Neuropsychometric outcome following aortic arch surgery: A prospective randomized trial of retrograde cerebral perfusion

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Background: Aortic surgery requiring hypothermic circulatory arrest is associated with a high incidence of brain injury. However, knowledge of neuropsychometric outcome is limited. Retrograde cerebral perfusion has become a popular adjunctive technique to hypothermic circulatory arrest. The aim of this study was to assess neuropsychometric outcome and compare the 2 techniques.

Methods: In a prospective randomized trial, 38 patients requiring elective aortic arch surgery were allocated to either hypothermic circulatory arrest plus retrograde cerebral perfusion or hypothermic circulatory arrest alone. Neuropsychometric testing was performed preoperatively, and at 6 weeks and 12 to 24 weeks postoperatively. Deficit was defined as a 20% decline in 2 tests or more. Standardized Z scores were calculated for each patient and test. Eighteen patients underwent hypothermic circulatory arrest and 20 patients underwent hypothermic circulatory arrest plus retrograde cerebral perfusion. The mean cardiopulmonary bypass, hypothermic circulatory arrest, and retrograde cerebral perfusion durations were 169, 30, and 25 minutes, respectively.

Results: There were 2 deaths and 2 neurological deficits. At 6 weeks postoperatively, 77% of the hypothermic circulatory arrest group and 93% of the hypothermic circulatory arrest plus retrograde cerebral perfusion group had a deficit ($P = .22$). At 12 weeks this was reduced to 55% and 56%, respectively ($P = .93$). There was a worse total Z test score in the hypothermic circulatory arrest plus retrograde cerebral perfusion group at 12 weeks ($P = .05$). Neuropsychometric change did not correlate with hypothermic circulatory arrest duration, presence of aortic atheroma, cannulation technique, or procedure.

Conclusions: Hypothermic circulatory arrest plus/minus retrograde cerebral perfusion is associated with a high incidence of neuropsychometric change despite ostensibly normal clinical outcomes and apparently safe arrest duration. Retrograde cerebral perfusion did not improve outcome in this small study.

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Aortic surgery requiring cardiopulmonary bypass (CPB) and hypothermic circulatory arrest (HCA) is associated with a higher incidence of brain injury than other cardiac operations. Previous reports have placed the incidence of stroke at 7% to 9%.^{1,2} More subtle transient neurological and neuropsychological deficits are less well-defined, but some degree of deficit may occur in most patients undergoing HCA.^{3,4}

Retrograde cerebral perfusion (RCP) has become a popular adjunctive cerebral protective technique. Although a metabolic effect has been seen in some species, this has not been demonstrated in man or other primates.^{5,6} Other potential benefits of RCP include flushing out atheromatous or gaseous emboli and toxic metabolites,⁷ and the potential maintenance of cerebral hypothermia.⁸ However, RCP may also increase the risk of cerebral edema due to raised venous and intracranial pressure.⁹ Despite its wide acceptance as a supplement to cerebral protection, the clinical efficacy of RCP has never been proven.¹⁰

As yet there has been very little data published on the incidence of neuropsychometric deficit following HCA.¹¹ In particular, there are no previously published prospective randomized trials. The aim of this study was to quantitate and compare neuropsychometric outcome in the context of a trial of HCA alone and HCA + RCP in aortic arch surgery. The study hypothesis was that there would be no difference in terms of neuropsychometric outcome between HCA and HCA + RCP. The primary outcome measure was incidence of neuropsychometric deficit at 6 weeks postoperatively.

Patients and Methods

Local research ethics committee approval and informed consent were obtained. In a prospective randomized trial, with a blinded neuropsychometric observer, 38 patients (mean age, 63; range, 22-85; 23 men, 15 women) requiring elective surgery of the aortic arch with HCA were allocated to either HCA alone or HCA supplemented by RCP (HCA + RCP). Randomization was by minimization and stratified for age and planned extent of aortic repair (to anticipate HCA duration). Recruitment for the study took place between June 1997 and March 1999. Aortic pathology, procedure details, and demographics are detailed in Table 1.

