CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

SIMILAR NEUROBEHAVIORAL OUTCOME AFTER VALVE OR CORONARY ARTERY OPERATIONS DESPITE DIFFERING CAROTID EMBOLIC COUNTS

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Objectives: The interrelationships among coronary and valvular operations, microemboli, and neurobehavioral outcome are unclear. We hypothesized that adult patients undergoing cardiac valve operations would have more total emboli delivered to the brain than patients undergoing coronary artery bypass grafting and that this would associate with worse neurobehavioral outcomes.

Methods: One hundred ninety-three patients undergoing coronary artery bypass grafting and 73 patients undergoing cardiac valve operations were compared. Patients received neurologic, neuro-ophthalmologic, and 11 standardized neurobehavioral tests preoperatively and 5 to 7 days, 1 month, and 6 months postoperatively. Left common carotid Doppler ultrasonographic embolus detection was performed intraoperatively. Repeated measures and logistic regression analyses of outcome were performed.

Results: Patients undergoing either coronary or valve operations were well matched by age (61 ± 10 and 59 ± 12 years, respectively), but a significantly greater fraction of patients undergoing valve operations were female, diabetic, or had undergone previous cardiac operations. Neurobehavioral scores of patients undergoing either coronary artery bypass grafting or cardiac valve operations did not differ significantly at any time. Total embolus counts differed significantly: the median was 105 during coronary artery bypass grafting and 479 during cardiac valve operations (geometric means of 104 and 412, respectively; $P = .0001$). Significantly more emboli were detected in the patients undergoing cardiac valve operations after removal of the left ventricular vent and after separation from cardiopulmonary bypass, but comparable numbers of emboli were seen in the 2 groups before cardiopulmonary bypass. In both groups decreased neurobehavioral performance was apparent at 5 to 7 days, with improvement at 1 and 6 months. Increasing numbers of carotid emboli significantly associated with worse performance on the letter cancellation test. There were no significant differences between patients undergoing valve and coronary operations in neurobehavioral outcomes, strokes, transient ischemic attacks, or deaths.

Conclusions: The significantly greater number of emboli in the group of patients undergoing cardiac valve operations is likely the result of the entrainment of intracardiac air. The greater numbers of emboli during cardiac valve operations do not appear associated with a commensurately greater risk of adverse neurologic or neurobehavioral outcome. (*J Thorac Cardiovasc Surg* 2001;121:125-36)

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Neurologic and neurobehavioral outcomes have been intensively studied in patients undergoing coronary artery bypass grafting (CABG) and cardiac valve operations. In the early years of CABG operations, the procedure was performed most often on middle-aged patients with relatively few comorbid conditions. More recently, with improvements in medical management of coronary artery disease and with wide application of percutaneous transarterial coronary interventions, the patient population presenting for CABG is older and sicker than in earlier times. During the same time period, patients with cardiac valve disease were being referred earlier in the natural history of their disease because of improvements in surgical-anesthesia techniques and prosthetic materials. The interrelationships among aging, coronary and valvular operations, gaseous and particulate cerebral microemboli, and neurobehavioral outcomes are unclear. We hypothesize that adult patients undergoing cardiac valve operations would have a greater number of emboli delivered to the brain than patients undergoing coronary artery bypass graft operations and that this greater embolic load would be associated with a worse neurobehavioral outcome.¹ We tested this hypothesis by using control data gathered during 2 randomized clinical trials evaluating neuroprotection in cardiac valve operations and CABG. The primary outcome results of these 2 trials have been reported.¹⁻³

Methods and materials

Our 2 clinical trial protocols were reviewed and approved by our institutional review board. Each patient gave his or her consent to participate. Three hundred eighty-one patients scheduled for elective CABG during 1991 through 1996 and 147 patients scheduled for elective cardiac valve operations from 1992 to 1995 were enrolled in 2 separate neuroprotection trials. The control group of the CABG study (193 patients) was then compared with the control group of the cardiac valve operation study (74 patients) with respect to neurobehavioral outcome. All patients undergoing cardiac valve operations underwent operations on the aortic valve, mitral valve, or both, with or without concurrent CABG. Exclusion criteria for the 2 studies are provided in Table I.

Each patient underwent a standard battery of neurobehavioral tests, including tests of memory function (Rey Auditory Verbal Learning and Nonverbal Memory Tests) and tests of attention, concentration and psychomotor performance (Trail Making Forms A and B, Grooved Pegboard in dominant and nondominant hands, Finger Tapping in dominant and nondominant hands, Letter Cancellation, Digit-Symbol, and Visual Reaction Time tests).⁴ The neurobehavioral tests were performed once preoperatively and on 3 occasions postoperatively. Because psychomotor ability is reversibly diminished by pain, fatigue, and anesthesia, all of which inevitably accompany operations, the first postoperative evaluation was delayed to between postoperative days 5 and 7. Testing was

repeated at 1 and 6 months after operations. Parallel forms of the Rey Auditory Verbal Learning, the Nonverbal Memory, Digit-Symbol, Wechsler Memory, Letter Cancellation, and Visual Reaction Time tests were used to minimize learning effects. There are no parallel forms for the other tests. Brief neurologic and neuro-ophthalmologic examinations (consisting of assessment of cranial nerves, deep tendon reflexes, motor and sensory function, cerebellar function, visual acuity, visual field deficits, and a fundoscopic examination for retinal emboli, optic nerve infarction, retinal hemorrhage, and papilledema) were performed on the same schedule. These examinations were recorded in part by using the National Institutes of Health Stroke Scale, in the use of which all test examiners were certified.

