CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

NEUROPSYCHOLOGIC IMPAIRMENT AFTER CORONARY BYPASS SURGERY: EFFECT OF GASEOUS MICROEMBOLI DURING PERFUSIONIST INTERVENTIONS

Michael A. Borger, MD
Charles M. Peniston, MD
Richard D. Weisel, MD
Marie Vasiliou, MSc
Robin E. A. Green, PhD
Christopher M. Feindel, MD

Objective: Neuropsychologic impairment is a common complication of coronary bypass surgery. Cerebral microemboli during cardiopulmonary bypass are the principal cause of cognitive deficits after coronary bypass grafting. We have previously demonstrated that the majority of cerebral emboli occur during perfusionist interventions (ie, during the injection of air into the venous side of the cardiopulmonary bypass circuit). The purpose of this study was to determine whether an increase in perfusionist interventions is associated with an increased risk of postoperative cognitive impairment.

Methods: Patients undergoing elective coronary artery bypass grafting (n = 83) underwent a battery of neuropsychologic tests preoperatively and 3 months postoperatively. Patients were divided into 2 groups according to the median value of perfusionist interventions during cardiopulmonary bypass. Group 1 patients (n = 42) had fewer than 10 perfusionist interventions, and group 2 patients (n = 41) had 10 or more interventions.

Results: The 2 groups of patients were similar for all preoperative, intraoperative, and postoperative variables, with the exception of longer cardiopulmonary bypass times in group 2 patients ($P < .001$). Group 2 patients had lower mean scores on 9 of 10 neuropsychologic tests, with 3 (Rey Auditory Verbal Learning, Digit Span, and Visual Span) being statistically significant. Group 2 patients had worse cognitive test scores, even when controlling for increased bypass times. Group 2 patients had a nonsignificant trend toward an increased prevalence of neuropsychologic impairment 3 months postoperatively.

Conclusions: Introduction of air into the cardiopulmonary bypass circuit by perfusionists, resulting in cerebral microembolization, may contribute to postoperative cognitive impairment. (J Thorac Cardiovasc Surg 2001; 121:743-9)

Neurologic complications are an important cause of morbidity and mortality during cardiac operations.^{1,2} Neuropsychologic impairment is a well-documented and very common complication, occurring in

the majority of patients in the early postoperative period and in approximately one third of patients several months after the operation.³⁻⁶ The principal cause of cognitive impairment is cerebral microemboli during cardiopulmonary bypass (CPB).⁷⁻¹⁰

We have previously demonstrated that the majority of cerebral microemboli during coronary artery bypass grafting (CABG) are caused by the injection of air into the venous side of the CPB circuit, events we have termed *perfusionist interventions*.^{11,12} The purpose of this study was to determine whether an increase in perfusionist interventions is associated with an increased risk of postoperative cognitive impairment.

From the Division of Cardiovascular Surgery, Toronto General Hospital, University Health Network, Department of Surgery, University of Toronto, Toronto, Ontario, Canada.

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Fig 1. Representative transcranial Doppler tracings of a single patient undergoing CPB during baseline (*top panel*), during a perfusionist intervention (*middle panel*), and during venous air entrapment by the atrial cannula (*bottom panel*). High-amplitude deflections represent cerebral emboli.

Methods

Patients were part of an ongoing, prospective, clinical trial assessing cognitive outcomes after CABG. Patients undergoing elective CABG were divided into 2 groups according to the median number of perfusionist interventions during CPB. Group 1 patients ($n = 42$) had fewer than 10 perfusionist interventions, and group 2 patients ($n = 41$) had 10 or more interventions. Perfusionist interventions were defined as the administration of drugs or the injection of blood into the venous reservoir during CPB, events we have previously demonstrated to be associated with cerebral microembolization.^{11,12}

Patients were excluded if they had a history of carotid disease, stroke, or other neurologic disease; if they were undergoing reoperative or concomitant surgical procedures; or if they had a poor understanding of English. The study protocol was approved by our institutional ethics review board, and participating patients gave signed informed consent.

Anesthesia and surgical management. Our standardized anesthetic and surgical protocols for CABG operations have been previously described.^{13,14} In brief, patients received an anesthetic consisting of induction with midazolam hydrochloride, fentanyl, and sodium thiopental, followed by maintenance with isoflurane and propofol. A pulmonary artery catheter was inserted through the right internal jugular vein. Antegrade cold blood cardioplegia was used in the majority of patients, with some patients receiving retrograde cardioplegia. The left internal thoracic artery was anastomosed to the left anterior descending coronary artery in all patients, and supplemental saphenous vein grafts were added as necessary. All proximal anastomoses were performed under a single aortic crossclamp application.

