CEREBRAL INJURY DURING CARDIOPULMONARY BYPASS: EMBOLI IMPAIR MEMORY

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Objectives: Cognitive deficits occur in up to 80% of patients after cardiac surgery. We investigated the influence of cerebral perfusion and embolization during cardiopulmonary bypass on cognitive function and recovery.

Methods: Cerebrovascular reactivity was measured in 70 patients before coronary operations in which nonpulsatile bypass was used. Throughout the operations, middle cerebral artery flow velocity and embolization were recorded by transcranial Doppler and regional oxygen saturation was recorded by near-infrared spectroscopy. Cognitive function was measured by a computerized battery of tests before the operation and 1 week, 2 months, and 6 months after surgery. Elderly patients undergoing urologic surgery served as controls.

Results: Cerebrovascular reactivity was impaired preoperatively in 49 patients. Median (interquartile range) regional cerebral oxygen saturation fell during bypass by 10% (6%-15%), indicating increased oxygen extraction, whereas mean middle cerebral flow velocity increased significantly by a median of 6 cm/s (both $P < .0001$, Wilcoxon), suggesting increased arterial tone. More than 200 emboli were detected in 40 patients, mainly on aortic clamping and release, when bypass was initiated, and during defibrillation. Cognitive function deteriorated more in patients having cardiopulmonary bypass than in control patients having urologic operations but recovered in most tests by 2 months. Measures of cerebral perfusion (poor cerebrovascular reactivity, low arterial pressures, and flow velocity in the middle cerebral artery) predicted poor attention at 1 week ($r = 0.3$, $P < .01$, Spearman). Emboli were associated with memory loss ($r = 0.3$, $P < .02$, Spearman).

Conclusions: Cognitive deficits were common after cardiopulmonary bypass. Occult cerebrovascular disease was more severe than expected and predisposed to attention difficulties, whereas emboli caused memory deficits. We believe this to be the first report of differing cognitive effects from emboli and hypoperfusion. (J Thorac Cardiovasc Surg 2001;121:1150-60)

Many patients have difficulty concentrating and returning to work after coronary artery bypass grafting (CABG), with cognitive deficits reported in up to 80% of all such patients.[1,2] Although most deficits resolve within 6 weeks to 6 months, up to 35% persist as a source of disability for at least 12 months, with important social and economic implications.[2,3]

The debate over etiology has raged for years, with intraoperative emboli arising from the cardiopulmonary bypass circuit and cerebral hypoperfusion both being implicated.[4,5] The influence of cerebral vascular disease is suggested to be important.[6,7] Emboli have been demonstrated in the retina of survivors and in the brain at postmortem examination.[8,9] Larger numbers of emboli detected by ultrasound of the carotid arteries or transcranial Doppler (TCD) studies are associated with neurologic and cognitive complications and longer inpatient stay.[10-12]

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The synchronous measurement of cerebral flow and emboli to the brain in patients undergoing cardiac surgery has not been attempted before, and the role of impaired cerebrovascular reserve is unclear. Our aim was to investigate the influence of preoperative cerebrovascular reserve and intraoperative cerebral perfusion and embolization on cognitive function after CABG.

We used TCD to measure blood flow velocity bilaterally in the middle cerebral arteries (MCAs) because it is the only continuous means of measuring changes in cerebral hemodynamics noninvasively and has become an essential part of neurologic monitoring.[13] A close relationship between changes in cerebral blood flow and changes in blood flow velocity as measured by TCD has been demonstrated in patients with symptoms suggesting cerebrovascular disease and in patients during cardiac surgery.[14-16] TCD can also be used to monitor embolization to the cerebral circulation using software that distinguishes between Doppler signal, noise, probe artifact, and embolic or high-intensity transient signals. "Embolic signals" must fulfil the following criteria[17]:

- The strength of the embolic signal is higher than the Doppler signal and background noise
- Embolic signals appear in only one direction because the material is traveling in the bloodstream
- The time duration of an embolus is short compared with the normal Doppler signal

We used near-infrared oxygen spectroscopy to measure regional oxygen saturation noninvasively because systemic saturation is a poor indicator of cerebral saturation.[18] The use of near-infrared oxygen spectroscopy during cardiopulmonary bypass has been criticized because of factors that may differentially influence the extracranial circulation. For this reason we used probe separation distances of 30 and 40 mm from the light source to enable subtraction of the extracranial component from that reflecting saturation predominantly in the brain. When the probe is sited over MCA territory, regional changes in oxygen extraction correlate well with TCD of MCA blood flow velocity as well as jugular venous saturation but are not subject to interindividual differences in cerebral venous anatomy.[19,20] The other advantage of near-infrared oxygen spectroscopy is that it does not require a pulse wave and therefore is the only means of monitoring during nonpulsatile perfusion.

In this study, we wanted to compare the change in MCA blood flow velocity and regional cerebral oxygen saturation (CsO_2) with the change in cognitive function and also to investigate the influence of embolization on cognitive change.

Patients and methods

Patients undergoing CABG. Seventy patients admitted for CABG were sequentially recruited after giving fully informed consent in writing. The project was approved by the hospital's ethical committee. Patients were excluded if unfit to travel from one hospital site to another for preoperative assessment or if unable to perform the cognitive test battery, for example, visual problems or non-English-speaking.

Urology control subjects. Nineteen patients admitted for urologic procedures formed a control group of elderly patients undergoing general anesthesia without cardiopulmonary bypass. Exclusion criteria were a diagnosis of cancer, previous stroke or neurologic disease, or an inability to perform the cognitive test battery.