Anesthetic and Cardiopulmonary Bypass Management

Anesthesia was induced using etomidate, pancuronium, and fentanyl, and maintained using intravenous propofol and alfentanil. CPB was conducted using a nonpulsatile roller pump, an arterial line filter, and a membrane oxygenator primed with 2 L of Hartmann's solution. Flows were maintained at 2.4 L/min per m². A mean blood pressure of 55 to 70 mm Hg was maintained using α agonists or glyceryl trinitrate as necessary. An α stat pH strategy was used in all cases. Cardioplegia was antegrade and either crystalloid or cold blood. A retrograde jugular bulb catheter was inserted to allow jugular venous blood sampling. The position of

% neuropsychometric deficit

Figure 1. Incidence of neuropsychometric deficit for each group at 6 and 12 weeks (hypothermic circulatory arrest = ■; hypothermic circulatory arrest + retrograde cerebral perfusion = □).

this was later checked by skull radiograph. Cooling and rewarming gradients of up to 10°C between blood and water bath temperatures were allowed, with rewarming achieved at a nasopharyngeal temperature of 37°C. Once a nasopharyngeal temperature of 36°C was achieved, the water bath temperature was switched to a maximum of 37°C. Topical head cooling with ice was employed in all cases and intravenous dexamethasone 100 mg, and mannitol 1g/kg were administered approximately 20 minutes prior to circulatory arrest. Circulatory arrest was commenced at 15°C nasopharyngeal temperature after positioning the patient in a head-down tilt.

Retrograde Cerebral Perfusion and Operative Technique

RCP was performed in addition to HCA, using perfusion via the superior vena cava to maintain a jugular bulb pressure of 25 mm Hg relative to a zero position at the level of the ear. The RCP circuit has been described previously.¹² Blood flow was maintained at 300 to 600 mL/min. In this series, the inferior vena cava was clamped during RCP.¹³ In all cases the intended site for arterial return was the aortic arch, but femoral cannulation was utilized where this was not technically possible. For this study, hemi-arch replacement was defined as a procedure requiring reimplantation of some but not all, epi-aortic ostia. Extended open distal anastomosis was defined as a single beveled anastomosis replacing the undersurface of the transverse aortic arch. All arch-replacement procedures were undertaken using an interposition graft with construction of a distal anastomosis, followed by reimplantation of the epi-aortic vessels as a single patch. During the completion of the anastomoses, rigorous de-airing of the aortic arch was conducted by the instillation of 4°C cold saline into the graft, displacing air and allowing aspiration of any visible particulate material. Orthograde perfusion of the graft was then established via a side-arm (Anteflo; Sulzer Vascutek, Inchinnan, UK) allowing air drill completion, recommencement of CPB and corporeal rewarming. For the purpose of this study the presence of arch atheroma was defined as the observation of friable, disinte-

TABLE 1. Demographics, aortic pathology, and procedure details

	Hypothermic circulatory arrest	Hypothermic circulatory arrest + retrograde cerebral perfusion	P value
Mean age (range), y	64 (22-83)	62 (27-85)	.649
Men:women	9:9	14:6	.32
Degenerative aneurysm	15	13	.278
Chronic dissection	0	3	.232
Open distal anastomosis	6	11	.21
Hemiarch or extended open distal anastomosis	6	3	.26
Total arch	5	6	1
Femoral cannulation	10	11	.741
Arch atheroma	6	3	.26

grating atheroma plaques within the aortic arch generating particulate matter during suture placement or manipulation.

Neuropsychometric Testing

Neuropsychometric testing was performed by a trained nurse investigator, blinded to the surgical technique used. Testing was performed preoperatively, then postoperatively at 6 weeks, and 12 to 24 weeks using a standard test battery. The tests chosen were consistent with the published recommendations of the consensus conference.¹⁴ The domains tested were memory (Rey Auditory Verbal Learning Test); attention, concentration, and psychomotor performance [Grooved pegboard (dominant/nondominant); Trail Making tests A and B; Rey-Osterrieth Complex Figure test; Digit symbol modalities test]; and higher cortical function (Speed and Capacity of Language Processing; Digit symbol modalities test; and National Adult Reading Test).¹⁵ Neuropsychometric deficit was defined as a 20% decline in 2 tests or more. Standardized Z scores were then calculated for each patient for each neuropsychometric test using the equation¹⁶:

$$\frac{\text{Postoperative score} - \text{Preoperative score}}{\text{Baseline standard deviation for whole group}}$$

Mean Z scores were then calculated for each group for each test. A total Z score for each group, HCA and HCA + RCP, was also calculated. Lower Z score indicates poorer performance.

