Cerebral Swelling after Normothermic Cardiopulmonary Bypass

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Background: Marked cerebral swelling visible on magnetic resonance images has been found immediately after hypothermic (28°C) cardiopulmonary bypass. The mechanism is unknown, but indices of cerebral ischemia are seen during rewarming from hypothermic bypass that are not present with normothermic bypass (37°C).

Methods: T1-weighted and fluid-attenuated inversion recovery magnetic resonance images were taken of seven patients undergoing routine coronary artery bypass surgery before, 1 h, and 7 days after the operation using normothermic bypass.

Results: Marked cerebral swelling was seen in fluid-attenuated inversion recovery images in five of seven patients 1 h after bypass. Scans in four patients taken 7 days after bypass showed that the cerebral swelling had returned to normal. There was no change in cerebral ventricular size, and all patients had uncomplicated postoperative courses.

Conclusions: Normothermic bypass is followed by acute postoperative cerebral swelling. However, the amount of swelling was similar to that found in a previous study after hypothermic bypass. The mechanism of swelling is still obscure, and its relation to neurologic outcome is unknown. (Key words: Brain; edema; magnetic resonance imaging; pathophysiology.)

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THERE is interest in the use of normothermic cardiopulmonary bypass in coronary artery bypass grafting (CABG)[1,2] because it is thought to offer better myocardial protection than standard hypothermic bypass. Although the benefits to the myocardium are generally accepted, there is conflicting data on cerebral damage after normothermic bypass.[3,4]

It is known from animal studies that core temperatures of <35°C reduce the amount of cerebral damage after an ischemic injury.[5] There are many opportunities for adverse complications to occur during bypass. Cells passing through the roller pumps are damaged and release free radicals, patients receive cerebral emboli (gaseous or solid), and bypass pump flow and pressure are set arbitrarily without knowledge of the perfusion needed by the individual patient. It is likely, therefore, that the brain suffers some insults during bypass, and the use of hypothermia to provide cerebral protection has been advocated.

In a previous study we found that in each of six patients magnetic resonance (MR) images obtained within 1 h of the end of hypothermic bypass (immediate images) showed marked cerebral swelling that had returned to normal after 1 week.[6] It was not possible at that time to study a control group, and it was not known whether this unexpected finding was physiologic or might be related to postoperative cerebral impairment.

Because normothermic bypass obviates cerebral desaturation during rewarming and may maintain normal capillary permeability, we studied patients having routine CABG under normothermic bypass (37°C) with preoperative, immediate, and late MR scans.

Materials and Methods

After we received approval from the hospital ethics committee and informed consent, seven patients (aged 54–72 yr; mean, 63 yr) suitable for MR imaging who

were having routine CABG were studied. Anesthesia was induced with 10 $\mu g/kg$ fentanyl, 0.05 mg/kg midazolam, and 0.1 mg/kg pancuronium and maintained with a $0.5-3$ mg $\cdot$ kg^{-1} $\cdot$ h^{-1} propofol infusion with an oxygen and air mixture for intermittent positive pressure ventilation (fractional inspired concentration of oxygen, 0.5) to a fractional expired concentration of carbon dioxide in expired gas of 3.5 to 4 kPa. Lactated Ringer's solution was given before bypass to maintain central venous pressure >1 cm H_2O. No aprotinin was used in these patients.

Bypass was carried out with pulsatile perfusion at 2.4 l/m^2 through a membrane oxygenator with 40-μm arterial line filtration; blood cardioplegia was used. The bypass prime (2 l crystalloid) was prewarmed and the patient was actively warmed to 37°C on starting bypass from the mild hypothermia (35°C) that resulted during preparation for bypass. Aortic manipulation was minimized with a single cross-clamp to reduce embolization. Mean arterial pressure was maintained between $40-70$ mmHg with 1-mg boluses of methoxamine or glyceryl trinitrate infusion. After separation from bypass, glyceryl trinitrate was infused at $3-20$ mg/h to facilitate transfusion of the pump reservoir blood; the rate of glyceryl trinitrate and transfusion were adjusted to keep the central venous pressure at <7 cm H_2O.

Propofol anesthesia was continued throughout transfer to and during the scanning in the MR unit. Electrocardiogram, pulse oximetry, arterial and central venous pressures, fractional inspired concentration of oxygen, and the fractional expired concentration of carbon dioxide in expired gas were monitored throughout the operation, transfers, and MR imaging. Chest drain losses and urine volume were recorded every 15 min in the MR suite.