Cerebrovascular disease. Duplex Doppler imaging of the carotid arteries was carried out by an experienced vascular technologist using spectral waveform analysis to measure the severity of common or internal carotid stenosis. TCD insonation of right and left MCAs was used to determine cerebrovascular reactivity to inhaled carbon dioxide preoperatively using a standard technique that measures the change in mean MCA blood flow velocity before and after a standard period of carbon dioxide inhalation for each side.[21] A normal cerebrovascular reactivity was more than 0.86.

Patient-reported outcome. Subjective outcome was assessed with the use of the Short Form 36 (SF-36) produced and validated by the Medical Outcomes Trust.[22,23] This was completed by each patient before the operation and 2 and 6 months after the operation.

Neurologic examination. Neurologic examination according to the National Institutes of Health Stroke Scale (NIHSS) was also performed before the operation and 1 week and 2 and 6 months postoperatively.[24]

Anesthesia. Drugs used and their doses per kilogram of body weight were standardized for premedication, induction, maintenance, during and after bypass, and during intensive care. Alpha-stat management of pH was used in all patients. Heart rate, mean arterial blood pressure (MAP), nasopharyngeal temperature, and end-tidal carbon dioxide were recorded every 5 minutes during the entire procedure. Hematocrit values and arterial blood gases were analyzed every 30 minutes during the operations.

Cardiopulmonary bypass. CABG was performed with the use of 32°C hypothermia, with full-flow nonpulsatile bypass ($2.4 L \cdot min^{-1} \cdot m^{-2}$ multiplied by the surface area of the patient) and a standardized circuit incorporating a membrane oxygenator and 40-µm arterial filter. Aortic root palpation was not performed and cannulas were inserted in standard locations.

Cerebral perfusion

TCD. MCA blood flow velocity was recorded bilaterally with TCD (Neuroguard CDS; Nicolet Biomedical Inc, Madison, Wis) at the following settings: gain of 8 dB, a range of 10 dB, and high-pass filter 75 kHz. Transducers were immobilized throughout the operations with a head ring.

CsO_2. Regional CsO_2 was measured with reflected near-infrared light spectroscopy (Somanetics Corporation, Troy,

Mich).[19] So that extracranial contribution could be eliminated, the oximeter comprised two detectors separated from the near-infrared emitter by 30 and 40 mm. Light entering the nearer receiver was subtracted from that entering the farther receiver to give a saturation predominantly reflecting that in the brain. Because cerebral blood is 75% to 80% venous, CsO_2 is a measure of oxygen saturation. The sensors were positioned over the parietal scalp after patches of hair had been shaved to improve correspondence between flow and saturation in the MCA territory.[19,20]

Measures of cerebral perfusion were recorded manually for each side at 5-minute intervals during the operation for each patient. Extra recordings were taken for each operative event (see Table II) if the event did not fall at a recording time point.

Cerebral emboli. High-intensity transient signals visible in the Doppler spectrum and audible as chirps or whistles were recorded manually by TCD in each MCA as they occurred, with particular attention being paid to operative event. Embolic signals fulfilled standard criteria.[17]

Cognitive function testing. As much as possible, we based the measurement of cognitive function on the criteria set down in The Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery.[25] A standardized, comprehensive, and computerized battery of tests produced and validated by Cognitive Drug Research Ltd (Reading, United Kingdom) was used.[26,27] Patients were examined in a controlled environment free from distractions and were supervised by a trained assessor. They were asked to respond to visual stimuli on a screen by pressing either a "yes" or a "no" button. To minimize the practice effect, patients were allowed to familiarize themselves with the equipment in a practice test. The following cognitive function tests were performed in all patients and control subjects:

- Simple reaction time—Alertness, power of concentration, and ability to respond rapidly. Subject must respond as fast as possible to a single presented stimulus ("yes") by pressing a single button.
- Choice reaction time—As above, but with stimulus discrimination and response organization. That is, "yes" and "no" are presented at random, and the subject must press "yes" or "no" as appropriate as fast as possible.
- Number vigilance—Intensive vigilance, sustained concentration, and ability to ignore distractions. A single number is displayed on the screen while a second series of numbers rapidly changes in an adjacent column. Each time the numbers match, the "yes" response button must be pressed as fast as possible.
- Memory recall—Ability to process short-term memory and working memory. A series of five numbers is committed to memory before a series of rapidly changing numbers is presented on the screen. The subject must distinguish those numbers remembered from the distractors as fast as possible.
- Word recognition—Ability to discriminate novel from previously presented words and long-term verbal memory capacity. The subject must press "yes" or "no" as appropriate to distinguish those words presented at the beginning of the test session from distractors.
- Picture recognition—Ability to discriminate novel from previously presented pictorial information. As above, except that pictures are used.

Sum variables were calculated as follows:

1. Overall memory reaction time = Sum of word, picture, and memory scanning reaction times and therefore a measure of speed of memory.
2. Overall attention reaction time = Sum of simple, choice, and number vigilance reaction times, and therefore a measure of attention test performance speed.
3. Overall reaction time = Sum of all reaction time tests and therefore equivalent to 1 + 2 above.
4. Overall accuracy = Sum of word recognition accuracy, picture recognition accuracy, and accuracy of memory scanning.