CPB. CPB was established with arterial inflow through the ascending aorta and venous drainage through a single, 2-stage, right atrial cannula. The hematocrit level was main-

Table I. Preoperative characteristics for patients with fewer than 10 perfusionist interventions (group 1) and for patients with 10 or more perfusionist interventions (group II)

Variable	Group 1 (n = 42)	Group 2 (n = 41)	P value
Male sex	35 (83)	32 (78)	.5
Age (y)	58.8 ± 9.8	61.8 ± 8.9	.15
CCS class 3 or 4	8 (19)	8 (20)	.9
LVEF <40%	8 (19)	6 (15)	.6
Left main disease	8 (19)	6 (15)	.6
Triple-vessel disease	23 (55)	29 (71)	.2
Hypertension	15 (36)	22 (54)	.10
Hypercholesterolemia	29 (69)	34 (83)	.14
Peripheral vascular disease	3 (7)	5 (12)	.4
Congestive heart failure	3 (7)	5 (12)	.4
COPD	3 (7)	0 (0)	.12
Renal failure	0 (0)	0 (0)	1.0

Values are given as numbers of patients (percentages) or mean ± SD as shown. CCS, Canadian Cardiovascular Society angina classification; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

tained between 20% and 25% during CPB, pump flow rates between 2.0 and 2.5 L · min⁻¹ · m⁻², and mean arterial pressure between 60 and 80 mm Hg by use of phenylephrine or nitroprusside as required. Systemic body temperature was allowed to drift to a minimum of 34°C, with active rewarming to 37.5°C at the end of CPB.

Our CPB circuit consisted of a collapsible soft-shell venous reservoir (Baxter BMR 1900, Uden, Holland), a hollow-fiber membrane oxygenator (Medtronic Maxima Plus, Mississauga, Canada), and nonpulsatile roller pumps (Cobe, Arvada, Colo). A 32-μm filter (Avecor Affinity, Minneapolis, Minn) was used in the arterial perfusion line. Perfusionists administered drugs into the bypass circuit by using a manifold directly connected to the bottom of the venous reservoir.

Neuropsychologic testing. Patients underwent a battery of neuropsychologic tests preoperatively and 3 months postoperatively. All tests were administered by a trained psychometrist in a quiet, isolated room. The test battery included those tests suggested by an international consensus conference¹⁵ and was designed to assess the following cognitive domains (with corresponding tests in parentheses): (1) learning and memory (Rey Auditory Verbal Learning Test and Rey Visual Design Learning Test); (2) psychomotor skills (Halstead-Reitan Trail Making Tests Parts A and B and Grooved Pegboard Test); (3) attention and concentration (Wechsler Memory Scale [WMS] Mental Control, WMS-R Digit Span, and WMS-R Visual Span); and (4) language and higher intellectual functioning (Verbal Fluency Test and American National Adult Reading Test).

Neuropsychologic impairment was analyzed by severity, defined as group mean scores on individual tests, and by prevalence, defined as a 20% decrease from preoperative scores on 20% or more of the tests.¹⁶

Statistical analysis. All statistical analyses were performed with the SAS system (SAS Institute, Cary, NC). Categorical data were evaluated with the χ^2 square or Fisher exact tests. Continuous variables were evaluated by using the Student *t* test. Associations between neuropsychologic test

scores and number of perfusionist interventions were examined with the Spearman rank correlation coefficient. Increased CPB time was tested as a possible confounding variable by using analysis of covariance. All categorical variables are expressed as percentages, and continuous variables are expressed as means ± SD. So that neuropsychologic test scores could be compared easily, all test data were transformed such that higher scores indicated better neuropsychologic test performance.

Results

Perfusionist interventions. Group 1 patients had 6.0 ± 3.2 perfusionist interventions during CPB compared with 13.4 ± 3.3 in group 2 patients (*P* < .001). Fig 1 displays transcranial Doppler tracings of the middle cerebral artery in a single patient undergoing CPB. The high-amplitude deflections represent cerebral emboli. These representative tracings illustrate the increased number of cerebral emboli during perfusionist interventions compared with those at baseline, as well as the tremendous amount of embolization that occurs during air entrapment by the atrial cannula.

