JECT. 2002;34:101–106
The Journal of The American Society of Extra-Corporeal Technology

Clinical Application of Retrograde Cerebral Perfusion for Brain Protection During Surgery of Ascending Aortic Aneurysm—A Report of 50 Cases

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Presented at the 39th International Conference of the American Society of Extra-Corporeal Technology, March 22–25, 2001, Miami, Florida

Abstract: This study was designed to discuss the effects on the brain by different protective methods in ascending aortic aneurysm surgery retrospectively. Two hundred seventy-one surgeries of ascending aortic aneurysm have been done in the past 15 years. There were 65 patients with a dissecting aneurysm of the aortic arch or right arch. To protect the brain, deep hypothermic circulatory arrest (DHCA) combined with retrograde cerebral perfusion (RCP) through superior vena cava ($N = 50$) and simple DHCA ($N = 15$) were used during the procedure. Blood samples for lactic acid level from the jugular vein were compared in both groups. Perfusion blood distribution and oxygen content difference between the perfused blood and returned blood were measured in 5 and 10 of RCP patients, respectively. The DHCA time was 35.86 ± 18.81 min (10 ~ 63 min) and DHCA + RCP time was 45.5 ± 17.21 min (16 ~ 81min). The resuscitation time was 7.11 ± 1.59 h (4.4 ~ 9.4 h) in DHCA versus 5.43 ± 2.15 h (2 ~ 9 h) in RCP patients. The operation death rate was 3/15 in DHCA group and 1/50 in RCP patients. Central nervous complication occurred in 3/12 of DHCA patients and 1/49 of RCP patients ($p < .01$). The overall survival rate was 96% (RCP) versus 67% (DHCA); the central nervous system dysfunction was 20% in DHCA versus 2% in RCP ($p < .001$). The blood lactic acid level increased significantly after reperfusion in DHCA than that in RCP. The measurement of blood distribution indicated that approximately 20% of the perfused blood returned from arch vessels. The difference of oxygen content between perfused and returned blood showed that the oxygen uptake was adequate in RCP group. The application of RCP can prolong the safety duration of circulation arrest. Continuous cerebral perfusion may maintain the brain at a cooler temperature and flush out particulate and air emboli while open anastomosis of the aortic arch to the prosthesis can be safely performed. Therefore, RCP is a preferable method for brain protection in our clinical practices.
Keywords: retrograde cerebral perfusion, hypothermic circulatory arrest, brain protection, aortic aneurysm. *JECT. 2002;34: 101–106*

Central nervous dysfunction is one of the serious complications after thoracic aortic surgery (1). Intraoperative brain protection is the key factor that influences the outcome of operation (2, 3). Retrograde cerebral perfusion through the superior vena cava has been used for brain protection over the last two decades (4–6). From September 1985 to October 2000, 271 patients with ascending aortic aneurysm were hospitalized in our institute. The dissection aneurysm was expanded to aortic arch or right arch in 65 patients (24%). During the procedure, deep hypothermic circulatory arrest (DHCA) combined with retrograde cerebral perfusion (RCP) through superior vena cava ($N = 50$) or simple DHCA ($N = 15$) were used, respectively. By retrospective investigation, the effects of both RCP and DHCA were compared.

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Received March 25 2001; revised January 15, 2002.

MATERIALS AND METHODS

Patient Profiles

There were 51 men and 14 women, with a mean age of 46 ± 12 years (range 21–72 years). Among 65 patients, 59 patients (90.77%) were diagnosed with aortic dissection by computerized axial tomography (CAT), echocardiography, and magnetic resonance imaging (MRI). There were 26 cases (40%) with aortic valve regurgitation. Hypertension was the most popular concurrent disease that presented in 32 patients (50%). Emergency operations were performed in 12 patients (18.5%).

Perfusion Technique

Anesthesia was induced with intravenous midazalam 0.15–0.3 mg/kg, droperidol 0.1–0.2 mg/kg, fentanyl 20–40 μg/kg, and pancuronium 0.1–0.2 mg/kg. After intubation, anesthesia was maintained with fentanyl and isoflurane, and a median sternotomy incision was made. An arterial cannula was placed into ascending aorta in 11 patients and into femoral artery in 54 patients. Separate venous cannulae were inserted into superior and inferior vena cava. Cardiopulmonary bypass (CPB) was established at flow rate of 2.2–2.4 L/min/m^2. The patients were cooled gradually. After the heart was fibrillated, the aorta was cross clamped, and myocardial protection was achieved by infusion of 4:1 blood cardioplegia, either antegrade or retrograde, either intermittently or continuously as required. After nasopharyngeal temperature reached 18°C and rectal temperature to 20°C, total circulation was arrested in 15 patients. Retrograde cerebral perfusion through superior vena cava conjunction with DHCA was performed at the same temperature in 50 patients. RCP flow rate was 100–600 mL/min and was adjusted by keeping the CVP around 25 mmHg.