Parallel forms of words and pictures were used so that new stimuli were presented at each sitting. The results were analyzed in terms of both reaction time and accuracy except for simple reaction time, which has no accuracy component. An improvement in a reaction time variable would be manifest as a shorter time (a decrease), whereas an improvement in an accuracy variable would be manifest as an increase in sensitivity. Data were recorded directly onto a floppy disk and then manipulated by computerized statistics software (SPSS for Windows; SPSS, Inc, Chicago, Ill). The majority of the data were not normally distributed. Therefore, nonparametric analysis was used: Mann-Whitney *U* test, Wilcoxon signed ranks, and Spearman correlation. By analyzing the change in cognitive function over time, we standardized for the influence of intelligence and education. There is no accepted standard for the analysis of cognitive function variables. We avoided using an absolute change as a definition of significant decline in cognitive function for the following reasons:

1. We wished to avoid missing changes in individuals on the basis of the larger differences that exist between individuals.
2. Reaction time and accuracy are closely reproducible in individuals, so that we were able to measure small changes.
3. Cognitive function data are not normally distributed, which makes it difficult to calculate a "normal" range.

Cognitive function was assessed preoperatively and then postoperatively at 1, 8, and 24 weeks.

Results

Controls. Nineteen patients with a mean age of 74 years (range 54-86 years), including 17 (90%) men, underwent urologic procedures under general anesthesia with a mean duration of 40 minutes (range 15-120 minutes). The proportion of control patients with a history of symptoms of cerebrovascular disease was similar to that in the CABG group (15.8%), and 89% were right-handed.

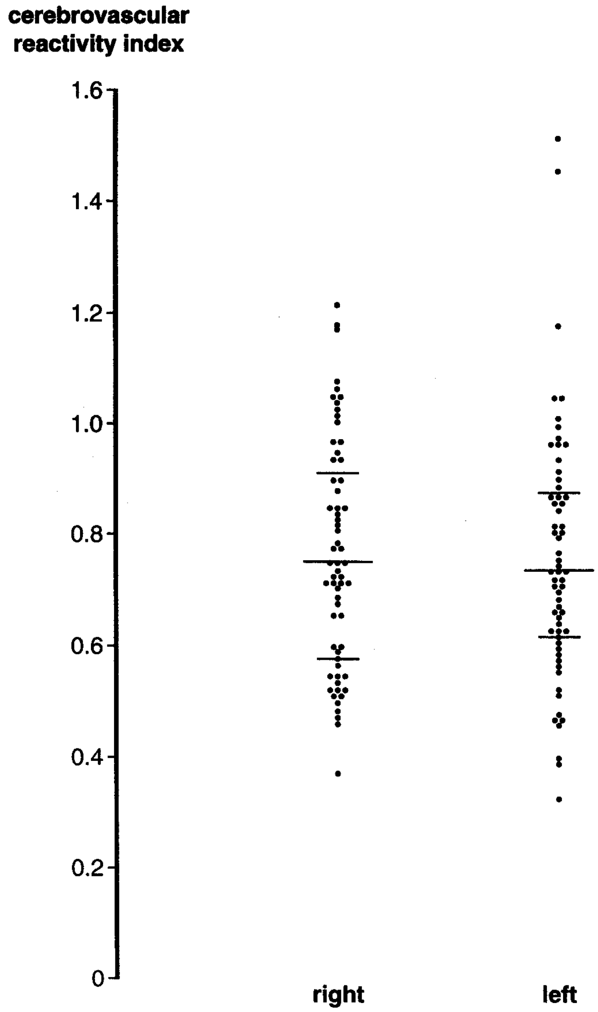

Fig 1. Preoperative cerebrovascular reactivity, for both cerebral hemispheres, for all patients undergoing CABG. Each *point* represents the cerebrovascular reactivity for an individual. The plot demonstrates that over 80% of patients undergoing CABG have impaired cerebrovascular reserve (<0.86). *Lines* depict median and IQR.

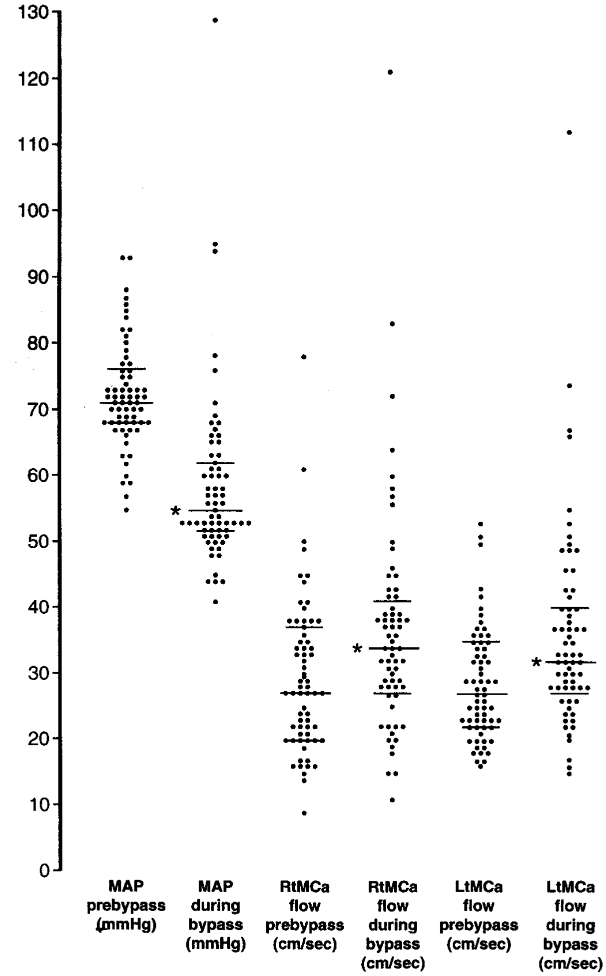

Fig 2. MAP and MCA flow velocity are plotted for all CABG patients before and during bypass. Each *point* represents an individual. Despite a significant fall in MAP, MCA flow velocity increased during bypass, suggesting increased arterial tone (*$P < .0001$, Wilcoxon). *Lines* depict median and IQR. *Rt,* right; *Lt,* left.

