Normothermic cardiopulmonary bypass is beneficial for cognitive brain function after coronary artery bypass grafting – a prospective randomized trial

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Abstract

Background: Hypothermic and normothermic cardiopulmonary bypass (CPB) have resulted in apparently contradictory cardiac and neurologic outcome. Cerebrovascular risk and cognitive dysfunction associated with normothermic CPB still remain uncertain. Materials and methods: In a prospective randomized study, we measured the effects of mildly hypothermic (32°C, n = 72) vs. normothermic (37°C, n = 72) CPB on cognitive brain function. All patients received elective coronary artery bypass grafting (mean age 62.1 ± 6.3 years, mean ejection fraction 60.4 ± 13%). Cognitive brain function was objectively measured by cognitive P300 auditory-evoked potentials before surgery, 1 week and 4 months after surgery, respectively. Additionally, standard psychometric tests (`trailmaking test A’, `mini-mental state’) were performed and clinical outcome was monitored. Results: Patients, operated with mild hypothermia, showed a marked impairment of cognitive brain function. As compared with before surgery (370 ± 45 ms), P300 evoked potentials were prolonged at 1 week (385 ± 37 ms; P < 0.001) and even at 4 months (378 ± 34 ms, P < 0.001) after surgery, respectively. In contrast, patients operated with normothermic CPB, did not show an impairment of P300 peak latencies (before surgery 369 ± 36 ms, 1 week after surgery 376 ± 38 ms, n.s.; 4 months after surgery 371 ± 32 ms, n.s.). Group comparison revealed a trend towards prolonged P300 peak latencies in the patient group undergoing mildly hypothermic CPB (P = 0.0634) 1 week after surgery. Four months postoperatively, no difference between the two groups could be shown (P = n.s.) Trailmaking test A and mini mental state test failed to discriminate any difference. Five patients died (mild hypothermia n = 3, normothermia n = 2) postoperatively (cardiac related n = 3, sepsis n = 2). None of the patients experienced major adverse cerebrovascular events. Conclusions: Objective cognitive P300 auditory evoked potential measurements indicate, that subclinical impairment of cognitive brain function is more pronounced in patients undergoing mildly hypothermic CPB as compared with normothermic CPB for CABG. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Coronary artery bypass grafting; Cognitive brain function; Cardiopulmonary bypass; Temperature

1. Introduction

Mildly hypothermic and normothermic cardiopulmonary bypass (CPB) currently represent the most widely applied temperature managements in coronary artery bypass grafting (CABG). Despite beneficial effects on cardiac function, the effect of normothermic CPB on cognitive brain function remains uncertain [1,2].

Perioperative level of neurocognitive injury after CABG performed with CPB is predictive for long-term outcome of cognitive brain dysfunction up to 5 years after surgery [3,4]. This markedly affects rehabilitation process, work performance and quality of life [4]. The negative impact of CPB on cognitive dysfunction is supported by other extensive test series by means of standard psychometric test batteries [5–7]. Primary targets have been pulsatility of flow and CO-management [5,6]. However, despite a higher stroke rate in high-risk patients [2], McLean et al. [7] were unable to demonstrate any neuroprotective effects from moderate hypothermia as compared with normothermia. This was also shown in terms of neuropsychological impairment [7]. As a consequence of these findings the authors specu-
lated that mild hypothermia (32–34°C) might be possibly more neuroprotective than normothermia (37°C) and moderate hypothermia (28°C), respectively. Since standard psychometric tests are adversely affected by various biases [8,9], these findings need to be confirmed by objective measures.

Cognitive P300 auditory evoked potentials, elicited by a tone discrimination paradigm, are objective measures related to information and cognitive processing, which allows a quantification of impaired cognitive brain function [10–11]. Evoked potential measurements detected by cortical leads, representing stable sequences of negative and positive electroencephalography (EEG) peaks within a period of several hundred milliseconds, are a highly sensitive and reproducible tool for evaluation of impaired cognitive brain function of various disorders [10,12,13] (Fig. 1). The use of the P300 technique was shown to be even more sensitive to detect subclinical impairment of cognitive brain function than EEG and standard psychometric tests, unequivocally confirming the high sensitivity of cognitive P300 auditory evoked potentials [14].