Data Collection

The blood distribution was investigated in five patients during the period of retrograde cerebral perfusion. The method was to maintain a certain pump flow rate and to collect the blood returning from the cephalic vessels and the inferior vena cava; the average value of three times of evaluation was recorded. Comparative study of the oxygen content of the perfused blood into the superior vena cava and the blood in the returning flow from the cephalic vessels was conducted in 10 patients. Blood samples for lactic acid level from the jugular vein were compared in 16 patients (8 in each group) in different phases. The time of total CPB, aortic cross clamping, awaking, and ventilation was collected. The hospital mortality including intraoperative and postoperative deaths were discussed. Neurologic complications were defined as delay regaining consciousness and nervous or psychiatric dysfunction.

Statistical Analysis

The data were expressed as mean ± standard deviation (X ± SD). Comparison between two groups was done by a set of *t*-tests and a chi-square test. A *p*-value less than .05 was considered significant.

RESULTS

The clinical data are listed in Table 1. Operative procedures consisted of Bentall in nine cases, Wheat in 17 cases, ascending aorta replacement in 13 cases, and the total aortic arch replacement or patch aortoplasty in 26 cases. Open aortic anastomosis technique was used in all RCP patients. The duration of DHCA was 35.86 ± 18.81 min (range 10 ~ 63 min), and that of RCP was 45.5 ± 17.21 min (range 16 ~ 81 min). The postoperative observation showed that the time of awaking in DHCA group was 7.11 ± 1.59 h (range 4.4 ~ 9.4 h), and that in RCP group was 5.43 ± 2.15 h (range 2 ~ 9 h). There were three intraoperative deaths (20%) in DHCA group; whereas, one in RCP group (2%, $p < .01$). The following observation indicated that there were three patients with permanent neurologic complications, and two died postoperatively in the DHCA group. Temporary neurological deficiency occurred in one patient, but there was no hospital death in RCP group (Table 2). The overall survival and morbidity of neurological complication were 96 and 2% in RCP group as compared with 67 and 20% in the DHCA group ($p < .001$), respectively. The measurement of blood lactic acid from the jugular vein also showed that blood lactic acid was lower in RCP group than that in DHCA group after the reperfusion ($p < .01$) (Table 3). The measurement of oxygen content indicated obvious difference in the perfused blood and returned blood during retrograde perfusion (Table 4). Approximately 18 ± 2% perfused blood returned from open cephalic vessels and about 80% perfused blood returned through inferior vena cava (Table 5).

DISCUSSION

With the advance in diagnostic techniques and understanding of atherosclerotic disease during the past two decades, the surgical cases of ascending aortic aneurysm has increased. Ascending aortic aneurysms involving the aortic arch offer a unique challenge (7). The key is protecting the brain effectively during surgery. DHCA (8) and selective antegrade cerebral perfusion (9) for cerebral

Table 1. Comparison of clinical profiles and parameters during CPB between the groups.

	Age (y)	Body Weight (kg)	CPB Time (min)	Aortic Cross Clamp Time (min)	Circulation Arrest (min)
DHCA group (N = 15)	50.33 ± 11.70	72.24 ± 12.33	204.27 ± 56.78	82.47 ± 32.17	35.86 ± 18.81
RCP group (N = 50)	48.50 ± 11.43	71.69 ± 14.39	219.72 ± 66.42	141.44 ± 48.92	45.5 ± 17.21
p-value	>.05	>.05	>.05	<.001	>.05

DHCA: Deep hypothermic circulatory arrest.
RCP: retrograde cerebral perfusion.

Table 2. Perioperative parameters of the two group.

	Time of Waking (h)	Time of Postoperative Intubation (h)	Outcome		
			Intraoperative Death	Neurological Complication	Postoperative Death
DHCA group	7.11 ± 1.59	42.46 ± 18.56	3/15 (20%)	3/12 (25%)	2/12 (16.67%)
RCP group	5.43 ± 2.15	23.51 ± 9.20	1/50 (2%)	1/49 (2.04%)	0
p-value	<.01	<.001	<.01	<.01	<.01

DHCA: Deep hypothermic circulatory arrest.
RCP: Retrograde cerebral perfusion.

