Surgery of the thoracic aorta with hypothermic circulatory arrest: experience with retrograde perfusion via the superior vena cava and demonstration of cerebral perfusion

Abstract  Objective. Retrograde cerebral perfusion (RCP) via the superior vena cava has been described as an adjunctive technique to enhance the safety of hypothermic circulatory arrest (HCA), but perfusion of cerebral tissue in humans during RCP has not been demonstrated to date. We report our clinical experience with RCP and our attempt to demonstrate "true" perfusion of the brain.

Methods. Between April 1993 and June 1995, 49 thoracic aortic procedures were performed in 48 patients (male:female = 26:22) (emergency: elective= 25:24). The indications for surgery were acute type "A" dissection (18), chronic aneurysm (28), and infected valved conduit (3). Hypothermic circulatory arrest (15 °C) and RCP were implemented in all cases (mean HCA time 29 min, range 11–69) (mean RCP time 26 min, range 10–65). The indications for surgery were acute type "A" dissection (18), chronic aneurysm (28), and infected valved conduit (3). Hypothermic circulatory arrest (15 °C) and RCP were implemented in all cases (mean HCA time 29 min, range 11–69) (mean RCP time 26 min, range 10–65). The 99mTc-Technetium labelled brain perfusion agent d,l hexamethyl propylene amine oxime (99mTc-HMPAO) was administered (100 MBq) into the cardiotomy reservoir following institution of HCA (15 °C) in three consecutive patients and planar dynamic brain imaging with a portable gamma camera was commenced at the start of RCP.

Results. Six hospital deaths (12.2%) occurred in the emergency group due to atheromatous embolic stroke in one patient, sepsis in one, ruptured infrarenal aortic aneurysm in one, myocardial failure in one, renal failure in one, and multi-system organ failure in one patient. The remaining patients suffered no major neurological complications (median Intensive Care Unit stay 1 day, range 1–5). Inspection of the images acquired showed 99mTc-HMPAO activity spreading quickly from the jugular bulb and the superior sagittal sinus throughout the cerebral white and gray matter. Time-activity curves calculated for both cerebral hemispheres showed homogeneous regional cerebral perfusion.

Conclusions. Retrograde cerebral perfusion is easy to establish, "safe" and provides blood flow to the brain during HCA. The flow quantification and metabolic contribution of RCP require further investigation.

Key words  Aortic arch replacement · Hypothermic circulatory arrest · Retrograde cerebral perfusion
Introduction

Hypothermic circulatory arrest (HCA) has been widely used for brain protection during the surgical repair of atherosclerotic disease or dissection involving the ascending and arch segments of the aorta. Although the depression of cerebral metabolism by anaesthesia and deep hypothermia protects against cerebral injury during short periods of circulatory arrest, a period of cerebral ischaemia exceeding 45 min has been associated with a higher incidence of stroke, while circulatory arrest periods exceeding 65 min have been associated with increased mortality [15]. This restriction has led to the development of adjunctive and alternative techniques to augment cerebral protection during HCA, such as retrograde cerebral perfusion (RCP) via the superior vena cava (SVC) [7, 17]. Different mechanisms of protection have been postulated for RCP when used in conjunction with deep hypothermia. These include the optimisation of cerebral metabolic function of oxygenation and removal of catabolic products, maintaining a low brain temperature and the flushing of gaseous and particulate microemboli from the arterial tree before the reinstitution of antegrade perfusion [12, 17, 18, 20]. Some of these hypotheses are based on the assumption that blood perfused retrogradely through the SVC actually reaches the cerebral tissue. While some experimental studies have demonstrated cerebral perfusion occurring during RCP [3, 19], by contrast, others have found that no cerebral perfusion occurs with this technique [2]. We describe our clinical experience with RCP and report three cases where cerebral perfusion during RCP was demonstrated in humans using the $^{99m}$Technetium labelled brain perfusion agent di-hexamethyl propylene amine oxime ($^{99m}$Te-HMPAO), and imaging with a portable gamma camera in the opening theatre.