To confirm the absence of postbypass hyperemia transcranial Doppler measurement of middle cerebral artery velocity was made through the right temporal window (LogiDop 3; Scimed Ltd., Bristol, UK) at a depth of $4-5$ cm as an index of change in cerebral blood flow (rather than absolute level). Jugular bulb saturation was measured from samples drawn through a 7.5-French fiberoptic thermodilution catheter (Oximetrics — Abbott Laboratories, North Chicago, IL) to assess potential cerebral oxygen desaturation. Samples were taken 5 min before the start of bypass; 10', 30', and 40' into bypass; and 10' after discontinuing bypass. After preinsertion calibration and flushing with saline, the catheter was inserted retrograde through an 8-French introducer

with a hemostatic valve into the right internal jugular vein until resistance at the base of the skull was felt. The catheter was withdrawn slowly until the saturation showed a step increase reflecting facial vein contribution; the catheter was then advanced 3 mm and secured. *In vivo* calibration was done with a sample from the catheter distal port, which was checked on the co-oximeter (IL 701). Jugular bulb saturation samples were drawn and measured on a co-oximeter. Temperature was measured from the jugular bulb catheter thermistor and from a nasopharyngeal probe to confirm the lack of temperature gradient between cerebral venous blood and brain.

Magnetic Resonance Imaging

Baseline MR images were obtained the evening before surgery (pre), followed by immediate images at the end of surgery before transfer to the intensive care unit (immediate). Late images (late) were obtained 7 days after surgery to determine if cerebral tissue had returned to normal. Two sequences were used on a 1.0T Picker HPQ system, a 4-min T1-weighted spin-echo sequence 720/20 ms TR/TE, 20 contiguous 7-mm slices on a 192×256 matrix with 2 NEX, followed by a 14-min fluid attenuated inversion recovery (FLAIR) sequence 6500/2100/160 msec TR/TI/TE, 10 7-mm slices with a 7-mm gap between each slice on a 128×256 matrix with 1 NEX. The T1 sequence was used to determine positioning to match the previous sequences; great care was taken to match the orientation and depth of postoperative scans to the preoperative positions. By design, FLAIR sequences enhance the contrast between cerebrospinal fluid and gray matter as the inversion recovery sequence is set around the null point for cerebrospinal fluid.

Analysis

There were six sets of images for each patient (pre, immediate, or late: T1 and FLAIR). To minimize any bias, each set of images was presented in random order for visual assessment of cerebral swelling based on width and clarity of cerebral sulci on our standard five-point score (0, none; 1, slight; 2, mild; 3, moderate; 4, severe) and for ventricular size (enlarged, normal, or compressed). Each set was scored independently by two radiologists. For swelling, their individual scores were recorded and then an average score was derived for each set of images: Change from pre to immediate or late images was then calculated for T1 and FLAIR for

Table 1. Jugular Bulb Saturation (Sj$_{O_2}$), Time-averaged Mean Middle Cerebral Artery Velocity (Vmca), Systolic/Diastolic Arterial Blood Pressure, and Arterial Pa$_{CO_2}$ before Bypass (Pre), after 30 min of Bypass (30′), and 10 min after the End of Bypass (E + 10′) for the Seven Patients

Patient No.	Sj$_{O_2}$ (%)			Vmca (cm·s^{-1})			BP (mmHg)			Pa$_{CO_2}$ (mmHg)		
	Pre	30′	E + 10′	Pre	30′	E + 10′	Pre	30′	E + 10′	Pre	30′	E + 10′
1	62	58	64	33.5	39.5	38.2	91/58	61/55	89/60	35	36	36
2	61	66	59	27.2	25.8	25.9	98/62	60/56	85/51	31	42	37
3	54	58	56	37.1	35.6	39.9	84/50	69/51	92/49	34	35	40
4	69	66	61	31.1	34.1	36.7	86/54	65/59	102/68	34	35	35
5	52	57	61	40.2	37.3	38.8	95/65	69/60	90/58	33	36	39
6	66	64	69	26.5	28.4	28.9	102/67	66/51	84/49	35	41	38
7	61	58	59	33.3	39.1	37.4	99/67	71/58	90/55	35	37	36

each patient. These difference scores were tested for significance using a two-tailed sign test.