Patients. Seventy patients were studied, but 5 were excluded from analysis because monitoring equipment was not available or could not be applied at the time of the operation. One patient was excluded from subsequent cognitive function analysis because he underwent combined carotid endarterectomy and CABG for symptomatic internal carotid artery stenosis (>70%). The mean age of the study patients was 60 years (range 43-77 years), and 53 (81.5%) were men. The median left ventricular ejection fraction was 60% (interquartile range [IQR] 50%-69.5%), and 88% were right-handed.

Nine patients had symptoms of cerebrovascular disease (transient ischemic attack, stroke, amaurosis fugax) and 10 had more than 70% stenosis or occlusion of one or both internal carotid arteries. The only patient with symptoms and more than 70% carotid stenosis was the one offered simultaneous carotid endarterectomy and CABG.

Cerebrovascular reactivity to inhaled carbon dioxide could not be measured in 3 patients who were unable to tolerate the nose clip and mouthpiece. Only 30% of patients had bilateral normal cerebrovascular reactivity (Fig 1), indicating a high incidence of occult cerebrovascular disease.

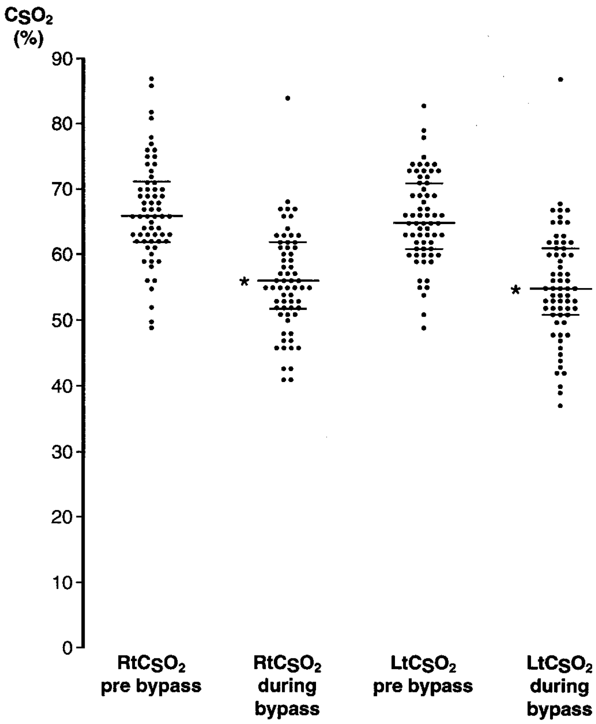

Fig 3. Regional CsO_2 is plotted for all patients undergoing CABG. Each *point* represents an individual. CsO_2 fell significantly during cooling and bypass, suggesting increased oxygen extraction (**P* < .0001, Wilcoxon). *Lines* depict median and IQR. *Rt,* right; *Lt,* left.

Cardiopulmonary bypass. Nonpulsatile cardiopulmonary bypass lasted a median of 73 minutes (58-93 minutes, IQR) and aortic crossclamping a median of 43 minutes (34-56 minutes, IQR). The difference between the ideal bypass pump flow (as calculated from a height-weight nomogram) and the actual pump flow for each patient (calculated by means of an area-under-the-curve method) during bypass was minimal at a mean (SD) of 0.05 L/min (0.37 L/min). The median hematocrit value during bypass was maintained within the normal physiologic range (21 mg/dL, IQR 19-24 mg/dL), and arterial blood gas measurements were within normal limits throughout surgery.

Immediate postoperative outcome. Median (IQR) duration of ventilation was 9 hours (5-17 hours), duration of intensive treatment unit stay 22 hours (19-25 hours), and inpatient stay 9 days (8-10 days). Two patients died of multiorgan failure, 1 had a frontal stroke, 2 had transient neurologic deficits, and the patient who had combined carotid and CABG surgery had diffuse embolic brain injury on declamping after carotid endarterectomy.

Cerebral perfusion

MCA blood flow. Mean values for MAP, MCA blood flow velocity, and CsO_2 bilaterally were calculated before and during bypass for each patient by means of an area-under-the-curve method (Table I, Figs 2 and 3).

Patients differed widely in the stability of their MAP and MCA blood flow velocity. In general, MAP tended to fluctuate before bypass but stabilized once bypass was established. MAP fell significantly at the start of bypass by a median of 16 mm Hg ($P < .0001$, Wilcoxon, Fig 2) and then tended to rise as a consequence of progressive systemic vasoconstriction during nonpulsatile perfusion. Peak MCA blood flow velocity fell to mean flow levels as nonpulsatile perfusion was established. Despite the fall in MAP, however, mean MCA flow velocity rose significantly by a median of 6 cm/s on bypass compared with prebypass levels ($P < .0001$, Wilcoxon, Fig 2). Like MAP, mean MCA blood flow velocity increased with temperature as the patient was rewarmed.

