Determination of optimum retrograde cerebral perfusion conditions

Retrograde cerebral perfusion through a superior vena caval cannula is a new technique used to protect the brain during operations on the aortic arch. We measured cerebral tissue blood flow, oxygen consumption, and cerebrospinal fluid pressure under various perfusion conditions in hypothermic (20° C) mongrel dogs ($n = 18$, 12.8 ± 0.6 kg) to determine the optimum conditions for retrograde cerebral perfusion. Retrograde cerebral perfusion was performed by infusion via the superior vena caval cannula and drainage via the ascending aortic cannula while the inferior vena cava and azygos vein were clamped. Retrograde cerebral perfusion was performed as the external jugular venous pressure was changed from 15 to 35 mm Hg in increments of 5 mm Hg. Cerebral tissue blood flow was measured by the hydrogen clearance method. Hypothermic retrograde cerebral perfusion with an external jugular venous pressure of 25 mm Hg provided about half the cerebral tissue blood flow of hypothermic (20° C) cardiopulmonary bypass with a flow rate of 1000 ml/min (13.7 ± 7.9 versus 32.7 ± 8.5 ml/min per 100 gm). It decreased significantly as the external jugular venous pressure was decreased from 25 to 15 mm Hg but did not increase significantly as the external jugular venous pressure was increased from 25 to 35 mm Hg. Whole-body oxygen consumption during hypothermic retrograde cerebral perfusion with an external jugular venous pressure of 25 mm Hg was one quarter of that during hypothermic cardiopulmonary bypass (3.4 ± 0.7 versus 12.7 ± 5.6 ml/min) and varied in proportion to external jugular venous pressure. The cerebrospinal fluid pressure was a little lower than the external jugular venous pressure (19.2 ± 4.5 mm Hg versus 24.8 ± 2.4 mm Hg) but also varied with the external jugular venous pressure. The cerebrospinal fluid pressure remained lower than 25 mm Hg so long as the external jugular venous pressure remained lower than 25 mm Hg. High external jugular venous pressure was associated with high intracranial pressure, which restricts cerebral tissue blood flow and may cause brain edema. We believe that a venous pressure of 25 mm Hg is the optimum condition for retrograde cerebral perfusion. (*J THORAC CARDIOVASC SURG* 1994;107:300-8)

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Retrograde cerebral perfusion through a superior vena caval (SVC) cannula is a new and simple technique for

protecting the cerebrum during operations on the aortic arch. Retrograde cerebral perfusion can provide the blood flow and oxygen to brain tissue.¹ Although it should reduce ischemic damage to the brain, retrograde cerebral perfusion may be associated with high pressure in the SVC system and may cause brain edema which, in turn, would cause brain damage. Optimum conditions for retrograde cerebral perfusion must be determined to minimize the disadvantages of this perfusion technique. We report our measurements of cerebral tissue blood flow (CBF), oxygen consumption, and cerebrospinal fluid (CSF) pressure under various perfusion conditions in mongrel dogs to determine the optimum conditions for retrograde cerebral perfusion.

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Methods

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985).

Preparation of animals and methods of retrograde cerebral perfusion. Eighteen mongrel dogs with a mean weight of 12.8 ± 0.6 (12 to 14 kg) were used for this study. Anesthesia was induced with ketamine hydrochloride, 10 mg/kg, given intramuscularly and thiopental sodium, 5 mg/kg, given intravenously. After endotracheal intubation, the animal was ventilated mechanically with 100% oxygen. The ventilatory rate and tidal volume were adjusted to maintain the arterial carbon dioxide tension around 35 mm Hg. Anesthesia was maintained with intravenous ketamine hydrochloride, 2 mg/kg per hour.

Catheters were placed in the right external jugular vein, right femoral vein, and brachiocephalic artery to measure blood pressures. CBF was measured by the hydrogen clearance method. A hydrogen electrode was inserted into the mid-central parietal lobe cortex through a burr hole in the skull. A perfusion cannula (8F) for retrograde cerebral perfusion was placed in both internal maxillary veins. A catheter was also placed in the subarachnoid cavity through the occipitocervical space to measure the CSF pressure.