Results

Bypass lasted 66 ± 15 min, and aortic cross-clamp time lasted 35 ± 7 min. The hematocrit concentration decreased from 38 ± 5% to 22 ± 3%. Central venous pressure increased from 1.6 ± 2 mmHg before bypass to 4.2 ± 3 mmHg 10 min after bypass. Patients were extubated without complication 2.6 to 6.4 h after return from the MR unit (our routine average). No patient had visible conjunctival edema. Nasopharyngeal temperature was 35.1°C (range, 34.8–35.5°C) before bypass and constant at 37°C (range, 36.2–37.5°C) throughout bypass; pulse oximetry was 98–100% throughout the study. Table 1 shows results of jugular bulb saturation, middle cerebral artery velocity, systolic and diastolic blood pressure, and partial pressure of carbon dioxide, which were unchanged. All patients had uncomplicated

operative and immediate postoperative courses and showed no gross neurologic defects.

Imaging began 64 min (range, 52–71 min) after the end of bypass. Five of seven patients showed marked cerebral swelling (mean, 3; range, 2–4) in the immediate postoperative images with marked obliteration of the sulci on the FLAIR sequences; there was no change in ventricle size. One patient showed minor and one no swelling (table 2). The mean difference for all seven patients between immediate and preoperative FLAIR images was 2.4 ($P = 0.03$). The two observers differed by one grade in two sequences and agreed in all others.

One patient died after 48 h (of myocardial failure), one was discharged early, and one refused the late scan. In the remaining four patients, swelling had returned to normal in the late scans (+7 days). T1-weighted images showed no significant change in immediate or late images. Figure 1, a sequence of T1-weighted images at the cortical level, shows the accurate repositioning and global reduction in sulcal width. Figure 2, the same

Table 2. Patient Details and Scores of Magnetic Resonance Images (Difference from Baseline Preoperative Images on a 5-point Scale)*

Patient No.	Age (yr)	CPB Time (min)	T1 (immediate)	T1 (late)	FLAIR (immediate)	FLAIR (late)
1	61	91	0	0	4	0
2	66	72	0	0	3	Died
3	59	109	0	0	3	0
4	44	88	0	0	1	Refused
5	60	75	0	0	3	Discharged
6	61	82	0	0	2	0
7	70	89	0	0	0	0

CPB = cardiopulmonary bypass.

* Scale: 0 = none; 4 = severe.

Table 3. Scores of Magnetic Resonance Images for Swelling (Difference between Immediate and Preoperative Images on a 5-point Scale)* from the Previously Published Study on Coronary Artery Bypass Graft after Hypothermic (28°C) Bypass for Each Observer A and B on Each of Two Occasions (2 Weeks Apart)

Patient No.	First Scoring (A/B)		Second Scoring (A/B)	
	T1	FLAIR	T1	FLAIR
1	0/0	2/2	0/0	2/3
2	0/0	3/3	0/1	3/3
3	2/1	4/4	1/2	4/4
4	1/1	2/3	1/2	2/3
5	0/0	3/4	1/0	4/4
6	0/1	2/3	0/0	2/3

* Scale: 0 = none; 4 = severe. The published data were restricted to 4 points on the scale by merging the two minor grades 1 and 2 as the variability is highest there.

slices with FLAIR imaging, shows the greater contrast in sulci with cerebrospinal fluid nulling of the FLAIR sequence.

Discussion

The use of normothermic bypass (37°C) is controversial, and it is not yet known whether it is associated with more or less cerebral impairment on neuropsycho-

metric testing.[7-10] In the present study using normothermic bypass, five of seven patients showed cerebral swelling on the immediate postoperative scans, whereas one patient showed complete absence and one only one point of swelling (mean, 2.4; range, 0–4). In the previous study of hypothermic bypass,[6] all six patients showed more than two points of swelling (mean, 2.5; range, 2–4). Although the techniques, protocols, and patient population were the same for the two studies, and for both studies interobserver variability was less than one grade, comparisons must be limited by the small study sizes and historical nature of the controls. The randomization of the three sets of images (preoperative, immediate, and late postoperative) should have minimized any bias in scoring, but the lack of randomized controls makes interpretation of the swelling speculative.

When hyponatremia is produced in animals, astrocytic swelling is seen with a microscopic profile similar to that after ischemia.[11] During hypothermic bypass with a crystalloid prime, colloid osmotic pressure decreases from 20 to 10.6 mmHg due to hemodilution, and intraocular pressure increases 31 mmHg,[12] although osmolarity shows little change.[13] There are no data during normothermic bypass, but the effects of hemodilution are likely to be similar. It is possible that these physiologic changes alone could cause mild cerebral edema.