The aim of this prospective randomized study was to measure the effects of mildly hypothermic (32°C) and normothermic CPB (37°C) on cognitive brain function in patients receiving CABG. Primary endpoint was cognitive brain function, which was measured by cognitive P300 auditory evoked potentials and standard psychometric tests (‘mini-mental test’ and ‘trailmaking test A’). Secondary endpoints were descriptive parameters of clinical outcome.

2. Materials and methods

The study protocol was approved by the ethics committee of the University of Vienna. After informed consent was obtained, 144 consecutive patients, who were referred for low-risk, elective CABG entered the study. The indication for CABG in all patients was multi-vessel coronary heart disease resulting in stable angina.

2.1. Cognitive P300 auditory evoked potentials

Cognitive P300 auditory evoked potentials were recorded with Ag/AgCl electrodes on a ‘Nicolet 2000’ (Nicolet, Madison, WI). P300 evoked potentials were generated following a binaurally presented tone discrimination paradigm with frequent (80%) tones of 1000 Hz and rare (20%) target-tones of 2000 Hz at 75 dB HL. Filter bandpass was 0.01–30 Hz. Active electrodes were placed at Cz (vertex) and Fz (frontal), respectively, and referenced to linked earlobe A12 electrodes (10/20 international system) [15]. During the paradigm, the subjects were instructed to keep a running mental count of the rare 2000 Hz target tones. To verify attention, P300 recordings with a discrepancy of >10% between the actual number of stimuli and the number counted by the subjects were rejected and repeated. P300 evoked potential recording resulted in a stable sequence of positive and negative peaks. Latencies (ms) of the ‘cognitive’ P300 peak were assessed. To confirm reproducibility, two sets of P300 measurements (double tracing, see Fig. 1) were recorded in all patients [16].

2.2. Psychometric tests

Immediately after P300 recording, the standard psychometric tests ‘trailmaking test A’ and ‘mini-mental-state test’ were performed to test cognitive impairment and psychometric performance. To minimize learning effects, five different trailmaking tables were randomly used.

To avoid any influence of biorhythm alterations, all P300 records as well as psychometric tests were performed in the morning under comparable conditions by the same physician.

2.3. Anaesthesia and surgical procedure

Patients were premedicated with midazolam. Additional midazolam in 1 mg increments was administered intravenously as needed for sedation during placement of monitors and invasive catheters. All patients received a standard general anesthesia with midazolam, etomidate, fentanyl and pancuronium. Patients were ventilated with oxygen in air, ventilation was set to a tidal volume of 8 ml/kg and a
respiratory rate of 12/min, PEEP 5. Transesophageal echocardiography probe was placed after anesthetic induction in all patients. The TEE views used to assess regional wall motion abnormalities included the transesophageal four and two-chamber views and the transgastric short and long-axis views.

Surgical access was gained via median sternotomy. After harvesting the arterial and venous bypass grafts the patients received heparin (300 U/kg). In patients undergoing CABG with CPB a standard technique was used. We performed normothermic CPB in all patients. Core temperature was assessed by a nasopharyngeal probe. Myocardial preservation during aortic cross clamping was achieved by 4°C cold intermittent ante- and retrograde blood cardioplegia. Heparin was antagonized with protaminsulfate until before surgery activating clotting times could be achieved. The cardiopulmonary bypass circuit consisted of a hollow-fibre oxygenator (Bard HF 5701, C.R. Bard Inc., Havorhill, MA) primed with Ringer’s lactate (2000 ml), mannitol (20 g), heparin (8000 IU) (Immuno, Vienna, Austria) and aprotinin (1 000 000 IU) (Trasylol Bayer, Leverkusen, Germany). Flow during CPB was maintained at 2.5 l/min per m². Blood cardioplegia in a 4:1 ratio was used. Hematocrit level was kept higher than 20% with donor blood if necessary. Phenylephrine injections (0.2 mg) were used to maintain perfusion pressure above 50 mmHg during CPB. After weaning from CPB, mean arterial pressure was maintained above 60 mmHg with fluid loading and appropriate vasoactive drugs. Treatment in the ICU was defined by institutional standards.