Material and methods

Patients

This report details 49 operations on the ascending aorta, the arch or both, performed in 48 patients (mean age 62 years, range 25–81) (26 male and 22 female) between April 1993 and June 1995. It represents a consecutive series of cases requiring HCA. The indications for surgery (emergency in 25 cases) are illustrated in Table 1. A summary of the types of operation performed is illustrated in Fig. 1. Eight patients required concomitant coronary artery revascularisation, and one patient underwent concomitant replacement of an innominate artery aneurysm.

Cardiopulmonary bypass and retrograde cerebral perfusion

A standard cannulation technique was adopted for all the cases, allowing the option of RCP if judged necessary. The basic perfusion circuit comprised a 1/2" venous line and a 3/8" arterial segment. Cannulation for cardiopulmonary bypass was undertaken with separate SVC and inferior vena cava (IVC) cannulae and a left ventricular vent, returning the aterialised blood to the right femoral artery. A parallel 1/4" cannula was connected between the arterial return and the IVC cannula by means of "Y" connections, primed and clamped at both ends. A membrane oxygenator (Compact-flo, Dideco, Mirandola (MO), Italy) was used and the circuit was primed with compound sodium lactate solution. Bypass was instituted with non-pulsatile flows of 2.4 l/min per m$^2$ and a mean arterial pressure of 50–60 mmHg was maintained. The body was cooled to a nasopharyngeal temperature of 15 °C with gradual reduction in the systemic flow as the nasopharyngeal temperature decreased. Continuous intraoperative electroencephalogram (EEG) monitoring is not currently available at our institution, and thus a core temperature nadir of 15 °C was used in all cases. During this period mobilisation of the aorta was undertaken. The aorta was clamped and myocardial protection achieved by antegrade infusion of 1 l of crystalloid cardioplegia solution (St. Thomas I). A snare was placed around the SVC cannula. At a nasopharyngeal temperature of 15 °C the circulation was arrested, ice packs were placed around the head, the arterial cannula was clamped and the blood was drained into the bypass reservoir. The SVC was isolated from the venous circulation and the clamp from the parallel arterial line was removed. Venous drainage from the IVC was allowed throughout. Retrograde cerebral perfusion was then commenced with the flow adjusted to keep a left jugular bulb pressure around 25 mmHg, measured by a dedicated single lumen retrograde internal jugular venous cannula isolated from drug infusions. Flow rates of 300–700 ml/min are achieved with this method. Effluent blood at the head vessels', ostia was returned to the reservoir by suction from within the open arch.

All the patients received thiopentone (5 mg/kg), mannitol (1 g/kg) and dexamethasone (100 mg) prior to circulatory arrest. The alpha-stat method of pH control was used and hyperglycaemia treated by intravenous insulin infusion. Further details of our perfusion protocol may be found in the report of our earlier experience with RCP [10].

Intraoperative brain perfusion scan

The protocol was approved by the local hospital ethics committee and by the Administration of Radioactive Substances Advisory Committee. Informed consent was obtained from the patients studied.

Prior to circulatory arrest, a portable gamma camera (Siemens LEM+) linked to a dedicated nuclear medicine computer system (Gamma 11) was placed anterior to the head of the patient. Following HCA and immediately prior to commencing RCP, $^{99m}$Te-HMPAO

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Indications for surgery</th>
<th>No.</th>
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<tbody>
<tr>
<td>Acute type &quot;A&quot; dissection</td>
<td>18</td>
<td></td>
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<tr>
<td>Chronic type &quot;A&quot; dissection (a)</td>
<td>5</td>
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<tr>
<td>Chronic aneurysm (b)</td>
<td>12</td>
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<tr>
<td>Megaaorta syndrome (c)</td>
<td>8</td>
<td></td>
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<tr>
<td>Infected valved conduit (d)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Patent ductus arteriosus + sinus Valsalva aneurysm</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Aberrant right subclavian artery aneurysm</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

a: 1 patient with acute left ventricular failure
b: 1 patient with concomitant acute type B aortic dissection; 1 patient with acute respiratory failure due to left main bronchus compression
c: 1 patient with unstable angina
d: all patients with septic shock
Fig. 1 Aortic segments replaced (in white) in the patient population (ET elephant trunk procedure, PDA patent ductus arteriosus, RSA right subclavian artery. Other n = 3; PDA&SV aneurysm = 1, Aberant RSA aneurysm = 1, Total aortic replacement = 1)