Patients were extubated within 6 h of the MR imaging
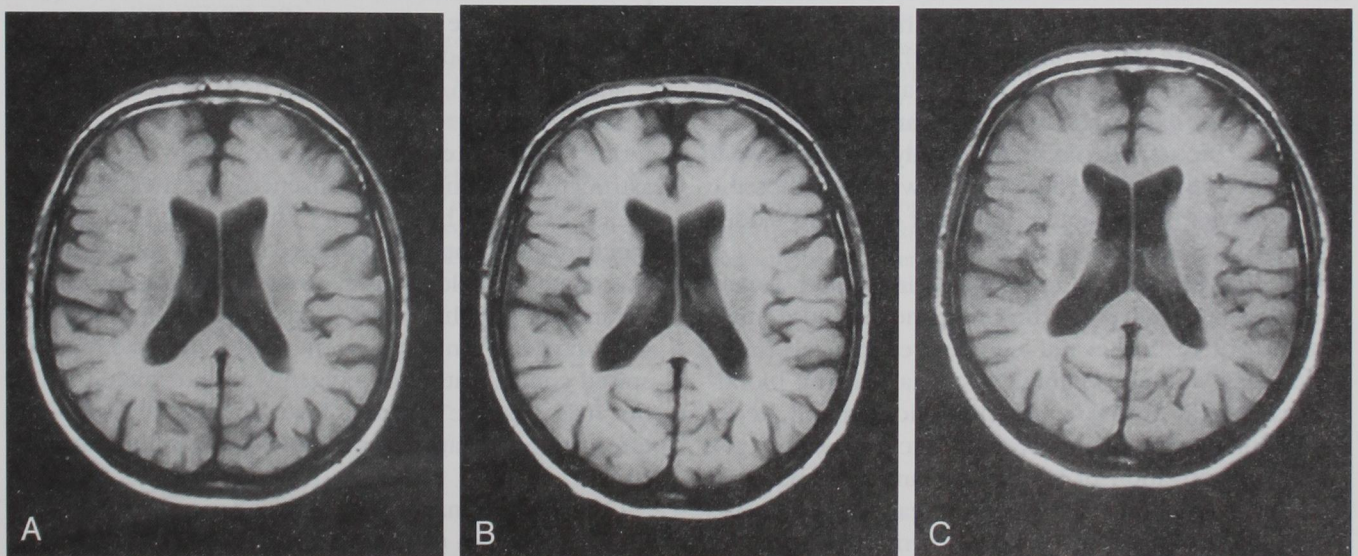
Fig. 1. T1-weighted images from patient 2 (*A*) before (*B*) immediately (1 h) after and (*C*) 7 days after normothermic cardiopulmonary bypass: positional markers show close correspondence of images. Little change seen in immediate or +7-day scans.
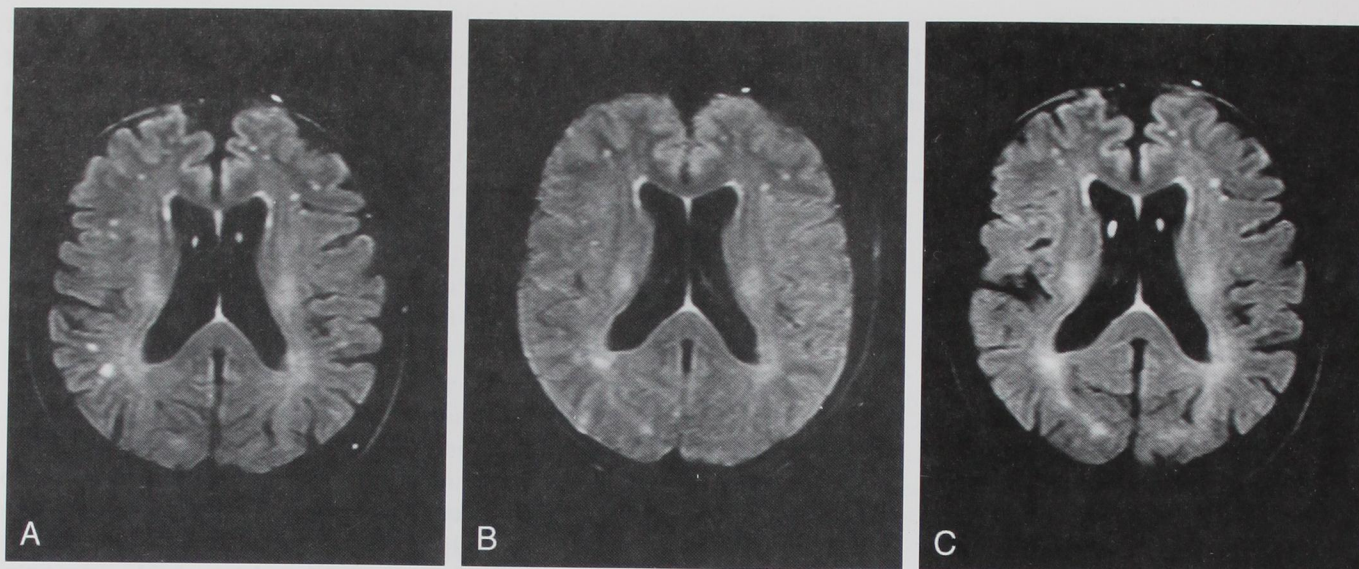
Fig. 2. Fluid attenuated inversion recovery images from patient 2, series as before, showing obliteration of sulci in immediate scan with return to normal in a +7-day scan (see also fig. 1). Swelling is cortical with little change in ventricular size.