A thoracotomy incision was made through the right fourth intercostal space. Heparin, 300 U/kg, was given intravenously. The ascending aorta was cannulated with a 16F metal-tipped perfusion catheter. The right atrium was cannulated with two separate venous cannulas (28F), vena caval tapes were applied, and the azygos vein was clamped. Cardiopulmonary bypass (CPB) was established at a flow rate of 1000 ml/min with administration of pure oxygen at 0.5 L/min. Mechanical ventilation was discontinued, a crossclamp was applied to the ascending aorta, the heart was arrested, and intermittent cold crystalloid cardioplegic solution was applied. Core cooling was used to maintain the difference in inflow and outflow blood temperature within 5°C . The nasopharyngeal core temperature was reduced to 20°C with an average cooling time of 17.5 ± 1.2 minutes and was maintained around 20°C with intermittent cooling of infused solution, whose temperature was around 18°C (control CPB). Then retrograde cerebral perfusion was established by perfusion of blood through cannulas in both internal maxillary veins with separate pumps to maintain a nasopharyngeal core temperature around 20°C with intermittent cooling of inflow blood. The aortic cannula was opened and directed by gravity to the cardiotomy reservoir while both caval cannulas were clamped (Fig. 1). The pump circuit consisted of a Capiiox 0.8 m² oxygenator with a cardiotomy reservoir (BPC-350, Aika Medical Corp., Matsudo City, Japan) primed with electrolyte solution and 500 ml of blood obtained from another dog. No intervention was made to control blood pressure during this study.

Experimental protocol. CPB was begun at a flow rate of 1000 ml/min. The animal was cooled to a nasopharyngeal temperature of 20°C and its temperature was maintained around 20°C with intermittent cooling of inflow blood (control CPB). Then perfusion was switched to retrograde cerebral perfusion

Fig. 1. Perfusion and drainage in retrograde cerebral perfusion through an SVC cannula. Only the aortic cannula (AO) was opened and directed by gravity to the cardiotomy reservoir while the caval cannulas were clamped. Returned blood (dark gray) was perfused through an oxygenator into both the internal maxillary venous cannulas with a separate pump (light gray).

while the external jugular venous pressure was monitored. During retrograde cerebral perfusion, external jugular venous pressure was varied from 15 to 20, 25, 30, and 35 mm Hg consecutively at 10-minute intervals. During each interval, external jugular venous pressure was maintained to be a certain pressure with varying perfusion flow rates. At the end of each period, the blood pressure in each catheter was recorded and blood was sampled from the inflow and outflow cannulas. Flow rate of blood returning from the aorta was measured directly. The CSF pressure and CBF were measured simultaneously. After each procedure the skull was opened and blood perfusion via each internal maxillary vein was observed directly to detect the interruption by venous valves.

Analysis. Blood pressure and CSF pressure were measured by a blood pressure monitor (HP7835, Hewlett-Packard Company, Andover, Mass.) with disposable transducers (SCK7178, Viggo Spectramed Co. Ltd., Singapore). The zero level was adjusted at the operating table. Perfusion flow was calculated by the numbers derived from the pump rotation rate, which was calibrated with each pump circuit system after each procedure. The blood samples were drawn into heparinized syringes, placed immediately on ice, and analyzed at 37°C for pH, oxygen tension, carbon dioxide tension, oxygen saturation, oxygen content, total carbon dioxide, and hemoglobin with the ABL-300 analyzer (Radiometer A/S, Copenhagen, Denmark). CBF was measured with the RBF-2 meter (Biomedical Science, Inc., Kanazawa, Japan) by the hydrogen clearance method.^{2,3} The CBF was calculated by subtracting blood flow at total circulatory arrest.

Fig. 2. Returned blood flow rates and perfusion blood flow rates during hypothermic (20° C) cardiopulmonary bypass at 1000 ml/min (CPB) and hypothermic (20° C) retrograde cerebral perfusion (RCP) at an external jugular venous pressure of 15, 20, 25, 30, or 35 mm Hg. N.S., Not significant.

Fig. 3. Pressures in the brachiocephalic artery, external jugular vein, and femoral vein during hypothermic (20° C) retrograde cerebral perfusion (RCP) at an external jugular venous pressure of 15, 20, 25, 30, or 35 mm Hg.