2.4. Statistical analysis

Data are reported as mean ± SD. Analysis was performed for categoric variables with the $\chi^2$-test or Fisher’s exact test as appropriate. Continuous variables were analyzed with the Student’s $t$-test or paired $t$-test for clinical parameters after testing for normality of distribution. Brain function parameters were analyzed with the Student’s $t$-test for differences between the two groups and the course of brain function throughout follow-up was computed as differences of P300 peak latency of the individual patient and statistical significance was calculated by the paired $t$-test. Significance level was set at 0.05 and modified according to Bonferroni correction for multiple comparisons. If a significance or a trend towards significance was found, the exact $P$-value was given, if no significance was found, n.s. was given.

3. Results

A total of 144 patients were randomized to either mildly hypothermic or normothermic CPB. Both patient groups were well comparable according to demographic data (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographic data$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypothermic</td>
</tr>
<tr>
<td>$n$</td>
<td>72</td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>61.0 ± 6.5</td>
</tr>
<tr>
<td>Sex (m:f, $n$)</td>
<td>65:7</td>
</tr>
<tr>
<td>Diseased vessels (mean ± SD)</td>
<td>2.90 ± 0.30</td>
</tr>
<tr>
<td>Ejection fraction (%; mean ± SD)</td>
<td>61.9 ± 15</td>
</tr>
<tr>
<td>Diabetes ($n$)</td>
<td>18</td>
</tr>
</tbody>
</table>

$^a$ Basic characteristics of patients undergoing mildly hypo- or normothermic CPB. Values are number or mean ± SD.

3.1. Clinical outcome

Operative data and patient outcome are shown in Table 2. Three patients in mild hypothermia group and two patients in normothermia group died (cardiac related $n = 2$, sepsis $n = 3$) died postoperatively. None of the patients suffered from clinically relevant cerebrovascular events. In patients operated with normothermic CPB blood loss was lower and intubation times were shorter as compared with patients operated with mild hypothermia. There was also no difference in postoperative myocardial outcome concerning ventricular function, as indicated in comparable discharge fractional shortening echo study (Table 2).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical outcome$^a$</th>
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<tbody>
<tr>
<td></td>
<td>Hypothermic</td>
</tr>
<tr>
<td>Major adverse events</td>
<td></td>
</tr>
<tr>
<td>Death ($n$)</td>
<td>3</td>
</tr>
<tr>
<td>Myocardial Infarction ($n$)</td>
<td>1</td>
</tr>
<tr>
<td>Stroke ($n$)</td>
<td>0</td>
</tr>
<tr>
<td>Minor adverse events</td>
<td></td>
</tr>
<tr>
<td>Wound infections ($n$)</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation ($n$)</td>
<td>25</td>
</tr>
<tr>
<td>Number of grafts (mean ± SD)</td>
<td>3.2 ± 0.6</td>
</tr>
<tr>
<td>Blood loss (ml, mean ± SD)</td>
<td>678 ± 93</td>
</tr>
<tr>
<td>Blood units ($n$, mean ± SD)</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td>Intubation time (hours, mean ± SD)</td>
<td>21.2 ± 3.5</td>
</tr>
<tr>
<td>In-ICU stay (days, mean ± SD)</td>
<td>1.6 ± 1.4</td>
</tr>
<tr>
<td>In-hospital stay (days)</td>
<td>9.2 ± 6.7</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>33.4 ± 3.1</td>
</tr>
</tbody>
</table>

$^a$ Operative outcome of patients undergoing mildly hypothermia or normothermia. Values are number or mean ± SD.
even at 4 months (378 ± 34 ms, \( P < 0.001 \)) after surgery, respectively. In contrast, patients with normothermic CPB measurements of cognitive P300 auditory evoked potentials also trended towards prolongation, however, this was not significant (before surgery 369 ± 36 ms, 1 week after surgery 376 ± 38 ms, n.s.; 4 months after surgery 371 ± 32 ms, n.s.). The \( t \)-test comparison revealed a trend towards prolonged P300 peak latencies in the patient group undergoing mildly hypothermic CPB (\( P = 0.063 \)) 1 week after surgery. Four months postoperatively, no difference between the two groups could be shown (\( P = \text{n.s.} \)).

3.3. Psychometric tests

In ‘mini mental state test’ both patient groups scored normal throughout the whole study period (ranging from 29 to 30 points). This only indicates that all patients were without an overt clinically relevant cognitive impairment at all points of measurement. Interestingly, even the standard psychometric ‘trailmaking test A’ failed to discriminate any difference between both patient groups, although it trended to increase in both groups 1 week postoperatively (Fig. 3).

