F = 2.5; P < 0.05$). Univariate post-hoc analyses showed this effect to be significant for the JLO task only ($F = 11.4; P < 0.01$), with the off-pump group showing better results. If a Bonferroni correction for multiple comparisons (with $P$-value <0.0025) was applied, no individual task was considered to be significant. There were no interaction effects between time of measurement and surgical technique.

Individual comparisons revealed that 29/49 (61%), with on-pump ($n = 17/30, 57%$) and off-pump ($n = 12/19, 63%$) of the patients undergoing CABG showed evidence of cognitive impairment soon after surgery. In 11% of all patients ($4/35, with on-pump 4/22, 18%$) the cognitive sequelae persisted at follow-up.

There was no significant correlation between the number of grafts, the number of affected vessels, the operation time, anesthesia time and neuropsychological outcome.

4. Discussion

Neuropsychological sequelae after CABG using the conventional CPB apparatus remain a major cause of concern among cardiovascular surgeons. Many authors believe that the use of CPB has a specific damaging effect on cerebral function [4,10–12]. The precise pathophysiological features of cognitive impairment are not certain but have been attributed to the microembolic, inflammatory, and non-physiologic perfusion factors associated with CPB [1,2]. In off-pump CABG, where the pump circuit (frequently blamed cause of microemboli) is eliminated, there is only partial clamping of the ascending aorta. Besides the suppression of cognitive deleterious effects of CPB (such as learning and memory disturbances, decline in psychomotor speed and complex attention), an important reduction in the costs and general perioperative morbidity and mortality are considerable arguments to promote OPCAB, although several studies included a certain bias in patient selection [13]. In multiple vessel disease, surgeons initially preferred on-pump technique relative to off-pump surgery to avoid hemodynamic instability caused by prolonged tilting of the heart. This was also the case in the present study where the on-pump group included more patients with a higher number of grafts resulting in increased operation time, although neuropsychological deficits did not correlate with operative variables. Both groups did not differ with regard to demographic variables and important risk factors. However, it has to be taken into account that, because of cognition-related methodological reasons, our patient group consisted of relatively young patients ($\leq 70$ years; mean age respectively 58 and 60 years) compared to other studies that focus mainly on medical variables.

In contrast to the expectations, several studies found no difference in early neurological and neuropsychological outcomes in patients subjected to CABG with or without CPB [14,15]. This is in agreement with the early post-operative results of the present study where patients undergoing off-pump or on-pump CABG showed comparable cognitive performance. These results indicate that, apart from CPB, a substantial portion of the immediate post-operative neurological and neuropsychological deficits may be related to general and hemodynamic aspects of surgery ranging from microembolic load to cerebral hypoperfusion [14]. Especially, the role of polypharmacy of the particular anesthetic regimen merits further investigation [15]. Furthermore, we...
believe that the vulnerability for intraoperative cerebrovascular stress in patients with a history of chronic cardiovascular disease has to be taken into account [16]. It appears that, besides the presence or absence of CPB, CABG remains a complex surgical technique with a lot of contributing parameters such as anesthesia, hypothermia, comorbidity, disease severity, etc, that all have an impact on the cerebral integrity of the post-operative patient. Cognitive dysfunction has been reported to persist for several months or even years after CABG. The return to baseline scores for most of our patients at 6 months is in accordance with data from recent studies that report important improvements in cognitive functions late after cardiac operation [17,18]. The reduction in late cognitive impairment for the on-pump group is probably due to refinements in extracorporeal circulation including the use of arterial line filters [4] and membrane oxygenators [19,20] and improved control of acid–base balance [21]. However, in contrast to the similar early neuropsychological outcome in the two groups, a significant difference was found between the two groups 6 months after surgery. From the 22 on-pump patients evaluated, 18% presented neuropsychological abnormalities at the follow-up post-operative examination. It appears that recovery to the preoperative level is more reduced in the on-pump group than in the off-pump group, where none of the patients suffered from late cognitive decline. This is in contrast with the follow-up study of Taggart et al. [22], who found no difference between the two groups after 3 months. Murkin et al. [22], however, found a significantly lower incidence of cognitive dysfunction at 5 days and 3 months post-operatively in off-pump surgery patients. As far as we know, this is the first study that shows evidence for a different pattern of early decline and late recovery of cognitive functions in patients undergoing CABG with and without CPB.

The hypothesis that both microemboli and cognitive impairment are strongly related to CPB could extend the present study. Other findings already confirmed the relation between cerebral microemboli and an impairment in post-operative cognitive tests [3,4,23,24]. The incidence of emboli detected by TCD is known to be associated to aortic instrumentation [25]. Although partial aortic clamping to perform proximal anastomoses is usually required in both CPB and non-CPB CABG (respectively, 93% and 89% in this study), only with CPB CABG are a transaortic cross-clamp and aortic and cardioplegia cannula required. Again, the relation of absent or present intraoperative microemboli and post-operative cognitive impairment compared to both groups warrants further investigation.

5. Conclusion

Although some selection bias cannot be excluded, we conclude that for those patients in whom beating heart surgery is an appropriate approach to myocardial revascularization, the expectation of improved outcome including a lower incidence of long-term post-operative neurocognitive dysfunction as compared with conventional CABG surgery, may be realized. No beneficial effects, however, have been shown for the short-term neuropsychological outcome. Further studies are required to corroborate these initial findings.

Acknowledgements

This research was supported by grant G.0011.98 from the Fund for Scientific Research, Flanders, Belgium.

References

Appendix A. Conference discussion

Dr A. Fabbrri (Verona, Italy): I have a question about the statistical model because with a little number of more patients you want to change your conclusion, because in the abstract you said no beneficial effect in the short and long term, and with a little number more patients you changed your conclusion then. This poses a question about the statistical method.

Dr Stroobant: That is because we also used another definition of cognitive decline. So for the abstract I have used the definition of standard deviation. This means that when the patient shows more than one drop in standard deviation concerning the preoperative score on two or more tests, he was considered to have a cognitive decline. Now, for the definition of standard deviation, there is a lot of discussion for the moment because the definition of standard deviation has to deal with floor effect, and also you measure the standard deviation on group results. So having another group means also another standard deviation, means also that you can define other patients or identify other patients to have cognitive decline, and for the present study I have used the more sensitive measure of cognitive decline based on a 20% decrease in the preoperative score.