Table 3. Lactic acid levels of two groups in the different phases (mmol/L).

	After Anesthesia	Establishment of CPB	Before DHCA	Reperfusion			
				25 min	30 min	35 min	End of Operation
DHCA Group (N = 8)	2.28 ± 0.12	2.42 ± 0.14	3.30 ± 0.23	6.18 ± 0.91	6.74 ± 1.29	6.92 ± 1.21	6.41 ± 1.20
RCP Group (N = 8)	2.31 ± 0.11	2.44 ± 0.13	3.36 ± 0.20	4.39 ± 0.60	4.82 ± 1.01	5.23 ± 1.12	4.75 ± 1.19
p-value	>.05	>.05	>.05	<.05	<.05	<.01	<.01

Table 4. Oxygen content of the perfused and returned blood during different RCP time ($N = 10$) (ml/L).

RCP Time (min)	Oxygen Content of the Perfused Blood	Oxygen Content of the Returned Blood	Oxygen Content Difference Between the Perfused and Returned Blood
5	21.2 ± 31.10	12.60 ± 0.85	9.00 ± 0.85
10	21.98 ± 0.43	8.33 ± 3.00	13.67 ± 2.49
15	21.73 ± 0.15	5.70 ± 0.85	15.95 ± 0.92
20	22.00 ± 0.22	10.80 ± 3.57	11.20 ± 3.34
25	21.70 ± 0.27	10.05 ± 6.01	11.70 ± 6.08

Table 5. The record of perfusion blood and returned blood in five patients (mL/min).

		Returned Blood Flow			
		Cerebral Vessel		Inferior Vena Cava	
Patient	Perfusion Blood Flow	Blood Flow	Percentage (%)	Blood Flow	Percentage (%)
1	200	38 ± 5	19 ± 2.5	152 ± 10	76 ± 5
2	200	36 ± 6	18 ± 3	155 ± 8	77.5 ± 4
3	300	60 ± 12	20 ± 4	230 ± 16	76.67 ± 5.3
4	300	58 ± 8	19.33 ± 2.7	240 ± 5	80 ± 1.7
5	350	66 ± 8	18.86 ± 2.3	280 ± 12	80 ± 3.4

protection have been reported in the past. However, some authors found that DHCA time more than 60 to 65 min were associated with serious neurologic morbidity and mortality (1, 4, 10). Since Ueda and colleagues first reported the technique of RCP to protect the brain during aortic arch operations in 1990 (11), ongoing research on the procedure became widespread. Several studies indicated that RCP has the advantages of safety and simplicity readily accepted by the surgeons (12, 13). Our group started DHCA + RCP as brain protection for aortic surgery in 1994 (14). The result of this investigation showed that there was obvious oxygen content difference in the perfused blood and returned blood during retrograde perfusion. This demonstrated that there was still metabolic activity during deep hypothermic state. This may be the basic reason that neurologic complications occurred once DHCA lasted for more than 45 ~ 60 min (1). We maintain the retrograde perfusion pressure at 25 mmHg in our clinical practice. To address this issue, Usui (15) and Nojima (16) reported that the blood returning from the aortic arch increased linearly when jugular pressure increased from 15 mmHg to 25 mmHg, then plateaued beyond the pressure. For this reason, they concluded that pressures between 20 – 25 mmHg, as measured in the jugular veins, provided optimal benefit during RCP. Our studies also demonstrated that approximately 20% of perfused blood returned from open aortic arch with retrograde perfusion pressure maintained around 25 mmHg. Ffytche has (17) shown that extrapolation of the pressure/velocity graph gave a theoretical no-flow point of 8 mmHg. The perfusion pressure was calculated by subtracting the intraocular pressure from the mean blood pressure (MBP). Therefore,

low perfusion pressure may not adequately perfuse the brain.

The comparisons between DHCA and RCP group in this study demonstrated that RCP can prolong safety duration of circulatory arrest, reduce the mortality ($p < .01$), decrease the morbidity of neurological complications ($p < .01$) and provide a safeguard for aortic arch surgery.