All patients were anesthetized with fentanyl (up to 100 $\mu\text{g/kg}$) and midazolam (up to 0.3 mg/kg) and were paralyzed with pancuronium (up to 0.2 mg/kg), metocurine (up to 0.4 mg/kg), or both. Some patients received enflurane as needed as a supplemental anesthetic. No other volatile anesthetics were permitted. Thiopental, ketamine, propofol, and nitrous oxide were not used. The operations were accomplished during moderate hypothermia (28°C) and cardiopulmonary bypass (CPB). During CABG operations, the distal anastomoses were accomplished with the aorta crossclamped, whereas proximal anastomoses were sewn after application of a side-biting partial occlusion clamp to the proximal aorta. Cardiac valve operations were accomplished during aortic crossclamping.

One hundred fifty (78%) of the patients undergoing CABG and 38 (51%) of the patients undergoing cardiac valve operations underwent continuous Doppler examination of the left common carotid artery during their operations for detection of carotid arterial emboli. The 5-MHz continuous wave Doppler probe (Carolina Medical Electronics, King, NC) was applied after induction of anesthesia. The data were individually recorded on VHS video tapes for post hoc analysis. Research personnel documented the precise times that specific surgical maneuvers took place and marked the tapes accordingly.⁵ Atherosclerosis of the proximal aorta was assessed by palpation and graded using a standard scale. Epi-aortic scanning was not used.

As part of the clinical neuroprotection trial, patients undergoing CABG were randomly assigned to have intraoperative blood glucose controlled with an insulin infusion or a placebo infusion. The patients undergoing cardiac valve operations were enrolled in a separate clinical neuroprotection trial in which they were randomly assigned to receive either nimodipine (total of 1.75 mg/kg over 4 oral doses) or placebo perioperatively. The present study used only the control patients from these 2 clinical neuroprotection trials.

Patients who died perioperatively lacked postoperative neurobehavioral, neurologic, and neuro-ophthalmologic assessment and were not included in neurobehavioral analyses. Data were included from patients with perioperative and postoperative strokes when neurobehavioral test scores were available.

Demographic differences between the patients undergoing CABG and cardiac valve operations were compared by using

the *t* test or exact χ^2 test as appropriate. If log-transformed data were analyzed, we report geometric means (the geometric mean is the antilog of the mean of the log-transformed data) in the text, tables, and figures. Differences between the patients undergoing cardiac valve operations and those undergoing CABG in their neurobehavioral test scores (as percentage change from baseline) were compared over the examinations at 5 to 7 days, 1 month, and 6 months by using mixed models repeated measures. Covariates for cardiac valve or CABG operations, sex, age (fit as linear and quadratic terms), surgeon, and number of emboli were included in the repeated-measures analyses. Interactions between number of emboli and examination date (eg, 5-7 days vs 1 month), number of emboli and type of operation, and type of operation and examination date were also included. A neurobehavioral deficit was defined as a decline of 20% or more from the baseline value that each subject scored preoperatively on any neurobehavioral test. Incidence of deficits was compared between patients undergoing CABG and cardiac valve operations at each examination date by using logistic regression. Explanatory factors for type of operation, sex, age class (≤ 60 vs > 60 years), extent of aortic atherosclerosis (assessed by palpation), and number of emboli were included in the models. Differences between the patients undergoing CABG and cardiac valve operations in total emboli counts were compared by using log-transformed *t* tests. In addition to the total counts, embolus counts were recorded within 2 minutes of predefined surgical maneuvers. The large number of zero embolus values (often for over 50% of the patients undergoing CABG) made *t* tests or log-transformed *t* tests impractical for analyzing the embolus counts during defined surgical maneuvers. Large differences between the shapes of the CABG and cardiac valve operation emboli distributions invalidated the Wilcoxon rank-sum test. Thus the distributional assumption-free Kolmogorov-Smirnov test was used to test for overall distributional differences in the embolus counts during the defined surgical maneuvers. Spearman rank correlation was used to test for an association between age and total number of emboli. All statistical analyses were accomplished by using the SAS (version 8.0) program (SAS Institute, Cary, NC).

