Neurocognitive Function and Cerebral Emboli: Randomized Study of On-Pump Versus Off-Pump Coronary Artery Bypass Surgery

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Background. Neurocognitive impairment can be a debilitating complication after coronary artery bypass graft surgery (CABG). Cardiopulmonary bypass, in particular, cerebral emboli, has been implicated. We compared neurocognitive function and cerebral emboli in patients undergoing on-pump and off-pump CABG.

Methods. 212 patients admitted for CABG were randomly assigned to on-pump (n = 104) or off-pump (n = 108) surgery. Embolic signals were detected with bilateral transcranial Doppler ultrasonography of the middle cerebral artery. Neurocognitive tests were administered preoperatively, on discharge from hospital, at 6 weeks, and at 6 months after surgery. Composite neurocognitive scores were derived using principal component analysis and were compared between the two groups, using analysis of covariance to adjust for baseline values.

Results. At discharge from hospital, the adjusted composite neurocognitive score was 0.25 standard deviations greater in the off-pump group compared with the on-pump group (95% confidence interval: 0.05 to 0.45; $p = 0.01$). There was no significant difference at 6 weeks (0.09 standard deviations, 95% confidence interval: −0.11 to +0.30; $p = 0.4$) and 6 months (−0.002 standard deviations, 95% confidence interval: −0.23 to +0.23; $p = 1.0$). Median number of embolic signals was 1,605 (751 to 2,473) during on-pump and 9 (4 to 27) in off-pump CABG ($p < 0.001$). Age, length of education, and on-pump status were independent predictors of the predischarge neurocognitive score ($p = 0.02$, 0.03, and 0.006, respectively).

Conclusions. Cerebral emboli are more prevalent during on-pump CABG. At discharge from hospital, neurocognitive function is better after off-pump surgery, possibly as a result of the lower embolic load. However, the difference in neurocognitive function does not persist at 6 weeks and 6 months.

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Coronary artery bypass graft surgery (CABG) is one of the most common operations performed, with approximately 800,000 patients each year undergoing this procedure worldwide [1]. Although advancements in surgical techniques have led to a reduction in mortality rate after CABG, neurologic injury remains an important complication. Neurologic injury after CABG is divided into two main subtypes [2]. Type I injury includes transient ischemic attack, stroke, which has an incidence of 1% to 2%, encephalopathy, and coma [3]. Type II injury is more subtle and includes impairment of neurocognitive function. These are defects associated with attention, concentration, short-term memory, fine motor function, and speed of mental and motor responses. The incidence of neurocognitive dysfunction varies from 30% to 80% depending on the timing of assessment of cognitive function after cardiac surgery, study design, and the statistical definition used to define neurocognitive decline [4]. Neurocognitive dysfunction after CABG can have an important bearing on long-term quality of life [5].

Traditionally, most neurologic complications after CABG have been attributed to the use of cardiopulmonary bypass (CPB) and manipulation of the aorta. Cerebral emboli [6] and hypoperfusion [7], as well as the systemic inflammatory response to CPB [8], are thought to be the main underlying causes. Most emboli arise from manipulation and instrumentation of the heart and aorta, and from the pump circuit [9]. With off-pump CABG (ie, surgery on the beating heart without the use of CPB), fewer emboli are generated [10].

The aim of this study was to determine whether there is a difference in postoperative neurocognitive function between patients undergoing off-pump and on-pump CABG, and whether that can be explained by the number of intraoperative cerebral emboli.

Patients and Methods

Study Design and Patients

Approval for the study was obtained from the local Research Ethics Committee, and all patients gave written

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informed consent. This trial was enlisted with a registry for randomized trials: Current Controlled Trials Limited (no. ISRCTN97967360).

Patients referred for elective first-time isolated CABG at St. George's Hospital, London, between August 2002 and March 2004 were candidates for inclusion in this study. Patients with the following criteria were excluded: (1) previous cerebrovascular accident or transient ischemic attack; (2) right or left internal carotid artery stenosis of 50% or greater; (3) previous cardiac surgery; (4) concomitant surgery, for example, valve replacement; (5) previous psychiatric illness, for example, depression, schizophrenia; (6) dialysis-dependent renal failure; (7) Q-wave myocardial infarction in the past 6 weeks; (8) very poor left ventricular function (ejection fraction $< 20\%$); (9) illiteracy or nonfluency in English; and (10) absence of an acoustic window for transcranial Doppler (TCD) ultrasound monitoring. Patients were not excluded because of their coronary anatomy.