Our research group began a series of animal experiments on RCP in 1992 (18, 19). The morphologic studies made with light and electron microscope indicated that retrograde perfusion could attenuate neuronal injury caused by DHCA. Electroencephalograph (EEG) monitoring showed that the electrical activity of brain resumed in 3.2 min in the RCP group after rewarming, and the signal became a continuous wave in 10 min. The electrical activity of brain resumed after 20 min in only some of the animals of the DHCA group. RCP can provide adequate blood supply to the brain tissue, thus avoiding the ischaemia–reperfusion injury after DHCA. During the previous animal study, technetium 99-labeled perfusion agent [ethyl cysteinate dimer (^{99m}Tc-ECD)] was injected into perfusion blood during RCP. Cerebral perfusion images showed homogeneous perfusion of cerebrum, cerebellum, and medulla oblongata 3 min after the start of RCP (18) (Figure 1). In a recent animal study (19), retinal microvascular perfusion was observed by using fundus fluorescein angiography (FFA) and color Doppler sonography before cardiopulmonary bypass and retrograde cerebral perfusion during DHCA. The results of FFA showed initial development of the fundus venae in 2.5 min and complete development in 4.5 min with partial development of the arteriae; the latter development completed in 8 min, and all of the arteriae and venae developed from 15 to 17 min (Figure 2). Color Doppler sonograghy showed that the flow signals can be detected in all of the fundus vessels during RCP. Because the retinal vessels stem from cerebral circulation, the study demonstrated that RCP could perfuse the cerebral tissue. In our recent clinical surgeries, we tried to make some preliminary clinic observations with an ophthalmoscope to visualize the changes of image similar to those seen in animal experiments. Pagano and associates (20) reported three cases in which technetium 99-labeled perfusion agent [d,l-hexamethyl propylene amine oxime (^{99m}Tc-HMPAO)] were used during RCP to obtain a perfusion image with a portable gamma camera in the operating theater. Time activity curves showed homogeneous perfusion of both cerebral hemispheres in all patients during RCP.

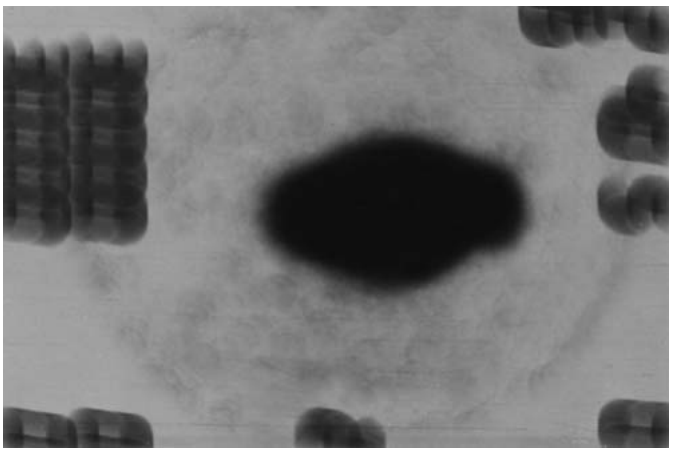

Figure 1. ^{99m}Tc-ECD was injected into perfusion blood during RCP. Cerebral perfusion images showed homogeneous perfusion of cerebrum, cerebellum, and medulla oblongata in 3 min after the start of RCP.

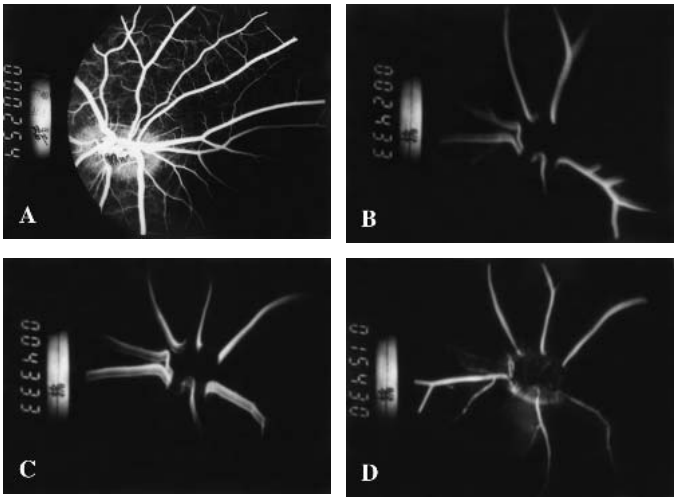

Figure 2. Normal fluorescein angiogram of the animals 24 s after single injection of 3 mL of 20% sodium fluorescein (A). After the initiation of retrograde perfusion, some branches of veins developed in 2.5 min (B). All branches of veins and partial branches of arteries developed in 4.5 min (C). All veins and arteries developed in 15 min (D).