Results

The demographic characteristics of the patients undergoing either CABG or cardiac valve operations are provided in Table II. As expected, female patients formed a much smaller fraction of the CABG ($n = 35$ [18%]) than cardiac valve operation ($n = 41$ [56%]) population, both because of the lower incidence of coronary artery disease in female as opposed to male patients and as a result of our having excluded insulin-dependent diabetic subjects from the CABG study population. The 2 groups were well matched by age. The patients undergoing cardiac valve operations had a much higher incidence of transient ischemic attacks (TIAs) and atrial fibrillation and were less likely to be undergoing their first cardiac operation. The duration

Table I. Exclusion criteria

CABG—glucose study
Age < 35 y
Pregnancy or lactation
Myocardial infarction within 30 d
Valvular heart disease requiring a concomitant operation
Insulin-dependent diabetes mellitus
Inability to perform neurobehavioral testing
Does not speak English
Alzheimer, Parkinson, or Huntington disease
Illiterate
Preoperative dementia
Major depression within 5 y
Alcohol or drug abuse
Renal (creatinine > 2 md/dL) or hepatic (AST or ALT $> 150\%$ of upper limit of normal) failure
Received investigational drug within 30 d
Cardiac valve operations—nimodipine study
Age < 21 y
Receiving calcium channel blocker drugs preoperatively
Pregnancy
NYHA class IV heart failure
Transmural myocardial infarction within 30 d
Left ventricular ejection fraction $< 35\%$
Inability to perform neurobehavioral testing
Does not speak English
Alzheimer, Parkinson, or Huntington disease
Illiterate
Preoperative dementia
Major depression within 5 y
Alcohol or drug abuse
Renal (creatinine > 2 mg/dL) or hepatic (AST or ALT $> 150\%$ of upper limit of normal) failure

AST, Aspartate aminotransferase; ALT, alanine aminotransferase; NYHA, New York Heart Association.

of CPB was significantly longer in cardiac valve operations than CABG (medians, 145 vs 116 minutes; geometric means, 142 vs 116 minutes, respectively; $P < .0001$) as was the duration of aortic clamping (medians, 93 vs 52 minutes; arithmetic means, 95 vs 57 minutes, respectively; $P < .0001$).

There were differences between the groups in myocardial protection and venting techniques. Eighty-two percent of patients undergoing cardiac valve operations and 80% of patients undergoing CABG received intermittent blood cardioplegia, 1% of patients undergoing CABG (and no patients undergoing cardiac valve operations) received no cardioplegia, and the remaining patients received intermittent crystalloid cardioplegia. These differences were not statistically significant. More patients undergoing cardiac valve operations than patients undergoing CABG were given retrograde cardioplegia (64% vs 38%, $P = .0003$). A greater percentage of patients undergoing cardiac valve operations than those undergoing CABG had left ventricular venting (99% vs 88%, $P = .008$). For 99% of patients undergoing CABG and 85% of patients undergoing

Table II. Preoperative demographic and medical characteristics

Parameter	Group	Mean $\pm$ SD (range) or %	P value
No. of subjects	CABG	193	
	CVO	74	
Female sex	CABG	18%	<.0001
	CVO	56%	
Age (y)	CABG	61 $\pm$ 10 (37-84)	.1
	CVO	59 $\pm$ 12 (21-84)	
Weight (kg)	CABG	84 $\pm$ 18 (41-173)	<.0001
	CVO	72 $\pm$ 17 (45-114)	
History of TIA	CABG	6%	.0035
	CVO	16%	
History of cerebral infarction	CABG	4%	.36
	CVO	8%	
History of cerebral hemorrhage	CABG	0%	.075
	CVO	3%	
History of atrial fibrillation	CABG	5%	<.0001
	CVO	33%	
Coronary artery disease	CABG	100%	<.0001
	CVO	29%	
Peripheral vascular disease	CABG	14%	.028
	CVO	4%	
Valvular heart disease	CABG	3%	<.0001
	CVO	100%	
History of CHF	CABG	4%	<.0001
	CVO	37%	
History of MI	CABG	61%	<.0001
	CVO	14%	
Previous cardiac operation	CABG	9%	.0042
	CVO	23%	
Diabetes mellitus*	CABG	2%	.0002
	CVO	15%	
Hypertension	CABG	57%	.0010
	CVO	34%	
Hyperlipidemia	CABG	63%	<.0001
	CVO	30%	

CVO, Cardiac valve operation; MI, myocardial infarction.

P values are reported for the *t* test or exact χ^2 test, as appropriate.

*Note that insulin-dependent diabetes was an exclusion criterion for the CABG study but not the cardiac valve operations study.

Table III. Palpation of the thoracic aorta by the surgeon

	CABG patients (n = 193)	CVO patients (n = 73)	P value*
Normal (%)	85	71	
Plaques in innominate artery (%)	12	11	.0012
Minor plaques of ascending aorta (%)	1	3	
Severe plaques of ascending aorta (%)	3	15	

The 4 categories were mutually exclusive, and the worst palpable lesion was coded in every case. CVO, Cardiac valve operation.