Statistical Methods and Power Analysis

Assessment of neuropsychometric change after HCA had not been documented before this study. Therefore, it was not possible to estimate study power or sample size at the time of study design. The study sample size was based upon an a priori power analysis of post-reperfusion fall in jugular venous Po_2 .¹³ Analysis was performed using a commercially available software package, Arcus Quickstat, on a standard personal computer. Univariate analysis between 2 dichotomous variables was performed using tests for 2 independent proportions and Fisher exact tests as appropriate. To determine which domains were primarily affected a $2 \times k \chi^2$ analysis was performed. Continuous data are presented as means and standard deviations, with analysis using Mann-Whitney U tests, as normality could not be confirmed. Simple linear regres-

sion was used to assess any association between number of deficits and duration of circulatory arrest.

Results

Eighteen patients underwent HCA and 20 patients underwent HCA + RCP. The mean CPB times were 162 minutes (SD = 30.6) (HCA) and 176 minutes (SD = 40.7) (HCA + RCP) ($P = .06$). The mean HCA durations were 30 minutes (SD = 13.6) (HCA) and 29 minutes (SD = 11.6) (HCA + RCP) ($P = .98$). The mean RCP duration was 25 minutes (SD = 10.1). Mean cooling periods were 58.5 minutes (SD = 14.6; range, 29-84; median = 62 minutes) and 89 minutes (SD = 40; range, 50-102; median = 63 minutes), respectively. The procedures performed for each group were comparable (Table 1). There were 2 deaths (overall mortality = 5.2%), 1 in the HCA group of myocardial failure, and 1 in the HCA + RCP group of pneumonia. One patient had a postoperative cerebrovascular accident (not retested) and 1 patient had temporary sensory loss over the distribution of the trigeminal nerve.

At 6 weeks postoperatively, 6 clinically well patients (3 HCA and 3 HCA + RCP) failed to attend for retesting. One HCA + RCP patient was unavailable due to being hospitalized for an acute Type B aortic dissection. At 12 to 24 weeks postoperatively, 7 clinically well patients failed to attend (5 HCA and 2 HCA + RCP). Testing was aborted in 1 HCA + RCP patient due to an exacerbation of arthritis precluding full testing.

At 6 weeks postoperatively, 77% of patients (10/13) in the HCA group and 93% of patients (14/15) in the HCA + RCP group had a neuropsychometric deficit ($P = .22$). At 12 weeks this was reduced to 55% of patients (6/11) in the HCA group, and 56% of patients (9/16) in the HCA + RCP group ($P = .93$) (Figure 1). The incidence of neuropsychometric deficit in the overall cohort fell significantly between the time points ($P = .014$). This fall was also significant in

Figure 2. Number of deficits per subject for each group at 6 weeks (hypothermic circulatory arrest = ■ hypothermic circulatory arrest + retrograde cerebral perfusion = □).

the HCA + RCP group ($P = .018$) but not the HCA group ($P = .247$).

Figure 2 indicates the number of deficits per subject in each group at 6 weeks. The mean number of deficits was 3.5 (SD = 2.11) in the HCA group and 4 (SD = 1.41) in the HCA + RCP group ($P = .59$). There was a significantly greater number of deficits in tests of higher cortical function ($P < .001$) in the overall group.

At 6 weeks postoperatively there were no differences between the study groups in cumulative Z test scores. However, 2 neuropsychometric tests in the domains of memory (Rey Auditory Verbal Learning Test 1) and higher cortical function (SCOLP 3) showed a significantly greater deterioration in HCA + RCP patients ($P = .03$) (Table 2). At 12 weeks postoperatively, the cumulative Z score for the HCA + RCP group was significantly lower than that of the HCA group ($P = .05$) (Table 3).

In view of the similar incidence of neuropsychometric change in both groups, we assessed any correlation between neuropsychometric deficit and perioperative risk factors for the overall cohort of patients. The incidence of neuropsychometric deficit was not associated with the duration of circulatory arrest (Figure 3). The mean circulatory arrest duration of patients with or without neuropsychometric deficit was very similar at both time points. The mean number of deficits in patients undergoing arrest durations above and below the median (24.5 min) was identical. Univariate analysis was also performed, dividing the patient group according to the dichotomous variables of presence of aortic atheroma ($P = 1.0$), initial arterial cannulation site ($P = .63$), type of procedure ($P = .20$), aortic pathology ($P = .89$), and mean age ($P = .35$). No association between the incidence of neuropsychometric deficit and any of these factors was identified and in view of this a multivariate analysis was not performed.