The basic reason for neuronal injury caused by DHCA was "oxygen debt" and release of such excitatory amino acid as glutamate and its analogs, which could result in intracellular calcium overload and even cell death (21). In our animal studies, the calcium fluorescent intensity of vital brain slices were examined with laser confocal scanning microscope (LCSM) (Leica TCS-NT, Germany). The results showed that the calcium fluorescent intensity of vital brain slice was lower in RCP group than that in DHCA group (Figure 3). The calcium fluorescent intensity of vital brain slice was correlated with the level of moderate and severe eosinophilic degeneration of neuron ($r = 0.86$, $p < .05$), which demonstrated that "calcium overload" contributed to the injury of neuron after DHCA. The morphologic studies made with light microscope and electron microscope showed moderate and severe eosinophilic degeneration were found in DHCA group; whereas, slight eosinophilic degeneration in

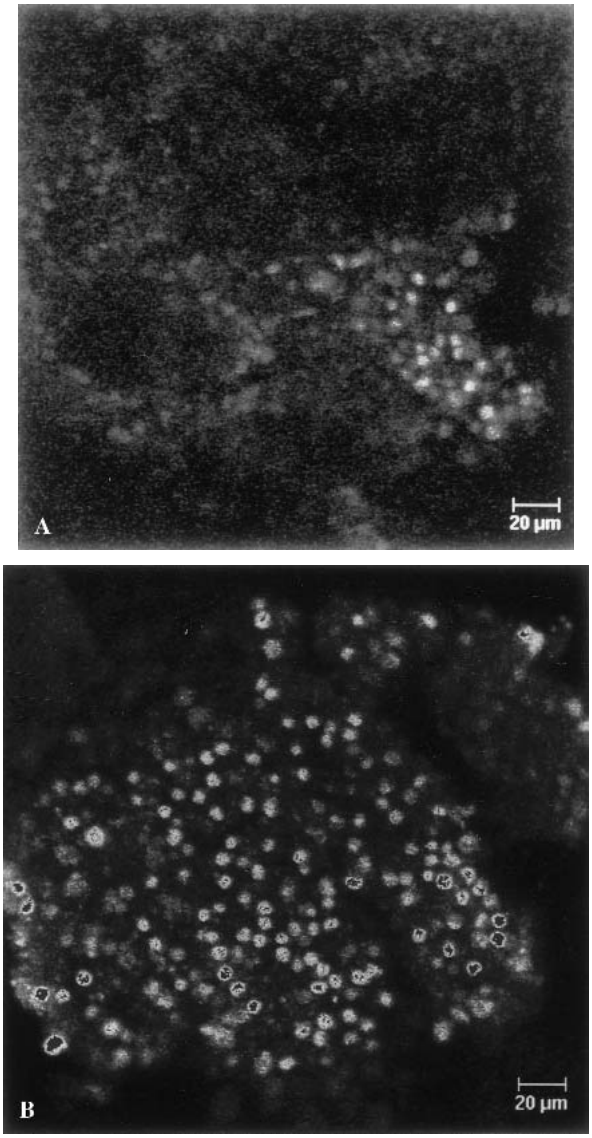

Figure 3. The photograph of calcium fluorescent intensity of vital brain slice (A) retinal photograph of RCP; (B) retinal photograph of DHCA.

RCP group ($p < .001$). Thus, RCP is able to attenuate "calcium overload," which has the effect of cerebral protection (22).

During RCP, the inferior vena caval line was unclamped, because we found in our animal experiment (19) that clamping the inferior vena cava during RCP resulted in slowing down the blood flow of the central retinal vein. Moreover, the speed of blood flow recovered after declamping. It was possible that 80% of the retrograde flow returned from the inferior vena cava and that all the blood returned to the aorta while the inferior vena cava was clamped and the resistance of blood flow might increase, resulting in cerebral edema. This opinion was identical with that of Juvonen and associates (23).

CONCLUSION

During aortic surgery, use of RCP can prolong the safety duration of circulation arrest. Continuous perfusion can maintain the hypothermic state. It was also simple to wash the particulate and air embolus away and easy to operate with open aortic anastomosis technique at the same time. Therefore, RCP is one of the preferable methods that can be used to protect the brain during aortic surgery.

ACKNOWLEDGMENT

This research work was supported by the National Natural Science Foundation. (Code: 39770733; Number: C03030304).

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