*Exact χ^2 test.

cardiac valve operations, venting was accomplished by using a catheter placed through the right superior pulmonary vein. The remaining patients were vented through the left ventricular apex (CABG, 0.5%; cardiac valve operations, 12.5%) or through an aortic cannula

(CABG, 0.5%; cardiac valve operations, 12.5%). These differences were statistically significant ($P < .0001$). It is our practice to always vent the aorta before and during separation from CPB to remove entrained air after cardiac valve operations, regardless of the venting technique used during the surgical repair. Palpation of the aorta by the surgeon revealed that a significantly greater number of patients undergoing cardiac valve operations ($n = 11$) than patients undergoing CABG ($n = 5$) had severe atherosclerosis of the ascending aorta (Table III).

There were significantly ($P = .0001$) more emboli in the patients undergoing cardiac valve operations (median, 479; geometric mean, 412) than in the patients undergoing CABG (median, 105; geometric mean, 104; Fig 1). Inspection of the data confirmed that the total number of emboli appeared to be log-normally distributed, and therefore we report geometric means and medians rather than arithmetic means. At certain times

Fig 1. Box plots of the total numbers of emboli counted during either CABG (n = 122 patients) or cardiac valve operations (n = 34 patients). Note that the data are plotted on a logarithmic scale. Bars denote the median, and shaded boxes include the 25th to 75th percentiles. Whiskers at each end of the shaded boxes provide the 5th and 95th percentiles of the data. There were significantly ($P = .0001$) more emboli in patients undergoing cardiac valve operations (geometric mean, 432 emboli) than in patients undergoing CABG (geometric mean, 111 emboli).

Table IV. Number of emboli occurring within 2 minutes of defined surgical maneuvers

Event	Treatment	N	Percentiles	P value*
			(10th-25th, median, 75th-90th)	
Aortic cannulation	CABG	145	(0-0, 2, 5-10)	.99
	CVO	34	(0-0, 2, 6-20)	
Initiation of CPB	CABG	144	(0-0, 1, 4-13)	.2
	CVO	37	(0-0, 0, 2-5)	
Removal of LV vent	CABG	115	(0-0, 0, 2-9)	.0004
	CVO	29	(0-0, 6, 31-82)	
Cessation of CPB	CABG	141	(0-0, 0, 0-7)	<.0001
	CVO	32	(0-1, 5.5, 26.5-88)	
Removal of aortic cannula	CABG	141	(0-0, 0, 0-2)	.0002
	CVO	35	(0-0, 2, 9-22)	

The number of subjects varied at different time epochs, depending on our ability to obtain a satisfactory Doppler signal from the left carotid artery. CVO, Cardiac valve operation; LV, left ventricular.

*Kolmogorov-Smirnov test.

during operations, there were significant differences between the patients undergoing cardiac valve operations and those undergoing CABG in the number of emboli (Table IV). Specifically, although there were no differences between patients undergoing CABG and cardiac valve operations in the number of emboli recorded

during aortic cannulation, there were significantly more emboli in the patients undergoing cardiac valve operations than in the patients undergoing CABG after removal of the left ventricular vent, separation from CPB, and removal of the aortic cannula. All these latter events occurred after cardiac chambers were opened for

Table V. Baseline group means and SDs for all neurobehavioral tests

Neurobehavioral test	Treatment	Mean $\pm$ SD	P value*
Letter Cancellation time (s)	CABG	136.0 $\pm$ 37.2	.82
	CVO	135.0 $\pm$ 43.0	
Grooved Pegboard, dominant hand (s)	CABG	93.4 $\pm$ 31.3	.97
	CVO	93.3 $\pm$ 37.1	
Grooved Pegboard, nondominant hand (s)	CABG	101.0 $\pm$ 29.0	.81
	CVO	102.4 $\pm$ 45.1	
Nonverbal Memory (s)	CABG	15.9 $\pm$ 2.5	.45
	CVO	15.6 $\pm$ 3.0	
Rey Auditory Verbal Memory Test (No. correct per 105)	CABG	46 $\pm$ 13	.21
	CVO	49 $\pm$ 13	
Digit Symbol Test (s)	CABG	214.0 $\pm$ 52.0	.86
	CVO	212.6 $\pm$ 58.5	
Trail Making Form A (s)	CABG	63.5 $\pm$ 23.6	.35
	CVO	66.9 $\pm$ 27.8	
Trail Making Form B (s)	CABG	147.0 $\pm$ 68.4	.49
	CVO	153.6 $\pm$ 73.2	
Finger Tapping, dominant hand (No. of taps/10 s)	CABG	31.8 $\pm$ 8.0	.054
	CVO	29.4 $\pm$ 9.0	
Finger Tapping, nondominant hand (No. of taps/10 s)	CABG	28.8 $\pm$ 6.8	.068
	CVO	26.8 $\pm$ 7.9	
Visual Reaction Time (s)	CABG	1.6 $\pm$ 0.9	.54
	CVO	1.7 $\pm$ 1.0	

CVO, Cardiac valve operation.

t* test.Table VI.** Incidence of neurobehavioral deficits

Examination	No. of deficits* per patient	CABG†	CVO†	P value
5-7 d	0	20%	17%	.80
	1	19%	17%	
	2	19%	17%	
	≥3	43%	50%	
1 mo	0	50%	52%	.96
	1	28%	29%	
	2	13%	10%	
	≥3	9%	9%	
6 mo	0	51%	44%	.46
	1	30%	27%	
	2	12%	13%	
	≥3	8%	15%	

CVO, Cardiac valve operation.