In 49 (75%) patients, blood flow velocities to each cerebral hemisphere were within 5 cm/s of each other during bypass.

Asymmetry of flow in the other 16 patients was not related to significant internal carotid artery stenosis.

CsO_2. During bypass, regional CsO_2 fell significantly by a median (IQR) of 10% to 11% (6%-15%), depending on hemisphere, suggesting an increase in oxygen extraction despite cooling ($P < .0001$, Wilcoxon, Fig 3). It also tended to recover with rewarming. The falls in CsO_2 were large and at the threshold for shunting after crossclamping of the internal carotid artery during carotid endarterectomy.[18]

Cerebral emboli. More than half (57%) the patients had more than 200 emboli entering the cerebral circulation during surgery as detected by TCD. Most occurred when bypass was initiated and when the heart was defibrillated at the end of bypass, although readjustment of clamps and aortic cannulation also caused large numbers (Table II). Six patients were predisposed to thrombosis on preoperative serum sampling: two heterozygous for prothrombin gene variant alone, two heterozygous for factor V Leiden alone, one heterozygous for factor V Leiden with low protein C and S, and one with only a low protein C. These patients had more emboli than those with no increased tendency to thrombosis (median of 225 compared with median of 136), although the difference was not statistically significant. The patient who had multiple emboli during combined CABG/carotid surgery had factor V Leiden and deficiencies in both protein C and S.

NIHSS scores. The left-handed patient who had a left frontal stroke had no focal signs but an NIHSS of 3. The patient having combined carotid/coronary

Table I. *Cerebral perfusion indices*

Parameter	*Before bypass* Median	*Before bypass* IQR	*During bypass* Median	*During bypass* IQR	*Statistic*
MAP (mm Hg)	71	68-76	55	52-62	$P < .0001$
Right MCA blood flow velocity (cm/s)	27	20-37	37	28-42	$P < .0001$
Left MCA blood flow velocity (cm/s)	27	22-35	36	28-41	$P < .0001$
Right CsO_2 (%)	66	62-71	56	52-62	$P < .0001$
Left CsO_2 (%)	65	61-71	55	51-61	$P < .0001$

IQR, Interquartile range; *MAP,* mean arterial pressure; *MCA,* middle cerebral artery; CsO_2, cerebral oxygen saturation.

Table II. *The number of emboli produced by operative event for all patients undergoing CABG*

Operative event	*Patients undergoing event*	*Patients who had emboli* No.	*Patients who had emboli* %	*No. of emboli* Median	*No. of emboli* IQR
Aortic purse-string sutures	64	17	27	1	0-6
Aortic cannulation	64	57	89	7	4-19
Venous cannulation	64	10	16	0	0-2
Start of bypass	64	58	90	10	5-22
Cardioplegia cannulation	64	26	41	2	1-5
Crossclamp on	64	31	49	1	0-4
Crossclamp off	64	45	70	3	0-17
Side clamp on	64	28	44	2	0-9
Side clamp off	64	42	66	4	3-16
Bypass discontinued	64	42	66	1	0-5
Venous cannula out	64	2	3	1	0-6.5
Aortic cannula out	64	2	3	2	0-5
Clamp reapplied	5	4	80	8	3-13.5
Heart manipulation	49	45	92	5	2-14
Defibrillation	28	27	96	17	7-36
Unexplained	45	42	93	13	3-27

CABG, Coronary artery bypass grafting; *IQR,* interquartile range.

surgery had an NIHSS of 6 on the 20th postoperative day when he could be assessed neurologically as sedation was discontinued. NIHSS was normal in both these patients by 6 months.

Patient-reported outcome. SF-36 scores for all measures of vitality, physical health, and emotional role were low before the operation (Table III). All patient-reported outcome scores were significantly improved 2 months after the operation. By 6 months most scores had improved from the 2-month assessment except the mental health and general health scores, which showed little change. When compared with preoperative responses, the improvement at 6 months was statistically significant for all measures.

There was no relationship between changes in SF-36 and cerebral perfusion, embolic load, or cognitive function.

Cognitive function

Control subjects. One week after the operation, the urology control subjects were significantly faster at all tests, although accuracy was unchanged. There was little change in most cognitive tests at 2 months compared with preoperative results, although accuracy of picture recognition was significantly worse ($P = .02$) and overall memory and reaction times were significantly better ($P = .02$ and .008, Table IV).

CABG group—preoperative results. Patients in the CABG group were a little faster and more accurate than control subjects preoperatively, with significant differences in accuracy of memory, speed of picture recognition, and overall attention, memory reaction time, and accuracy (Table V). The explanation is probably that urologic procedures may be offered to older and less healthy patients who would not be considered fit for major cardiac surgery.

CABG group—one week postoperatively. The patient who had a frontal stroke was only able to perform part of the cognitive test battery because he found it difficult to concentrate; those tests he could complete were performed with slow reaction times and poor accuracy.