Discussion

This study demonstrates that neuropsychometric change has a disturbingly high incidence following aortic arch surgery regardless of age, aortic pathology, arrest duration, or the use of retrograde cerebral perfusion. Six weeks postoperatively, nearly all patients have a measurable deficit and 3 months after surgery, a deficit is still present in over half. We also found that neuropsychometric deficit in the HCA + RCP group was similar to that of the HCA group, but at 6 weeks it was significantly worse in 2 Z test subgroups, and at 12 weeks it was worse overall. The greatest neuropsychometric change occurred in the domain of higher cortical function. A significant neuropsychometric deterioration has been previously reported following hypothermic circulatory arrest.³ Our findings are also consistent with the adverse predictive value of early poor performance on late outcome shown by Reich and colleagues.³

In coronary artery bypass surgery, there has been a measurable decline in neurocognitive dysfunction incidence since assessment commenced 2 decades ago. Published incidence of neuropsychometric deficit in recent series, suggest an incidence of 18% to 36% 1 month postoperatively.¹⁷⁻¹⁹ This improvement in outcome has been attributed to safer CPB, including recognition of the importance of aortic atheroma, CO₂ management, and embolic reduction strategies. The evidence provided by the current study, however, suggests that the addition of hypothermic circulatory arrest plus/minus retrograde cerebral perfusion increases the incidence of neuropsychometric deficit even in young patients with nonatheromatous aortas within “safe” circulatory arrest durations. This finding is at variance with previous work demonstrating a correlation between duration of circulatory arrest, in excess of 25 minutes, and adverse late outcome.³ This discrepancy may be explained by the relatively short arrest durations and small sample size of our study. The

TABLE 2. Mean Z scores at 6 weeks

Test	HCA* (baseline SD)	HCA + RCP† (baseline SD)	P value
Rey auditory verbal learning 1	0.84 (1.6)	−0.21 (1.59)	.032
Rey auditory verbal learning 2	0.04 (1.99)	−0.15 (1.77)	.418
Groove peg dominant	0.11 (27.5)	0.06 (39.9)	.857
Groove peg nondominant	−0.06 (23.8)	0.01 (59.3)	.508
Trails A	0.32 (21.3)	−0.01 (18.44)	.782
Trails B	−0.24 (43.4)	−0.1 (43)	.914
Rey-Osterrieth Complex Figure 1	−1.47 (11.27)	−2.42 (8.06)	.162
Rey-Osterrieth Complex Figure 2	−1.01 (10.4)	−1.24 (10.03)	.782
Digit Symbol 1	−1.47 (19.73)	−2.11 (14.4)	.162
Digit Symbol 2	−1.41 (19.56)	−2.12 (14.16)	.135
Speed and Capacity of Language Processing (SCOLP)			
SCOLP 1	−1.43 (22.16)	−1.79 (17.06)	.572
SCOLP 2	−1.36 (21.87)	−1.79 (16.8)	.392
SCOLP 3	−1.55 (20.63)	−2.2 (15.73)	.037
National Adult Reading Test	1.29 (11.01)	1.5 (10.53)	.781
Total Z score	−7.4	−12.57	.241

*Hypothermic circulatory arrest.

†Hypothermic circulatory arrest + retrograde cerebral perfusion.

TABLE 3. Mean Z scores at 12 weeks

Test	HCA* (baseline SD)	HCA + RCP† (baseline SD)	P value
Rey Auditory Verbal Learning 1	0.88 (1.6)	0.13 (1.59)	.14
Rey Auditory Verbal Learning 2	0.4 (1.99)	0.6 (1.77)	.93
Grooved peg dominant	0.02 (27.5)	0.13 (39.9)	.3
Grooved peg nondominant	0.1 (23.8)	0.04 (59.3)	.95
Trail Making A	0.18 (21.3)	0.32 (18.44)	.63
Trail Making B	0.24 (43.4)	0.13 (43)	.33
Rey-Osterrieth Complex Figure 1	0.1 (11.27)	−0.12 (8.06)	.73
Rey-Osterrieth Complex Figure 2	−0.12 (10.4)	−0.14 (10.03)	.77
Digit Symbol 1	0.5 (19.73)	−0.04 (14.4)	.36
Digit Symbol 2	0.36 (19.56)	0.05 (14.16)	.48
Speed and Capacity of Language Processing (SCOLP)			
SCOLP 1	0.27 (22.16)	0.04 (17.06)	.71
SCOLP 2	0.24 (21.87)	0.05 (16.8)	.97
SCOLP 3	0.38 (20.63)	−0.01 (15.73)	.54
National Adult Reading Test	1.36 (11.01)	0.9 (1.53)	.41
Total Z score	4.91	2.07	.05

*Hypothermic circulatory arrest.