*Deficit is defined as a decrement of 20% or more from the patient's baseline score on any neurobehavioral test.

†Total percentage may not be 100 because of rounding.

cardiac valve operations. There was no association between the total number of emboli and age ($P = .9$).

There were no significant differences between patients undergoing cardiac valve operations and those undergoing CABG in their baseline neurobehavioral scores (Table V). There was a significant effect of time on the neurobehavioral performance of both groups of patients. On most tests, the patients demonstrated a significant decline in their performance when comparing

the baseline measurement and the measurement recorded at 5 to 7 days (Fig 2). There were no significant differences between the patients undergoing cardiac valve operations and those undergoing CABG in their performance preoperatively or postoperatively on our neurobehavioral test battery (Fig 2), even after covariate adjustments. When patients were divided into those either 60 years of age or older or those less than 60 years of age (60 years was chosen because it was the mean value of our 2 groups), the older patients scored significantly worse overall on the tests of Nonverbal Memory, Symbol-Digit, Trail Making Form B, and Finger Tapping (nondominant hand). There were no differences between patients undergoing CABG or those undergoing cardiac valve operations in the incidence of neurobehavioral deficits ($\geq 20\%$ declines in performance on a neurobehavioral test) at any of the postoperative examination times (Table VI). Moreover, the distribution of deficits was strikingly similar after the 2 types of cardiac operations.

Extent of proximal aortic disease, as assessed by palpation (see Table III for categories and distribution) had no significant influence on postoperative neurobehavioral performance as assessed either by raw neurobehavioral test scores or the incidence of deficits.

Increasing numbers of carotid emboli were significantly associated ($P = .003$) with adverse postoperative performance on the Letter Cancellation test. There was

Table VII. *Results on the NIH Stroke Scale*

<i>Neurologic measure</i>	<i>Date of examination</i>	<i>Change from baseline</i>	<i>CABG (n)</i>	<i>CVO (n)</i>	<i>P value</i>
Best gaze	5-7 d	Declined	1	0	1.00
		No change	142	57	
		Improved	0	0	
	1 mo	Declined	0	2	1.00
		No change	153	58	
		Improved	0	0	
	6 mo	Declined	0	0	1.00
		No change	122	49	
		Improved	0	0	
Best visual	5-7 d	Declined	1	0	1.00
		No change	142	57	
		Improved	0	0	
	1 mo	Declined	0	2	.08
		No change	153	57	
		Improved	0	0	
	6 mo	Declined	0	1	.08
		No change	122	48	
		Improved	0	1	
Facial palsy	5-7 d	Declined	1	0	1.00
		No change	144	57	
		Improved	0	0	
	1 mo	Declined	2	1	1.00
		No change	150	58	
		Improved	2	0	
	6 mo	Declined	3	0	.51
		No change	119	48	
		Improved	1	2	
Level of Consciousness (obeys commands)	5-7 d	Declined	0	0	1.00
		No change	145	57	
		Improved	0	0	
	1 mo	Declined	0	0	1.00
		No change	153	59	
		Improved	0	0	
	6 mo	Declined	0	0	1.00
		No change	123	50	
		Improved	0	0	
Level of Consciousness (response to questions)	5-7 d	Declined	0	0	1.00
		No change	144	57	
		Improved	1	0	
	1 mo	Declined	1	0	.71
		No change	150	59	
		Improved	2	0	
	6 mo	Declined	0	0	.59
		No change	121	50	
		Improved	2	0	
Best motor response (arm)	5-7 d	Declined	2	0	.23
		No change	143	56	
		Improved	0	1	
	1 mo	Declined	0	1	.28
		No change	154	58	
		Improved	0	0	
	6 mo	Declined	0	0	.08
		No change	122	48	
		Improved	0	2	
Other arm (for vertebrobasilar stroke)	5-7 d	Declined	0	2	.09
		No change	130	54	
		Improved	1	0	
	1 mo	Declined	7	0	.10
		No change	123	59	
		Improved	0	0	
	6 mo	Declined	0	0	1.00
		No change	108	46	
		Improved	1	0	

P values are presented for exact χ^2 comparisons between patients undergoing CABG and cardiac valve operation. *CVO*, Cardiac valve operation, *NIH*, National Institutes of Health.