Table III. *SF-36 health questionnaire data*

	Preoperative		*Two months*			*Six months*		
Scale	*Median*	*IQR*	*Median*	*IQR*	P *value*	*Median*	*IQR*	P *value*
Physical functioning	35	20-50	65	50-80	<.0001	68	50-85	<.0001
Role-physical	0	0-0	0	0-50	.05	25	0-100	<.0001
Bodily pain	32	27-52	42	32-62	.004	52	41-74	<.0001
General health	40	28-57	65	47-82	<.0001	62	39-82	<.0001
Vitality	30	20-49	45	35-55	<.0001	55	41-69	<.0001
Social functioning	50	25-72	63	50-88	<.0001	75	50-100	<.0001
Role-emotional	0	0-67	33	0-100	.026	100	0-100	.002
Mental health	64	52-76	68	52-80	.021	68	56-84	.003

Median and interquartile range *(IQR)* statistics by Wilcoxon signed ranks test. Possible score range for each scale: 0-100, where 100 is better than 0. *SF-36,* Short Form 36.

Table IV. *Cognitive function in urology control patients*

	Initial		*One week*		*Two months*	
Cognitive test	*Median*	*IQR*	*Median*	*IQR*	*Median*	*IQR*
Simple RT	293	265-341	292	278-340	303	263-352
Choice A	93.33	90-100	96.67	90-100	96.67	91-100
Choice RT	474	446-542	475	439-535	478	436-540
Number vigilance A	95.56	90-100	95.56	90-100	96.67	91-100
Number vigilance RT	447	432-474	443	415-463	443	411-491
Vigilance false alarms	2	0-4	1	1-2	1	0-3
Memory A	0.83	0.73-0.94	0.88	0.80-0.94	0.87	0.76-0.94
Memory RT	1150	863-1361	1122	849-1292	982	830-1460
Word recognition A	0.71	0.54-0.80	0.68	0.50-0.79	0.63	0.48-0.74
Word recognition RT	1112	899-1325	982	878-1206*	980	831-1161
Picture recognition A	0.83	0.75-0.91	0.80	0.71-0.91	0.80	0.63-0.91*
Picture recognition RT	1060	918-1352	1020	845-1260*	998	822-1250
Overall Attention RT	1282	1201-1415	1228	1163-1325*	1256	1134-1301
Overall Memory RT	3265	2884-4499	3117	2580-3741†	3032	2569-3823*
Overall RT	4697	4126-6026	4454	3825-4975†	4235	3785-5179*
Overall A	2.30	2.09-2.56	2.3	2.11-2.59	2.39	1.92-2.47

One-week and 2-month measurements compared with initial cognitive function. Median and interquartile range *(IQR)* statistics, Wilcoxon signed ranks test. *RT,* Reaction time; *A,* accuracy.
*$P < .05$
†$P < .001$.

For the CABG group as a whole, the patients' performance deteriorated significantly in most tests of cognitive function 1 week postoperatively; reaction times were slower and accuracy was reduced (Table V). The exceptions were memory tests, accuracy of choice reaction time, and word recognition reaction time. These deteriorations in memory may not be statistically significant, but the results are poor when compared with those of the urology control patients, who showed a significant improvement in memory at 1 week as a consequence of learning.

CABG group—two months postoperatively. When questioned directly, 18 patients reported having difficulties with memory, concentration, or attention. However, on formal testing there was a significant improvement in 11 cognitive variables compared with preoperative values (Table V).

CABG group—six months postoperatively. One patient died of intracranial hemorrhage before the 6-month assessment. On direct questioning, 17 patients were still having difficulty with memory, attention, and concentration. On cognitive testing, however, there was still a general trend toward improvement (Table V). Patients were significantly better than preoperatively at 7 cognitive tests but were still worse than preoperatively in the following tests: choice reaction time, accuracy of word, speed of picture recognition, and overall accuracy.

Table V. *Cognitive function in patients undergoing CABG*

	Initial		*One week*		*Two months*		*Six months*	
Cognitive test	*Median*	*IQR*	*Median*	*IQR*	*Median*	*IQR*	*Median*	*IQR*
Simple RT	282	261-309	325	291-376‡	286	258-332	288	269-317
Choice A	93.33	93.33-96.67	93.33	90-98.34	96.67	93.33-100‡	96.67	93.33-100†
Choice RT	466	441-515	503	452-574‡	456	432-499*	470	421-504*
Number vigilance A	97.78	88.89-100	95.56	84.44-98.89*	97.78	95.59-100‡	100	96.11-100†
Number vigilance RT	424	407-466	444	418-503‡	419	390-449	423	397-461
Vigilance false alarms	2	1-3	1	0-2	1	0-2‡	1	0-2‡
Memory A	0.94	0.85-1.00	0.94	0.79-0.94	0.94	0.87-1.00	0.94	0.83-1.00
Memory RT	955	798-1220	954	824-1148	855	771-989‡	891	771-1063‡
Word recognition A	0.75	0.65-0.80	0.65	0.54-0.75*	0.73	0.67-0.80	0.72	0.66-0.80†
Word recognition RT	1012	878-1173	1021	875-1219	883	797-1001‡	870	795-1015
Picture recognition A	0.90	0.80-0.95	0.78	0.69-0.90‡	0.85	0.77-0.95	0.83	0.73-0.91
Picture recognition RT	929	827-1020	1012	904-1191‡	880	817-984*	931	825-1024‡
Overall Attention RT	1177	1119-1284	1280	1182-1443‡	1202	1133-1340*	1160	1103-1276
Overall Memory RT	3002	2588-3451	2980	2678-3463	2700	2422-2910‡	2692	2460-3079‡
Overall RT	4148	3763-4768	4269	3912-4897*	3914	3600-4295‡	3880	3601-4348‡
Overall A	2.53	2.40-2.65	2.32	2.12-2.50‡	2.49	2.37-265	2.47	2.29-2.60*

One-week, 2-month, and 6-month measurements compared with initial cognitive function. Median and interquartile ranges *(IQR)* statistics, Wilcoxon signed rank test. *RT,* Reaction time; *A,* accuracy.
*$P < .05$.
†$P < .001$.
‡$P < .0001$.