and showed no clinical evidence of conjunctival or cerebral edema; it is not known what, if any increase, in CSF volume or pressure is represented by these MR images, which show reduction in sulcal width but normal ventricular size. Olson[14] has proposed a system for measuring brain water content with MR; this could provide useful data but was not possible with the sequences used in this study. Sellman *et al.*[15] found no increase in ventricle size after CABG, and Schmidt *et al.*[16] found increased preoperative ventricle size but no further increase unless encephalopathy developed.

Returning the pump prime to the patient after bypass can result in high right heart pressures, which could promote cerebral edema. In this study, the increase in central venous pressure after bypass was small, possibly due to slower transfusion or to higher doses of vasodilators used during transfusion.

Exposure of blood to the bypass circuit and damage to cells and platelets by the pump heads cause an inflammatory response and release free radicals[17]; this produces cerebral swelling,[18] especially if the blood–brain barrier has been damaged by microemboli. Reperfusion injury after release of the aortic cross-clamp also results in activation of leukocytes, and administration of protamine causes a transient increase in cerebrovascular permeability.[19] It is not known if these factors would be different between normo- and hypothermic bypass.

Although regional or microvascular ischemia has not been excluded, no patients had jugular bulb temperatures >37.5°C or jugular bulb–nasopharyngeal gradients >1°C, and jugular bulb saturation remained >55% in all patients. Because cerebral swelling was observed both during our previous hypothermic bypass study, which includes rewarming reported to be associated with indices of global cerebral ischemia,[20] and in our present normothermic study without rewarming, it seems reasonable to hypothesize that rewarming is not necessary to produce postbypass cerebral swelling.

The pattern of MR change in both bypass studies is described as cytotoxic[21] (*cellular* may be a better term[22]), characterized histologically by generalized astrocytic swelling in the absence of a measurable increase in blood–brain barrier permeability: No specific mechanism is implied and there is rarely a single cause of edema. A mild degree of swelling is also seen in volunteers breathing 100% oxygen, although not after 40% oxygen.[23] In the current study, the fractional inspired concentration of oxygen was controlled to 40%, but it is possible that this level could still have some effect on MR images in patients after cardiopulmonary bypass.

T1-weighted images were not enhanced after intravenous gadolinium (molecular weight, 547) in our previous MR study, suggesting that the blood–brain barrier was intact 1 h after the end of bypass. Astrocytic swell-

ing peaks at 40 min after experimental head injury and is prolonged to 100 min by hypoxia. It is possible, therefore, that increased blood–brain barrier permeability after minor cerebral injury may have occurred toward the end of bypass but had recovered by the time of the scans 1 h later. Because the FLAIR images are acquired 60–90 min after bypass, it is not known whether the swelling seen reflects changes occurring at the time of imaging or previous intraoperative changes.

In conclusion, cerebral swelling is seen after normothermic bypass, as assessed by FLAIR MR. The degree of swelling is similar to that previously seen after hypothermic bypass, even though jugular bulb hemoglobin desaturation and postbypass hyperemia were avoided. It remains to be determined whether the cause is physiologic or pathologic.

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