4. Discussion

By objective P300 auditory-evoked potential measures this prospective, randomized study for the first time indicates that mildly hypothermic CPB leads to a more pronounced impairment of cognitive brain function as compared with normothermic CPB in patients undergoing CABG.

The Warm Heart Surgery Investigators assessed 1732 patients and reported a decreased incidence of low-output syndrome and lower cardiac isoenzyme fractions in patients randomized to normothermic CPB as compared with hypothermic (28°C) CPB [1]. In this study there was no difference in major adverse cerebrovascular events (1.6 vs. 1.5% stroke rate). In a similar study by Martin et al.[2], 1001 patients were randomized to hypothermic (28°C) and normothermic CPB, and again marginally better myocardial protection was demonstrated with normothermic CPB. However, there was also significantly higher stroke rate in patients undergoing normothermic CPB as compared with patients undergoing hypothermic CPB (3.1 vs. 1.0%). This difference in stroke rate appears to be related to a higher preoperative risk-score of the patients, as there were more diabetics (25.0 vs. 5.5%) and more patients who had undergone prior CABG (14.5 vs. 8.0%) than in the Toronto trial [2].

Neuropsychological test impairment in CABG patients is a quite common adverse event, that had varied enormously in published series and was reported up to an incidence of 79% [3–7]. The most frequently reported deficits related to CPB are those of concentration, memory and learning, and speed of visual-motor responses [17]. Neurologic as well as neuropsychologic impairment related to CPB have tremendous social and economic implications, which affect practice of surgery. So far, impairment of cognitive brain function in patients undergoing CABG has only been suggested by psychometric testing [18]. Psychometric testing in this study failed to reveal this subtle cognitive decline. In our study, for example, all patients undergoing either mildly hypothermic or normothermic CPB scored almost normal in ‘mini mental state test’ and ‘trailmaking test A’. However, it is generally accepted, that psychometric testing is adversely affected by various biases, e.g. long performance times (stressing attention), visual impairment, influence of psychometric function, level of education or learning effects [8,9]. The latter are of particular interest for follow-up studies [19]. Cognitive P300 evoked potentials, elicited by a tone discrimination paradigm, represent an objective and valid measure of cognitive brain function. P300 peak latencies, increasing with age in healthy subjects, [10] were shown to be related to cognitive impairment rating [11], rapid evaluation of cognitive function test
[20], orienting [21], stimulus evaluation [22], selective attention [23], visual pattern recognition [15], digit span [11] and were shown to be much more sensitive to detect metabolically induced cognitive brain dysfunction than psychometric tests or electroencephalography [10,14,16]. Moreover, P300 technique has a very low intra-individual test-retest variability with a coefficient of variation of 2%, which further stresses its usefulness for cognitive follow-up studies [10].

Based on objective P300 measurements we could show that mild hypothermia significantly affects cognitive brain function as compared with normothermia. Interestingly, McLean et al. [7] failed to demonstrate any neuroprotective effect from moderate hypothermia (28°C) as compared with normothermia in CABG patients. By means of a more sensitive and demanding technology (P300 evoked potentials) we suggest that even mild hypothermia (32°C) adversely affects cognitive brain function in CABG patients. An explanation might be given by Newman et al. [24] who showed that cerebral arteriovenous oxygen difference on rewarming after hypothermia on CPB was significantly associated with neurocognitive decline. Animal experiments support our findings by showing that even minimal temperature differences in the brain may cause the release of toxic, excitatory amino acids that cause brain injury [25].

By objective cognitive P300 auditory evoked potential measurements, this prospective randomized study indicates that normothermic CPB does not adversely affect cognitive brain function as compared with mildly hypothermic CPB in patients undergoing CABG.

References


Appendix A. Conference discussion

Dr A. Corno (Lausanne, Switzerland): How did you control the other variables during bypass in terms of hematocrit, mean perfusion pressure and mean perfusion flow, because in the last slide you stated that you have a trend towards high flow in normothermia?
Second, how do you adapt the flow and/or the pressure in a patient with preoperative systemic hypertension?

*Dr Grimm:* Concerning the first question, it is in some way difficult to measure, but what we took was 5 min after onset of cross-clamp, we did all 5 min measurements, and this was 5 min after cross-clamping the aorta, and what is very correct is that it is in some way difficult, the adaptation, but with calcium antagonists the patients, when they were hypotensive, had a pressure of about 70 mm.