Calculation. Total vascular resistance (R) was calculated by the following formula:

$$R = 79920 \times (P_i - P_o) / Q \text{ (dynes} \cdot \text{sec} \cdot \text{cm}^{-5}\text{)}$$

where P_i is external jugular venous pressure, P_o is brachiocephalic arterial pressure, and Q is flow rate (ml/min) of blood returning via the aortic cannula during retrograde cerebral per-

fusion and where P_i is brachiocephalic arterial pressure, P_o is central venous pressure, and Q is 1000 ml/min at control CPB.

Oxygen consumption (CMO_2) was calculated from the equation:

$$CMO_2 = (O_2CTf - O_2CTr) \times Q / 100 \text{ (ml/min)}$$

where O_2CTf is the oxygen content of perfused blood, O_2CTr

Fig. 4. Cerebrospinal fluid pressure during hypothermic (20° C) cardiopulmonary bypass at 1000 ml/min (CPB) and hypothermic (20° C) retrograde cerebral perfusion (RCP) at an external jugular venous pressure of 15, 20, 25, 30, or 35 mm Hg. N.S., Not significant.

is the oxygen content of returned blood, and Q is the flow rate (ml/min) of blood returning via the aortic cannula during retrograde cerebral perfusion and 1000 ml/min at control CPB.

Exudation of carbon dioxide (EXCO₂) was calculated by the formula:

$$ExCO_2 = (tCO_{2r} - tCO_{2f}) \times Q / 1000 \text{ (mmol/min)}$$

where tCO_{2f} is the carbon dioxide content of perfused blood, tCO_{2r} is the carbon dioxide content of returned blood, and Q is the flow rate (ml/min) of blood returning via the aortic cannula during retrograde cerebral perfusion and 1000 ml/min at control CPB.

Results are expressed as the mean ± standard deviation and statistical significance was determined by means of the paired *t* test.

Results

Blood flow. During hypothermic retrograde cerebral perfusion with the external jugular venous pressure at 25 mm Hg, flow rate of blood returning via the aorta was 164 ± 53 ml/min and perfusion blood flow rate was 185 ± 46 ml/min, rates which were only one sixth of the control CPB. The aortic return blood flow rate was smaller than perfusion flow rate due to bleeding, blood retention into the liver or spleen, or making ascites retention, and it varied in proportion as did external jugular venous pressure (Fig. 2).

Blood pressure. During hypothermic retrograde cerebral perfusion with an external jugular venous pressure of 25 mm Hg, the femoral venous pressure was also increased (14.4 ± 3.6 mm Hg) and exceeded the bra-

Fig. 5. Relation between cerebrospinal fluid pressure and external jugular venous pressure during hypothermic (20° C) retrograde cerebral perfusion.

chiocephalic arterial pressure (9.0 ± 2.9 mm Hg). The difference between the external jugular venous pressure and the brachiocephalic arterial pressure increased as the external jugular venous pressure increased (Fig. 3).

CSF. The CSF pressure was lower than the external jugular venous pressure (19.2 ± 4.5 mm Hg versus 24.8 ± 2.4 mm Hg) but also increased in parallel with

Fig. 6. Whole-body vascular resistance during hypothermic (20° C) cardiopulmonary bypass at 1000 ml/min (CPB) and hypothermic (20° C) retrograde cerebral perfusion (RCP) at an external jugular venous pressure of 15, 20, 25, 30, or 35 mm Hg. N.S., Not significant.

Fig. 7. Cerebral tissue blood flow of 100 gm wet volume during hypothermic (20° C) cardiopulmonary bypass at 1000 ml/min (CPB) or hypothermic (20° C) retrograde cerebral perfusion (RCP) at an external jugular venous pressure of 15, 20, 25, 30, or 35 mm Hg. N.S., Not significant.

any increase in the external jugular venous pressure (Fig. 4). The CSF pressure remained lower than 25 mm Hg so long as the external jugular venous pressure was lower than 25 mm Hg (Fig. 5).

Total vascular resistance. Total vascular resistance

did not change significantly from CPB to retrograde cerebral perfusion and did not change significantly under various retrograde cerebral perfusion conditions (Fig. 6).

CBF. Hypothermic retrograde cerebral perfusion with an external jugular venous pressure of 25 mm Hg provid-

Fig. 8. Whole-body oxygen consumption calculated during hypothermic (20° C) cardiopulmonary bypass at 1000 ml/min (CPB) and hypothermic (20° C) retrograde cerebral perfusion (RCP) at an external jugular venous pressure of 15, 20, 25, 30, or 35 mm Hg. *N.S.*, Not significant.