The primary outcome measure was a postoperative composite neurocognitive score at 6 months. The neurocognitive score at discharge and at 6 weeks, and the total intraoperative microemboli count formed secondary outcomes. Measurement of primary and secondary outcomes was carried out blinded to patient details and group allocation.

Patients were randomly allocated according to a computer-generated randomization list. Blocking was used to construct the allocation sequence, with block size varying randomly from 4 to 10 patients. Assignments were on cards and enclosed in serially numbered, opaque, sealed envelopes, and each bearing on the outside the name and date of birth of the enrolled patient. Envelopes were opened sequentially and only on the day of surgery for that patient.

Transcranial Doppler Ultrasonography Monitoring

Bilateral TCD ultrasonography of the middle cerebral arteries was performed using a Nicolet/EME Companion II machine (Eden Medizinische Elektronik, Kleinstheim, Germany) with two 2 MHz transducers. A sample volume of 10 mm and sweep speed of 5.1 s was set for all patients. A 128-point fast Fourier transform was used for spectral analysis. Fast Fourier transform time-window overlap was more than 50%. The middle cerebral arterey was identified at a depth of 48 to 58 mm through the transtemporal window, and the transducers were fixed in position using a Welder headset (Nicolet/EME GmbH, Kleinstheim, Germany). The Doppler signals were stored onto digital audiotapes using TCD-D8 recorders (Sony Corp, Tokyo, Japan). Recording of signals would commence after opening the pericardium and terminate upon sternal closure.

Audiotapes were individually coded and played back through the same TCD machine for off-line analysis at a later date. A single observer (R.M.) therefore conducted analysis blinded to subject identity and treatment group. An embolic signal (ES) was identified as a unidirectional short-duration intensity increase, accompanied by a characteristic "click" or "chirp" using Consensus criteria [11]. An intensity threshold of 7 dB was one of the criteria used to identify ES. The total number of ES for the whole procedure was counted, and the number of ES for 1 minute after surgical maneuvers was also documented.

Neurocognitive Assessment

Neuropsychologic test selection was based on the Statement of Consensus on assessing neurocognitive outcomes after cardiac surgery [12]. The examination included a battery of tests designed to test memory, visuomotor skills, attention, cognitive speed, and executive functions. The following tests were administered: Medical College of Georgia Complex Figure Test [13]; Grooved Pegboard Test—dominant and nondominant hand [14]; Rey Auditory Verbal Learning Test [15]; Letter Cancellation Test [14]; Trail Making Test—parts A and B [14]; Symbol Digit Modalities Test [16]; and Verbal Fluency Test [14].

Premorbid estimates of verbal intellectual abilities were obtained by administering the vocabulary subtest, and those of nonverbal intelligence by administering the matrix reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI) [17]. All neurocognitive assessment was conducted blinded to treatment details.

Subjects underwent baseline neurocognitive testing 1 week before surgery, and at three subsequent stages: on discharge from hospital and at 6 weeks and 6 months postoperatively. Testing was performed in a standardized manner. Patients were seated in a private room, and testing would only commence after a clear verbal indication that all instructions were understood.

Surgical Procedures

Premedication was administered with morphine (5 to 10 mg intramuscularly) and hyoscine (200 to 600 μg intramuscularly). Anesthesia was induced with either fentanyl (500 μg), propofol (0.5 to 1.0 mg/kg), and vecuronium (0.1 mg/kg) or alfentanil (1 mg), propofol, and pancuronium (0.5 mg/kg). Maintenance anesthesia was provided with isoflurane and propofol.

On-pump CABG was performed with a roller pump (Stöckert S3, Munich, Germany), membrane oxygenators (Avant Sorin, Mirandola, Italy), and a 40 μm arterial blood filter (Dideco, Mirandola, Italy). Moderate hypothermia (32°C) and α-stat control of acid-base management was used. Perfusion pressure was kept at 60 mm Hg, and a pump flow of 2 to 2.4 $L \cdot min^{-1} \cdot m^{-2}$ was maintained throughout CPB. Blood from cardiotomy suction catheters was separated from the pump circuit and washed with a cell saving device (Dideco). In this way, recirculation of fatty microemboli was minimized [18]. After completing the distal anastomoses, the aortic cross-clamp was removed, and the proximal anastomoses then performed using a single side-clamp on the aorta.

Off-pump CABG was carried out through a median sternotomy using a CTS stabilizer (Cardio Thoracic Systems, Cupertino, California). After all distal anastomoses, proximal anastomoses were fashioned onto the aorta using a single side-clamp. Near normothermia (35°C) was maintained, and systolic blood pressure was kept at 70 mm Hg or greater throughout.