Relationships between flow and emboli and specific cognitive dysfunction

Attention, flow, and pressure. We examined the relationship between cerebrovascular reactivity (as a measure of the ability to increase flow in times of stress), MAP during bypass, MCA blood flow velocity, and changes in sustained attention as measured by number vigilance.

We found a significant positive correlation between the accuracy of number vigilance and cerebrovascular reactivity, suggesting that the worse the cerebrovascular reactivity preoperatively, the larger the deterioration in accuracy with more false positive errors being made ($r = 0.3$, $P = .01$ for both right- and left-sided cerebrovascular reactivity, Fig 4).

The lower the MAP during bypass, the greater the deterioration in accuracy of number vigilance ($r = 0.3$, $P < .01$, Spearman) and the greater the number of false positive errors during the test ($r = 0.3$, $P < .01$, Spearman).

Low flow in both MCAs during bypass caused greater deteriorations in accuracy of sustained attention and a higher number of false positive errors ($r = 0.3$) for both cerebral hemispheres separately ($P < .05$, Spearman).

Memory and emboli. We examined the relationship between the number of embolic signals detected in the MCA during surgery and memory tests. We found a direct correlation between the number of emboli and the deterioration in accuracy of memory ($r = 0.3$, $P < .005$ for the right hemisphere and $r = 0.4$, $P = .001$ for the left, Spearman, Fig 5).

Emboli produced during placement of aortic purse-string sutures, aortic cannulation, cardioplegia cannulation, and application, removal, or readjustment of aortic crossclamps and side clamps can be assumed to be particulate. The greater the number of particulate emboli, the greater the deterioration in accuracy of memory ($r = 0.3$, $P < .02$, Spearman).

Those patients with more emboli to the left (and probably dominant) hemisphere did worse in 9 of 14 cognitive tests than did those with more emboli to the right MCA territory. The differences were greatest for memory tests and overall reaction time, although none of the differences was statistically significant.

Likewise, those patients with relatively greater flow to the left MCA territory than the right during bypass had greater deteriorations in a greater number of tests than those with equal hemispheric flow or more flow to the right, although these differences did not reach statistical significance.

Discussion

Occult cerebrovascular disease as measured by impairment of cerebrovascular reactivity to inhaled carbon dioxide was surprisingly high and may indicate patients at risk. No comparative data are available, because this investigation is normally performed on patients with carotid disease. The duration of bypass, aortic crossclamping, and inpatient stay was similar to

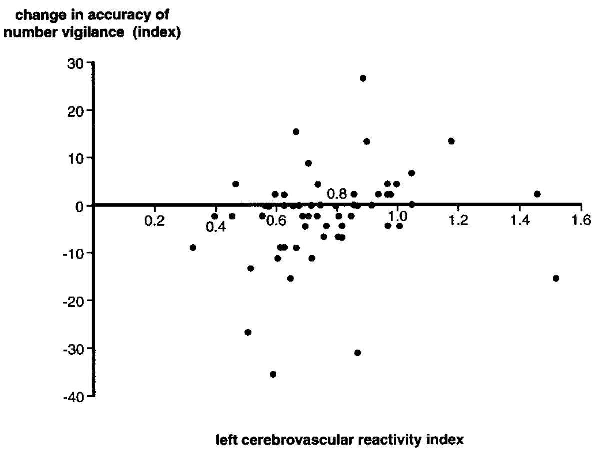

Fig 4. Cerebrovascular reactivity is plotted against accuracy of number vigilance 1 week postoperatively for all patients undergoing CABG. Each *point* represents an individual. Patients with poor cerebrovascular reactivity were found to perform poorly in this test of attention (r = 0.34, P = .01, Spearman).

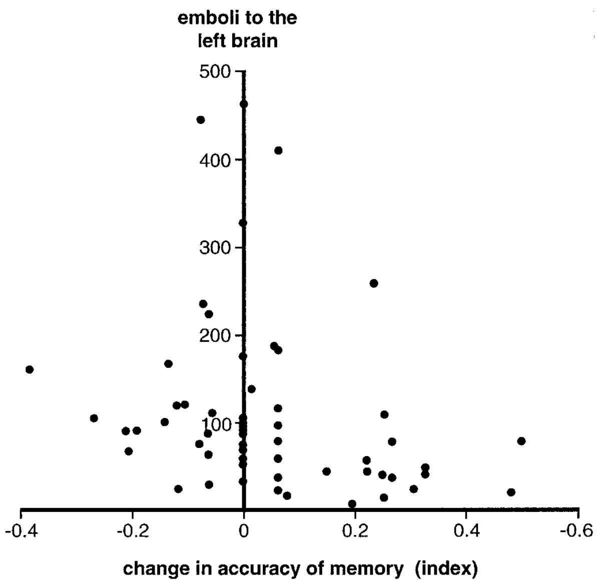

Fig 5. The number of emboli detected in the left MCA by TCD was plotted against the change in accuracy of memory 1 week postoperatively for all patients undergoing CABG. Each *point* represents an individual. Memory was impaired by high embolic counts (r = 0.4, P = .001, Spearman).

those previously reported.[6,28,29] The incidence of stroke in this study was low, and NIHSS scores did not prove useful. However, cognitive deficits were almost universal after CABG surgery and were emphasized when compared with the improvements seen 1 week after urologic surgery, which suggests a practice effect. It was unfortunate that we were unable to age- and education-match our control population selected to represent an elderly population undergoing general anesthesia without the risk of cerebrovascular injury, as occurs in patients undergoing orthopedic or vascular procedures, where cerebral embolization is recognized.