Fig 2. Percentage change in neurobehavioral test scores achieved by patients undergoing either cardiac valve operations (filled boxes) or CABG (open boxes). Bars denote the median, and boxes include the 25th to 75th percentiles. Whiskers at each end of the shaded boxes provide the 5th and 95th percentiles of the data. There were no significant differences at any time comparing cardiac valve operations and CABG. For each test, a decline in performance is indicated as either a percentage increase (+) or a percentage decrease (-) relative to this baseline score. *Baseline*, Baseline. * $P < .01$ compared with the baseline (visit 1) value; † $P < .01$ compared with the value on day 5 to 7 (visit 2).

no evidence for a significant difference between patients undergoing CABG and those undergoing cardiac valve operations in the association between increasing numbers of carotid emboli and worsening performance on this test ($P = .85$). There were no overall associations between increasing numbers of emboli and neurobehav-

ioral test performance, and there were no other neurobehavioral tests that demonstrated associations with emboli that differed significantly between patients undergoing cardiac valve operations and those undergoing CABG. There were no overall associations between increasing numbers of carotid emboli and the number of

Fig 2. Cont'd.

neurobehavioral deficits that a patient might demonstrate during any one of the 3 postoperative examinations. Moreover, there were no significant interactions suggesting that emboli might have differing consequences when comparing patients undergoing cardiac valve operations with patients undergoing CABG.

Results of examinations using the National Institutes of Health (NIH) Stroke Scale are provided in Table VII. There were no significant differences between patients undergoing CABG and those undergoing cardiac valve

operations detected by using the NIH Stroke Scale. Frank strokes, TIAs, and deaths are presented in Table VIII. After CABG operations, 4 of the 5 strokes appeared in the first postoperative neurologic examination in the intensive care unit. Two of these patients died subsequently of medical complications on postoperative days 20 and 161, respectively. One additional patient had a stroke after being transferred from the intensive care unit but before hospital discharge. One patient undergoing cardiac valve operations had a stroke after

Table VIII. Incidence of strokes, TIAs, and death

	CABG (n = 190)	CVO (n = 66)	95% CI for difference	P value
Strokes	2.6%	1.5%	(-7.0% to 7.7%)	.69
TIAs	0%	0%	ND	ND
Deaths	3.7%	1.5%	(-8.4% to 6.7%)	.47

CVO, Cardiac valve operation; CI, confidence interval; ND, Not done.

discharge from the hospital. There were no other significant differences between the patients undergoing CABG and those undergoing cardiac valve operations on their neurologic or neuro-ophthalmologic examinations. No patients had new TIAs. Seven deaths in the CABG group occurred a median of 43 days after operations (range, 12-161 days). The single cardiac valve operation death occurred on postoperative day 2.

Discussion

We and others have previously shown that cardiac surgical patients commonly experience neuropsychological deficits, usually defined by declines in one or more tests of a given amount (often defined as at least 20% or 1 SD from a baseline measurement) and may be more likely to do so than patients undergoing other types of operations.⁶⁻⁸ The present study indicates that not only do cardiac surgical patients have a risk of neurobehavioral deficits but the typical patient can expect an early postoperative decline in performance, irrespective of whether the typical patient's performance may reach the limiting definition for a deficit.

It is also notable that patients undergoing cardiac valve operations and those undergoing CABG demonstrated significant differences between their scores at days 5 to 7 and their scores at 1 month but did not demonstrate significant differences between their scores at 1 and 6 months. Similarly, Murkin and colleagues⁹ showed almost no difference in the incidence of cognitive dysfunction when comparing 2-month and 3-year postoperative assessments. These results suggest that for purposes of neurobehavioral assessment, clinical neuroprotection trials can be limited to a 1-month follow-up examination. In the older age group that typically undergoes CABG, limiting the duration of follow-up examinations helps to reduce the possibility that a postoperative decline in neurobehavioral performance might be due to an event occurring after discharge and essentially unrelated to the surgical procedure. Our results support the recent report by Müllges and colleagues,¹⁰ showing decline in neurobehavioral testing 3 days after CABG, with rapid improvement only a few days thereafter.

In our 2 groups of contemporaneously enrolled patients undergoing cardiac valve operations and those

undergoing CABG, there were few significant differences in their neurobehavioral performances over time. Both groups declined significantly on many test scores at 5 to 7 days. By the 1-month examination, test scores were either not significantly different from baseline or had significantly improved, reflecting a learning effect or some other factor related to completion of cardiac operations. Moreover, the distributions of postoperative neurobehavioral deficits were remarkably similar in the groups of patients undergoing cardiac valve operations and those undergoing CABG. These results are similar to those reported by Townes and colleagues¹¹ in a study comparing 65 patients undergoing CABG with 25 others undergoing intracardiac operations with CPB.

The incidence and number of deficits depends on the brain area affected, and therefore the number of deficits a patient demonstrates is not necessarily associated with the volume or severity of brain injury, just the location. We recognize that the likelihood of our detecting a decline in postoperative neurobehavioral performance likely increases as the battery of neurobehavioral tests increases. However, both patients undergoing CABG and those undergoing cardiac valve operations were evaluated with the same battery of neurobehavioral tests. We also observed no significant differences between patients undergoing cardiac valve operations and those undergoing CABG in strokes, TIAs, or deaths. Confidence intervals are inconsistent with a trend favoring either class of patients but must be interpreted with caution given the minimal number of these adverse outcomes observed in our patients.