Group characteristics. Table I displays the preoperative characteristics for the 2 groups of patients. The 2 groups had similar preoperative profiles. Intraoperative variables are displayed in Table II. Group 2 patients had significantly longer CPB and aortic crossclamp times (both *P* < .001). Postoperative characteristics for the 2 groups of patients are revealed in Table III. There were no significant differences between the 2 groups for any postoperative variable.

Neuropsychologic test results. Fig 2 reveals the change in neuropsychologic test scores for the 2 groups of patients. The percentage change in test score was calculated as the 3-month postoperative test score

Table II. Intraoperative characteristics for the 2 groups of patients

Variable	Group 1 (n = 42)	Group 2 (n = 41)	P value
Atherosclerotic ascending aorta	5 (12)	4 (9)	.7
Retrograde cardioplegia	3 (7)	2 (5)	.8
Right internal thoracic artery	1 (2)	1 (2)	.9
No. of bypasses	3.6 ± 0.9	4.0 ± 0.8	.08
Crossclamp time (min)	57 ± 17	73 ± 20	<.001
CPB time (min)	75 ± 21	101 ± 34	<.001
Time to rewarm (min)	23 ± 11	23 ± 10	.8

Values are given as numbers of patients (percentages) or mean ± SD as shown.

Table III. Postoperative characteristics for the 2 groups of patients

Variable	Group 1 (n = 42)	Group 2 (n = 41)	P value
Use of inotropic agents	8 (19)	4 (10)	.2
Low-output syndrome	0 (0)	1 (2)	.5
Intra-aortic balloon pump	0 (0)	1 (2)	.5
Myocardial infarction	0 (0)	1 (2)	.5
Renal failure	0 (0)	0 (0)	1.0
Stroke/TIA	0 (0)	0 (0)	1.0
Ventilation time (h)	6.3 ± 3.0	6.8 ± 3.8	.2
ICU time (h)	23 ± 9	25 ± 12	.14
Hospital length of stay (d)	5.8 ± 2.3	6.4 ± 2.3	.18

Values are given as numbers of patients (percentages) or mean ± SD as shown. TIA, Transient ischemic attack; ICU, intensive care unit.

minus the preoperative (baseline) score divided by the preoperative score. Patients with increased perfusionist interventions (group 2) had lower mean scores 3 months postoperatively on 9 of the 10 neuropsychologic tests. In 3 tests, Rey Auditory Verbal Learning, Digit Span, and Visual Span, these differences were statistically significant ($P < .05$).

We also examined the association between the number of perfusionist interventions, expressed as a continuous variable, and neuropsychologic test percentage change in scores. There was a significant negative correlation between perfusionist interventions and Digit Span ($r = -0.34$, $P = .004$) and Visual Span ($r = -0.31$, $P = .009$) test scores. There was a moderate negative correlation between perfusionist interventions and Rey Auditory Verbal Learning test scores ($r = -0.24$, $P = .10$).

Although group 2 patients had longer CPB times than group 1 patients, analysis of covariance did not reveal CPB time as a confounding variable for the Rey Auditory Verbal Learning Test, Digit Span, or Visual Span scores. That is, an increased number of perfusionist interventions was associated with worse neuropsychologic test scores, even when controlling for increased CPB times.

Prevalence of neuropsychologic impairment, as defined by a 20% decline on 20% or more of the neu-

ropsychologic test scores, was also compared between groups. Group 2 patients had a nonsignificant trend toward a higher prevalence of neuropsychologic impairment 3 months after CABG (50% vs 34%, $P = .18$).

Discussion

Neuropsychologic impairment is a very common complication of coronary bypass operations.³⁻⁶ Cerebral microemboli during CPB, events that occur in virtually all patients undergoing CPB, are thought to be the principal cause of postoperative cognitive deficits.¹⁰ Several investigators have demonstrated that patients who have less cerebral microemboli during CPB have a lower incidence of postoperative neuropsychologic impairment.^{8,9,17,18}

The precise composition of cerebral microemboli during CPB is not known. However, we have previously reported evidence that the majority of emboli probably consist of air.^{11,12} We used transcranial Doppler scanning to continuously monitor patients undergoing isolated CABG, carefully noting the timing of cerebral embolism occurrence. We defined perfusionist interventions as those time periods immediately after the injection of drugs, along with small amounts of air, into the venous side of the CPB circuit. Perfusionist interventions resulted in a 7-fold increase in cerebral