Fig. 9. Carbon dioxide elimination during hypothermic (20° C) cardiopulmonary bypass at 1000 ml/min (CPB) and hypothermic (20° C) retrograde cerebral perfusion (RCP) at an external jugular venous pressure of 15, 20, 25, 30, or 35 mm Hg. *N.S.*, Not significant.

ed about half the CBF provided by hypothermic controlled CPB (13.7 ± 7.9 versus 32.7 ± 8.5 ml/min per 100 gm). CBF decreased significantly as the external jugular venous pressure decreased from 25 to 15 mm Hg;

however, it did not increase significantly as the external jugular venous pressure increased from 25 to 35 mm Hg (Fig 7).

Oxygen consumption. During hypothermic retro-

grade cerebral perfusion with an external jugular venous pressure of 25 mm Hg, the oxygen consumption was one quarter of that during hypothermic control CPB (3.4 ± 0.7 versus 12.7 ± 5.6 ml/min). The oxygen consumption varied in proportion to the external jugular venous pressure. It decreased significantly in decrements of 5 mm Hg from an external jugular venous pressure of 25 mm Hg. However, it increased significantly only in increments of 10 mm Hg when external jugular venous pressure was higher than 25 mm Hg (Fig. 8).

Elimination of carbon dioxide. The elimination of carbon dioxide during hypothermic retrograde cerebral perfusion with an external jugular venous pressure of 25 mm Hg was one quarter of that during hypothermic control CPB. The elimination of carbon dioxide varied in proportion to the change in the external jugular venous pressure. It increased significantly in increments of 5 mm Hg when the external jugular venous pressure was lower than 25 mm Hg; however, significant increase was observed only in increments of 10 mm Hg when the external jugular venous pressure exceeded 25 mm Hg (Fig. 9).

Discussion

Protection of the brain is of great importance when the cerebral circulation is interrupted during operations on the aortic arch. Deep hypothermic circulatory arrest or isolated cerebral perfusion has been commonly used to protect the brain.⁴⁻⁸ However, neither technique is entirely satisfactory. Retrograde perfusion through an SVC cannula is a new technique used to protect the brain during circulatory arrest. It was first used to manage massive air embolism during CPB.⁹ As a technique for protecting the brain, retrograde cerebral perfusion was first reported by Lemole and Ueda.^{10,11} We have been using retrograde cerebral perfusion during operations on the aortic arch since January 1990.

The patient is cooled to a nasopharyngeal core temperature of 20° C during normograde CPB. Then retrograde cerebral perfusion is performed by infusing via the SVC cannula and draining via the aortotomy while the inferior vena cava (IVC) is clamped and while SVC pressure is being monitored. We maintain a nasopharyngeal core temperature around 20° C with intermittent cooling of infused solution and also maintain SVC pressure around 30 mm Hg while controlling inflow rate. However, the optimum pressure for retrograde cerebral perfusion is not clear. We¹ have already reported that retrograde cerebral perfusion can provide blood and oxygen to both the brain and the body and that this perfusion may reduce ischemic damage to the brain. In this study,

we sought to determine the optimum parameters for retrograde cerebral perfusion.

We found that CSF pressure varied in parallel with external jugular venous pressure. CBF, however, did not increase significantly as external jugular venous pressure increased over 25 mm Hg. Venous pressure, arterial pressure, intracranial pressure, and cerebral vascular resistance are principal factors to reflect CBF during retrograde cerebral perfusion. As venous pressure, a driving pressure during retrograde cerebral perfusion, increases, cerebral tissue blood flow should be increased. However, high venous pressure is associated with high intracranial pressure, which restricts CBF. Therefore, CBF does not increase once the external jugular venous pressure exceeds 25 mm Hg. According to the Monro-Kellie doctrine, the amount of the brain, CSF, and intracranial blood does not change at any time because of a certain volume in the intracranial space, and CSF pressure is almost equal to intracranial venous pressure at any time. Therefore, as venous pressure increases, CSF pressure increases simultaneously and high intracranial pressure compresses the vascular vessels and decreases CBF.