†Hypothermic circulatory arrest + retrograde cerebral perfusion.

etiology of brain injury following hypothermic circulatory arrest is most likely multifactorial. The predominant mechanism may not be solely related to the cold global cerebral ischemic insult of hypothermic circulatory arrest but may also be related to the very process of opening the aorta and the propensity for gaseous and particulate embolization during reperfusion despite rigorous de-airing techniques. These findings are concordant with the finding of a high incidence of transient neurological deficit also observed in patients with short HCA durations.²⁰

There is conflicting evidence for and against the use of RCP both in laboratory and clinical studies. Although some

true reverse brain perfusion has been demonstrated during RCP in humans,^{21,22} such perfusion has not been demonstrated to produce a significant metabolic effect.¹³ In addition, while RCP may facilitate maintenance of brain hypothermia during HCA, an effect greater than that achieved with head-packing in ice has not been demonstrated clinically.¹³ There is no data as yet demonstrating an ability of RCP to wash out potentially toxic metabolites and excitotoxins generated during the period of brain ischemia. Perhaps the most important potential benefit of RCP may be its ability to flush out particulate and gaseous emboli from the arterial tree. Experimental models have produced conflict-

Figure 3. Scattergram of hypothermic circulatory arrest duration versus number of identified neuropsychometric deficits at 6 weeks postoperatively. Analysis by simple linear regression.

ing results. While RCP has the capacity to reduce embolic load, this capacity is greatest when the cranial distribution of the reverse flow is augmented by occlusion of the inferior vena cava, restricting diversion of blood via the azygous-hemiazygous venous collateral network. This improved delivery of reverse flow may augment embolic flush-out, but is at the expense of raised intracranial pressure, increased cerebral edema, and worse behavioral and histopathological outcome.^{7,9} These data have received clinical support by the finding of worse neurological outcome in patients receiving RCP at driving pressures in excess of 25 mm Hg.²³

Nevertheless, a clinical advantage of RCP has been shown in several uncontrolled large clinical series.²⁴⁻²⁶ However, these series can be criticized for being retrospective and comparing contemporary series of RCP patients with historical HCA controls. Such studies should be interpreted with caution as the earlier HCA control group may have a more adverse risk factor profile and may have benefited from the improvements in anesthetic, perfusion, and surgical management.

Study Limitations

This study suggests a detrimental effect of RCP in neurocognitive outcome following aortic surgery. However, the authors acknowledge its main limitation to be its small sample size. There were also a number of confounding

variables, such as the presence of aortic atheroma and the use of femoral versus proximal aortic cannulation. On univariate analysis, none of these variables approached significance for an association with neuropsychometric deficit, hence a multivariate analysis was not performed. The presence of arch atheroma was confirmed by visual inspection due to the unavailability of transesophageal echocardiography or epi-aortic scanning at the time of the study. We are not aware, however, that the use of such modes of investigation has proven superior to visual inspection in aortic arch surgery so far. We also acknowledge the lack of any objective imaging such as computed tomography or magnetic resonance imaging to document a difference between the 2 groups in terms of cerebral edema. Electroencephalographic monitoring was also unavailable, though the mean cooling durations in both groups were longer than that required to achieve electrocerebral silence in a recent study by Stecker and colleagues.²⁷ We acknowledge the difference in mean cooling duration between the groups. This was due to the randomization of redo procedures requiring a more complex proximal anastomotic construction during cooling, to the RCP group.¹³ We chose neuropsychometric deficit as opposed to transient neurological deficits as the main outcome measure, as we felt that transient neurological deficit was a more subjective term and not easily measured, whereas neuropsychometric deficit was easier both to measure and define objectively and also more prevalent.

Conclusions

The main strength of this study is its randomized design with blinded observation of neuropsychometric outcome. With the foresight provided by neuropsychometric outcome data from this study, further studies would require approximately 200 patients, randomly allocated to demonstrate a 25% risk reduction in neuropsychometric deficit incidence, with an α of 0.05 and power of 80%. The current trial is, therefore, too markedly underpowered to state that a beneficial effect of RCP has been completely excluded in certain patient categories.

In conclusion, HCA $\pm$ RCP is associated with a disturbingly high incidence of neuropsychometric deficit, despite ostensibly normal clinical outcomes and the absence of neurological deficits. This data is important as it aids the design of future, very necessary studies focused on improving brain outcomes in aortic surgery and may facilitate clinical decision making and patient counseling. The role of RCP during aortic surgery remains uncertain. Although strategies of cerebral protection for different patients may need to be individualized,²⁸ core neuropsychometric outcome data for comparable groups of patients is an essential prerequisite for a step-by-step improvement in patient care.

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