![Diagram of aortic segments and root configurations](image)

Fig. 2 Frontal planar image 3 min after commencement of RCP in patient #1. $^{99m}$Tc-HMPAO activity is mainly seen in the right jugular bulb, superior sagittal sinus and transverse sinus

Fig. 3 $^{99m}$Tc-HMPAO activity can be seen throughout the cerebral white and gray matter with diminution in the superior sagittal sinus, 10 min after commencement of RCP in patient

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99mTc-Technetium labelled brain perfusion agent dl, hexamethyl propylene amine oxime ($^{99m}$Tc-HMPAO, Amersham International Amersham, UK), were administered into the cardiotomy reservoir and allowed to diffuse. Planar dynamic brain imaging was commenced when the first sign of activity was seen in the SVC. Images were acquired every 2 s for the first 2 min and every minute thereafter for the duration of RCP.

Results

Retrograde cerebral perfusion was adopted in all cases with a mean flow rate of 310 ml/min (range 100–700). No RCP-related complications occurred. Details of the procedures performed are illustrated in Fig. 1. The mean cardiopulmonary bypass time was 163 ± 34 min (range 92–231 min), the mean aortic cross-clamp time was 95 ± 29 min (range 20–180 min), the mean HCA time was 29 ± 13 min (range 11–69 min) and the mean RCP time was 26 ± 11 min (range 10–65 min).

Mortality

Six postoperative deaths occurred (12.2%) in patients requiring emergency operations. In one patient with widespread soft atheromatous disease within the aortic arch, death occurred as a consequence of multi-embolic atheromatous stroke as confirmed by postoperative computed tomographic scan. The causes of death in the remaining five patients were persistent sepsis and renal failure in one, rupture of infrarenal aortic aneurysm in one, myocardial failure in one, renal failure in one and multi-system organ failure in the last patient. Four patients of this group awoke from surgery neurologically intact and the patient who died...
of myocardial failure was electively sedated during the postoperative period and therefore no neurological assessment was possible.

Neurological morbidity

Three patients suffered transient postoperative confusion, which resolved spontaneously within 24 h from extubation. One patient suffered transient dysphasia, and one patient suffered transient hemiparesis. All the remaining patients awoke from surgery with no neurological complications. Taking all patients into account, the incidence of new postoperative permanent neurological deficit was minimal. The median stay in the intensive care unit for all the survivors was 1 day (range 1–5 days). At follow-up (mean 15 months, range 1–26 months) two patients had died (stroke and myocardial infarction, respectively) and all the survivors were in New York Heart Association class I or II.

Discussion

Despite the widespread use of HCA during surgery for complex proximal aortic pathology, the optimal level of hypothermia and the "safe" duration of circulatory arrest have not yet been defined. Clinical experience suggests that when the duration of HCA is kept below 45 min at core temperatures of 15°–20°, a lower incidence of neurological complications is recorded, while stroke and mortality rates are increased with longer periods of HCA [15]. Even with safe periods of circulatory arrest, manifest brain in-
jury occurs in up to 15% of adults [4, 6], indicating that HCA alone does not provide adequate cerebral protection for all patients. This may be due to the variability of the cerebral metabolic state at the range of temperatures considered safe by many clinicians [5].