There were significantly more emboli in the patients undergoing cardiac valve operations than in the patients undergoing CABG. Notably, there were significantly more emboli in the time between removal of the left ventricular vent and termination of CPB in the patients undergoing cardiac valve operations than in the patients undergoing CABG. This difference is consistent with the common observation of intracardiac air bubbles on transesophageal echocardiography (TEE) near the time of termination of CPB in patients undergoing cardiac valve operations, although not in patients undergoing CABG. Unfortunately, we are not able to relate our carotid Doppler findings with TEE observations. During the course of these 2 studies, TEE examination gradually became a routine part of the care of first the patients undergoing cardiac valve operations and then later the patients undergoing CABG but was inconsistently performed during the course of these 2 clinical trials.

There were other important differences between patients undergoing cardiac valve operations and those undergoing CABG. The factors previously reported to

have the greatest effect on the incidence of post-CPB neurologic dysfunction are increasing age^{12,13} and increasing duration of aortic crossclamping and preexisting congestive heart failure (CHF).¹⁴ Although the ages of the 2 groups in our study were similar, the group of patients undergoing cardiac valve operations had both a higher incidence of preexisting CHF and longer aortic crossclamping times. A greater fraction of patients undergoing cardiac valve operations had severe atherosclerosis of the ascending aorta by palpation. We were unable to demonstrate an association between worsening aortic atherosclerosis and adverse neurobehavioral outcomes. We recognize that palpation will not detect many patients with severe aortic atherosclerosis that might easily be detected by using epiaortic scanning techniques.^{15,16} Despite these differences, the groups of patients undergoing cardiac valve operations and CABG had similar neurologic outcomes. This might suggest that cognitive dysfunction has a differing association with atherosclerosis and emboli in the 2 groups. Alternatively, these results could mean that both groups have a similar exposure to some form of threshold injury (eg, some minimal duration of CPB or some minimal number of cerebral emboli). Finally, these results are also consistent with there being a weak or absent relationship between common carotid embolic signals and long-term outcome. Our data also found limited differences between patients undergoing CABG and those undergoing cardiac valve operations in the effect that increasing age had on their neurobehavioral scores.

The similar outcomes despite greater numbers of emboli in the patients undergoing cardiac valve operations is also consistent with the idea that some of the additional emboli in the patients undergoing cardiac valve operations consist of air rather than the atheromatous material that would be expected to be more prevalent in the patients undergoing CABG. Alternatively, patients undergoing CABG have fewer emboli, but these emboli are more likely to be particulate. The particulate emboli may cause more brain injury than gaseous emboli, thus equalizing the neurobehavioral results between the 2 groups. We recognize that our patients undergoing cardiac valve operations appeared to have a greater incidence of severe aortic atherosclerosis than did our patients undergoing CABG. Although we were unable to demonstrate an association in this data set, we recognize that severe aortic disease is a risk factor for adverse neurobehavioral outcomes.¹⁶ In previous studies of a much larger data set, we have observed associations between emboli and short-term neurobehavioral outcome.^{16,17} We found only limited association between neurobehavioral outcomes and the

number of emboli we counted in the common carotid artery. However, our observations suggest that emboli counts may have no prognostic significance for longer term outcomes in patients undergoing either CABG or cardiac valve operations.

For many years, it was believed that patients undergoing cardiac valve operations were at higher risk for neurologic and neurobehavioral deficits when compared with patients undergoing CABG. During the 1980s, Townes and colleagues¹¹ reported that patients undergoing either CABG or open-chamber procedures with CPB had similar neurobehavioral outcomes. More recently, Kuroda and colleagues¹⁸ reported that patients undergoing CABG had a greater incidence of postoperative deficits, although the patients undergoing CABG were on average 8 years older. We have now shown in 2 groups of similar ages an equal risk of postoperative neurobehavioral dysfunction. The pathophysiologic cause of this dysfunction is unclear. Microembolic load has been shown to be important in patients undergoing CABG as a cause of post-CPB neurologic dysfunction.^{17,19} Measures that minimize the number of microemboli, especially particulate microemboli, are associated with improved neurobehavioral outcome.¹⁶ The role of gaseous microemboli, as well as the effect of preexisting CHF and the duration of aortic crossclamping in patients undergoing cardiac valve operations, remains unclear.