These deficits were transient for most cognitive tests, improving by 2 months postoperatively, although deficits were still present at 6 months. Newman and associates[2] described resolution of deficits within 6 weeks to 6 months of surgery, although others describe persistent deficits for at least 12 months.[3] In this study, the recovery of most cognitive function at 2 months was accompanied by an improvement in general well-being reported by patients using the SF-36 questionnaire. These improvements were in physical health, vitality, social functioning, and mental health, and it may be that cognitive function plays an important part in subjective outcome after surgery. The lack of correlation between cognitive outcome and patient-reported health status is not new and reflects the difficulties encountered when comparing objective and subjective measurements.[30]

Cognitive deficits after cardiac surgery are similar to those occurring with aging[31]: attention, concentration, memory, and speed of response were the areas most affected.[30] The right hemisphere appears to be more vulnerable than the left as the brachiocephalic artery has a more direct origin from the aortic arch, which may predispose to the capturing of emboli from the heart or CABG circuit.[32,33] However, greater cognitive disability occurs if flow is impaired or embolic load is greater to the left (and usually dominant) hemisphere.

Although lesion analysis suggests that specific areas of the brain relate to specific functions, there is still considerable overlap when cognitive pathways are being mapped. Impaired MCA flow in our study related to a subsequent inability to perform cognitive tests requiring attention. The vulnerable areas of the brain in hypoperfusion are the watershed areas at the junction of the major cerebral arterial territories. However, emboli may cause a more diffuse injury to relatively well-perfused brain and appear to relate to subsequent inability to perform memory tests. The relationship between handedness and cerebral dominance is not entirely clear but is improving with functional magnetic resonance imaging.[34] A separate analysis with respect to handedness was not possible because of the small number of left-handed patients.

During cardiopulmonary bypass, MAP was low at only 55 mm Hg. Perioperative hypotension is associated with an increased incidence of neurologic complications, especially if below 40 mm Hg.[35,36] However, a recent retrospective study failed to detect any difference between those patients receiving perfusion above 65 mm Hg or those below.[37] None of these studies has addressed changes in cognitive function. In patients with significant carotid disease, it is generally thought better to maintain MAP above 50 mm Hg during bypass[38]; however, there are no controlled prospective studies to support this.

Mean MCA blood flow velocity fell with temperature as bypass was established, implying preservation of autoregulation.[39] MCA flow rose during bypass, implying increased vascular tone from nonpulsatile perfusion similar to that occurring in the systemic circulation.[40] MCA flow was not infrequently greater to one hemisphere than the other. Inasmuch as this did not relate to the side of severity of carotid artery stenosis, it may relate to directed flow from the aortic cannula during bypass.

Falls in regional CsO_2 on cardiopulmonary bypass were substantially greater than those during internal carotid crossclamping for carotid endarterectomy, where a 10% fall is considered sufficient to justify the insertion of a shunt.[19,20] If cerebral perfusion was adequate during bypass, one would not expect a fall in CsO_2, especially because oxygen extraction should fall due to cooling. It is generally thought that rewarming increases metabolism and hence oxygen requirements. The rise in CsO_2 to above preoperative levels when CABG patients were rewarmed suggests a state of luxury perfusion that may be a response to previous hypoxia where blood flow exceeds the oxygen requirements for some hours after ischemia.[41]

The prevalence of cerebrovascular symptoms was high and matched by the substantial proportion of patients (70%) with impaired cerebrovascular reactivity to inhaled carbon dioxide. These patients are less able to cope with the abnormal flow and cerebral perfusion pressures during cardiopulmonary bypass.

A substantial number of cerebral emboli were produced on establishing cardiopulmonary bypass and on defibrillation after bypass. Although TCD cannot clearly differentiate between gas and solid emboli, emboli produced at certain times, such as aortic clamping, are likely to be particulate. These were associated with poorer memory, especially if the left cerebral hemisphere was involved. This suggests that long-term repetitive emboli may be a cause of vascular dementia. In the Western world, vascular dementia is second only to Alzheimer disease as the leading cause of cognitive impairment and is the only preventable cause.[42,43] No systematic attempt has been made to correlate focal lesions with specific brain dysfunctions in multi-infarct dementia.[44]

Conclusion

Cognitive deficits after CABG remain common. They are related both to low MCA flow during bypass and to the number of emboli entering the MCAs, especially to the left (dominant) hemisphere. Occult cerebrovascular disease was more frequent than expected and predisposed to postoperative cognitive problems. Despite 40-μm arterial filters, embolic brain injury still occurred and caused memory problems, presumably because emboli are arising from beyond the arterial pump cannula, for example, from the aortic wall. Cerebral hypoperfusion impaired subsequent attention. A strategy for prevention should therefore address both the adequacy of flow and the prevention of emboli. The association between cerebral embolization and memory impairment suggests the need for further research on the role of emboli in the causation of dementia.

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