CSF pressure represents the pressure of the intercellular space in the brain. Therefore, high venous pressure is associated with high intercellular fluid pressure, which may cause brain edema. Any CSF pressure that exceeds 17.5 mm Hg or 200 cm H₂O may be associated with brain edema.

As external jugular venous pressure increased, so did oxygen consumption. However, CBF did not increase once venous pressure exceeded 25 mm Hg. Increase of oxygen consumption, when external jugular venous pressure exceeded 25 mm Hg, may reflect an increase of blood flow except to the brain. It is important, therefore, that the optimum venous pressure for retrograde cerebral perfusion, the lowest pressure that provides effective CBF and the highest pressure under which brain edema does not result, be determined. We believe that a venous pressure of 25 mm Hg can be used safely with the maximum CBF.

During retrograde cerebral perfusion, a high SVC system pressure is associated with a high IVC system pressure, and both are higher than that in the arterial system. This indicates that the SVC communicates well with the IVC system and that blood infused through the SVC may also perfuse visceral organs. This may be an added advantage to the use of retrograde cerebral perfusion. However, flow rate of blood returning via the aortic cannula was smaller than perfusion flow rate despite blood loss resulting from bleeding. This fact may indicate that blood is retained in the body, causing hepatic and splenic distention. Portal venous pressure was almost equal to

femoral venous pressure and also increased in parallel with SVC system pressure (unpublished data). It causes ascitis, which results in circulatory volume loss.

Inasmuch as the aortic cannula is directed by gravity to the cardiectomy reservoir during retrograde cerebral perfusion, aortic root pressure presumably would be zero. However, average brachiocephalic arterial pressure was 9 mm Hg at an external jugular venous pressure of 25 mm Hg. According to the Monro-Kellie doctrine, as intracranial pressure increases, pressure in any intracranial vessels increases. This may be one of the reason that brachiocephalic arterial pressure was high.

In this study CBF was measured by the hydrogen clearance technique, a standard technique that has been confirmed by many studies. We also measured CBF by the colored microsphere method, which consists of 50 μ m of microspheres, in another 12 dogs (unpublished data.). Tissue blood flow of the cerebral cortex in the midparietal lobe, which was measured by the colored microsphere method, was 36.2 ± 16.9 ml/min per 100 gm at hypothermic control CPB and 11.0 ± 10.5 ml/min per 100 gm at hypothermic retrograde cerebral perfusion with an external jugular venous pressure of 25 mm Hg. These values were almost same as those measured by the hydrogen clearance method.

Whole-body oxygen consumption decreases greatly as body temperature decreases,¹²⁻¹⁵ and deep hypothermia can minimize ischemic damage to the brain. A safe duration of circulatory arrest during deep hypothermia was reported to be 45 to 60 minutes.¹⁶⁻¹⁹ Retrograde cerebral perfusion at an external jugular venous pressure of 25 mm Hg can supply one quarter of the oxygen provided by CPB at 1000 ml/min and may also minimize ischemic damage to the brain. Deep hypothermic retrograde cerebral perfusion, therefore, should extend the period of time during which the cerebral circulation may be safely interrupted. Retrograde cerebral perfusion can also be used to lower brain temperature. The brain temperature was measured in six dogs in this study. During retrograde cerebral perfusion the brain can be maintained at a certain temperature, which is almost the same as the nasopharyngeal core temperature, with intermittent cooling of the infusion solution. This may be yet another advantage for retrograde cerebral perfusion.

In this study, blood was perfused directly into the temporal sinus bilaterally via the internal maxillary veins to avoid venous valves that would interfere with retrograde perfusion.^{20, 21} Blood perfusion via each internal maxillary vein was observed directly after each procedure to confirm no interference by venous valves. The dog, which has a small internal jugular vein with many venous valves,

is not a good model for retrograde cerebral perfusion.²² Nevertheless, this experimental study may suggest some parameters for using retrograde cerebral perfusion in human beings.

Retrograde cerebral perfusion can be performed without clamping or cannulating the cervical arteries. It should reduce any chance of cerebral thrombosis and also provide a better operative field. Retrograde cerebral perfusion can extend the duration of safe cerebral circulatory arrest; however, there is a limit to this duration of circulatory arrest and, furthermore, high venous pressures may cause brain edema.

This study was prepared in consultation with a statistician, Nobuyuki Hamajima, MD.

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