Our study has clear limitations, and our results should be interpreted cautiously. Our patients were enrolled in 2 separate clinical trials with slightly different exclusion criteria. Our exclusion criteria may have eliminated risk factors that, if included, might have resulted in significant outcome differences between the 2 groups. Insulin-dependent diabetic subjects were excluded from the CABG study, disproportionately reducing the number of female subjects who were enrolled. Patients with severe heart failure were excluded from the cardiac valve operations study. All patients had to consent to undergo repeated neurobehavioral assessments, and it is unclear whether the outcomes of these consenting patients might differ from those who refused to participate. All patients underwent an opioid-based general anesthetic. This was typical practice at the time. Now anesthetics that support early extubation are more common, and it is unclear whether choice of general anesthetic might influence neurobehavioral outcomes. We have shown, subsequent to this study, that return of shed blood is associated with lipid microembolization to the brain.²⁰ Unfortunately, we did not measure shed blood return in these patients and thus could not determine whether this might differ between patients undergoing cardiac valve operations

and those undergoing CABG. We counted emboli in the left common carotid artery, and it is clear that some of these emboli will not be directed to the brain. The fraction of common carotid artery emboli that enter the internal carotid artery may differ between patients undergoing cardiac valve operations and those undergoing CABG. We recognize that the number of emboli is almost certainly less important than the brain location where the emboli lodge and whether the emboli are particulate or gaseous. Finally, the total number of patients we studied is relatively small compared with the several hundred thousand adults who undergo CPB each year in North America.

REFERENCES

1. Wagenknecht LE, Furberg CD, Hammon JW, Legault C, Troost BT. Surgical bleeding: unexpected effect of a calcium antagonist. *BMJ* 1995;310:776-7.
2. Legault C, Furberg CD, Wagenknecht LE, et al. Nimodipine neuroprotection in cardiac valve replacement: report of an early terminated trial. *Stroke* 1996;27:593-8.
3. Rogers A, Stump D, Coker L, Kon N, Brooker R. Does insulin treatment improve neurobehavioral outcome following coronary artery bypass grafting? [abstract]. *Anesthesiology* 1997;87:A126.
4. Stump DA. Selection and clinical significance of neuropsychologic tests. *Ann Thorac Surg* 1995;59:1340-4.
5. Stump DA, Stein CS, Tegeler CH, et al. Validity and reliability of a device for detecting carotid emboli. *J Neuroimaging* 1991;1:18-22.
6. Murkin JM, Newman SP, Stump DA, Blumenthal JA. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. *Ann Thorac Surg* 1995;59:1289-95.
7. Murkin JM, Stump DA, Blumenthal JA, McKhann G. Defining dysfunction: group means versus incidence analysis—a statement of consensus. *Ann Thorac Surg* 1997;64:904-5.
8. Shaw PJ, Bates D, Cartledge NE, et al. Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. *Stroke* 1987;18:700-7.
9. Murkin JM, Baird DL, Martzke JS, Adams SJ, Lok P. Long-term neurologic and neuropsychological outcome 3 years after coronary artery bypass surgery. *Anesth Analg* 1996;82:S328.
10. Müllges W, Berg D, Schmidtke A, Weinacker B, Toyka KV. Early natural course of transient encephalopathy after coronary artery bypass grafting. *Crit Care Med* 2000;28:1808-11.
11. Townes BD, Bashein G, Hornbein TF, et al. Neurobehavioral outcomes in cardiac operations: a prospective controlled study. *J Thorac Cardiovasc Surg* 1989;98:774-82.
12. Tuman KJ, McCarthy RJ, Najafi H, Ivankovich AD. Differential effects of advanced age on neurologic and cardiac risks of coronary artery operations. *J Thorac Cardiovasc Surg* 1992;104:1510-7.
13. Gardner TJ, Horneffer PJ, Manolio TA, et al. Stroke following coronary artery bypass grafting: a ten year study. *Ann Thorac Surg* 1985;40:574-81.
14. Guyton RA, Mellitt RJ, Weintraub WS. A critical assessment of neurological risk during warm heart surgery. *J Cardiol Surg* 1995;10(Suppl 4):488-92.
15. Sylivris S, Calafiore P, Matalanis G, et al. The intraoperative assessment of ascending aortic atheroma: epiaortic imaging is superior to both transesophageal echocardiography and direct palpation. *J Cardiothorac Vasc Anesth* 1997;11:704-7.
16. Hammon JW, Stump DA, Kon ND, et al. Risk factors and solutions for the development of neurobehavioral changes after coronary artery bypass grafting. *Ann Thorac Surg* 1997;63:1613-8.
17. Stump DA, Brown WR, Moody DM, et al. Microemboli and neurologic dysfunction after cardiovascular surgery. *Semin Cardiothorac Vasc Anesth* 1999;3:47-55.
18. Kuroda Y, Uchimoto R, Kaieda R, et al. Central nervous system complications after cardiac surgery: a comparison between coronary artery bypass grafting and valve surgery. *Anesth Analg* 1993;76:222-7.
19. Moody DM, Brown WR, Challa VR, et al. Brain microemboli associated with cardiopulmonary bypass: a histologic and magnetic resonance imaging study. *Ann Thorac Surg* 1995;59:1304-7.
20. Brooker RF, Brown WR, Moody DM, et al. Cardiectomy suction: a major source of brain lipid emboli during cardiopulmonary bypass. *Ann Thorac Surg* 1998;65:1651-5.

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