Fig 2. Change in neuropsychologic test scores for patients with fewer than 10 perfusionist interventions (group 1) and for patients with 10 or more perfusionist interventions (group 2). Values shown are mean $\pm$ SD percentage change in scores (see text for definition), with more positive values representing better cognitive performance. RAVLT, Rey Auditory Verbal Learning Test; RVDLT, Rey Visual Design Learning Test; AMNART, American National Adult Reading Test.

embolic rate when compared with any other time period (Fig 1).¹¹ We also noted that if perfusionists carefully removed air from the syringe before injecting drugs into the CPB circuit, much fewer cerebral emboli occurred. Administration of drugs by a continuous infusion, rather than by syringe injection, did not result in any emboli production. In addition, we noted that a tremendous number of cerebral emboli occurred during accidental venous air entrapment (Fig 1). We concluded from our studies that the majority of emboli during CPB consist of gaseous microbubbles and that simple techniques can be used to minimize embolization.

It should be emphasized that all drugs were administered into the venous side of the CPB circuit during the

aforementioned studies, with resultant microbubbles traversing the membrane oxygenator and arterial line filter before being detected in the middle cerebral arteries of the patients. The ability of venous air to result in arterial line emboli has been noted by other investigators.^{19,20} It should also be noted that different CPB circuits may have varying capabilities to remove gaseous emboli.^{20,21} Therefore, the association between perfusionist interventions and cerebral emboli may not be as strong in CPB circuits, which differ from ours, particularly in those with hard-shell venous reservoirs.

The current study was intended to determine whether perfusionist interventions, and therefore gaseous microemboli, are associated with post-CABG cognitive

impairment. We focused on 83 patients undergoing CABG who also underwent detailed neuropsychologic testing as part of an ongoing trial of neurologic outcomes. (The patients in the current study did not receive intraoperative transcranial Doppler monitoring.) Patients were divided into 2 groups according to the median number of perfusionist interventions. We found that patients with increased perfusionist interventions had worse mean scores on the majority of tests 3 months postoperatively (Fig 2). In particular, patients with more gaseous microemboli had significantly worse scores on the Rey Auditory Verbal Learning Test, the Digit Span test, and the Visual Span test. We also found negative correlations between the number of perfusionist interventions and postoperative test scores. Although the group with increased perfusionist interventions had longer CPB times, our results remained unchanged when we controlled for CPB times. We failed to demonstrate a significant difference in the prevalence of neuropsychologic impairment (as defined by a 20% decrease on 20% or more of test scores),¹⁶ probably because of our small sample size.

Patients with increased perfusionist interventions had significantly worse cognitive performance on tests of learning and memory (Rey Auditory Verbal Learning Test) and attention and concentration (Digit Span and Visual Span). The cognitive domains of learning, memory, and attention and concentration are particularly sensitive to the deleterious effects of CPB.^{3,22} It should be noted that improvement occurred on several of the neuropsychologic tests 3 months postoperatively (Fig 2). Improved performance is expected on repeated administrations of neuropsychologic tests because of their intrinsic practice effects.²³

The deleterious neurologic effects of massive arterial air embolism (>20 mL) have long been recognized.²⁴ Massive air embolism is an infrequent but well-documented risk of CPB.^{25,26} To the best of our knowledge, this is the first report of an association between air microemboli and cerebral dysfunction. There are 2 methods by which air microemboli can cause cerebral injury. First, microbubbles may occlude small arterioles and cause distal ischemia. Bubbles with a diameter of 200 μ m that are composed of 100% oxygen will take approximately 16 minutes to absorb.²⁷ Second, bubbles can activate platelets, leukocytes, and complement.²⁸⁻³⁰ Activation of the inflammatory cascade can in turn lead to local injury and exacerbation of the ischemic insult.²⁴

Conclusions

We found that patients with increased perfusionist interventions, and therefore increased gaseous

microemboli, had significantly worse performances on tests of learning, memory, and attention and concentration. We therefore conclude that introduction of air into the venous aspect of the CPB circuit should be minimized to decrease the risk of postoperative cognitive impairment.

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Address for reprints: Christopher M. Feindel, MD, Division of Cardiovascular Surgery, The Toronto Hospital, Room EN 14-222, 200 Elizabeth St, Toronto, Ontario, Canada, M5G 2C4.

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