A number of strategies have therefore been developed to increase the safety limits of HCA and to optimise cerebral protection, even during operations requiring shorter arrest times. These include the use of different pharmacological “cerebroprotective” agents [14, 20], optimisation of pH control during the hypothermic period [16], maintenance on normoglycaemia [11] and attempts to provide cerebral perfusion during the arrest period antegradely [1] via the supraaortic vessels, or retrogradely via the SVC [7, 17]. Although the use of selective antegrade cerebral perfusion may have the advantage of being physiological, its implementation requires direct cannulation of the supraaortic vessels with multiple cannulae, thus potentially increasing the risk of embolisation from aortic manipulation and from the cannulation procedure. The difficulty in identifying the vessel lumen responsible for the distal perfusion in the presence of acute or chronic aortic dissection and the reduction of the operative field caused by the presence of tubings and extra clamps add to the potential limitations of this technique.

Retrograde perfusion via the SVC, originally described as a method to clear accidental air embolism occurring during cardiopulmonary bypass [9], has been used as a method of enhancing cerebral protection during HCA. This technique can be implemented by adopting a simple modification of the cardiopulmonary bypass circuit and has been used in association with profound hypothermia in an increasing number of patients, with no related complications reported to date, thus demonstrating its feasibility and safety. In addition, RCP allows the performance of an “open distal anastomosis” technique [8] without the need to apply vessel clamps and with better exposure and no anatomical distortion, thus making the performance of the anastomosis potentially easier and safer. The rationale for the use of RCP include the possibility that it may optimise cerebral metabolic function by providing oxygen and removing catabolic products, may keep a constant temperature and even cooling of the brain and flush particulate and gaseous microemboli from the arterial tree prior to re-institution of antegrade flow. The confirmation of these hypothesised mechanisms of action rests on the demonstration that cerebral blood perfusion occurs when blood is retrogradely perfused via the SVC.

In our study we adopted $^{99m}$Tc-HMPAO as a brain perfusion agent. This is a lipophilic compound that freely diffuses across the blood-brain barrier and is routinely used for clinical brain imaging. Within the brain it becomes intracellularly bound either by a change in lipophilicity or binding to intracellular components [3]. It is useful for perfusion imaging as its deposition is proportional to blood flow during the first pass through the cerebral circulation and it has a very slow washout rate, thus acting as a chemical microsphere [3]. Although single photon emission tomography (SPECT) would have provided more information on the regional distribution of blood flow, this was not possible in the context of the operating theatre. However, planar imaging with time-activity curve analysis was sufficient to demonstrate conclusively that cerebral perfusion occurred in the three patients studied.

Activity can be seen in the entire brain (Fig. 3) during RCP; if RCP had provided only perfusion of the brain surface, the images would have resembled the “hot shell” appearance of the scalp of a bone scan study. The analysis of time-activity curves (Fig. 4) for both cerebral hemispheres, taking into account the in vivo properties of $^{99m}$Tc-HMPAO, provides further confirmation of cerebral tissue perfusion by RCP. These curves demonstrate the continuous accumulation of activity for the duration of RCP, indicating extraction from the vascular compartment. If such extraction had not occurred, the time-activity curves would have resembled the one for the vascular background, with an early plateau on achievement of constant blood concentration, without further changes with time. Finally, although quantitative information on regional perfusion cannot be deduced from the technique used, the analysis of the time-activity curves for the second patient (Fig. 4) shows less activity than the one recorded in the first patient. This difference could be explained by a number of factors, including the presence of anatomical constraints to retrograde caval perfusion in some patients, the different cerebral metabolic rates among the patients studied, even at similar core temperatures, or the instability of the $^{99m}$Tc-HMPAO molecule with time.

![Distribution of Circulatory Arrest Times](https://academic.oup.com/ejcts/article-abstract/10/10/833/477343/77343)
Although this preliminary study on a small number of patients confirms that blood perfused retrogradely through the SVC does reach the cerebral tissue, there is no definitive demonstration that RCP enhances cerebral protection during HCA. In all the reported series, including ours, the mean circulatory arrest time is within the limits considered safe when using HCA alone (Fig. 5). No study has yet compared the neurological outcome of patients with and without RCP in a prospective, randomised and objective way. In addition, even if RCP provides a degree of cerebral blood flow, the question of whether this amount of flow is sufficient to meet the metabolic demands of the brain remains unanswered.

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References
Dr. H. Borst (Hannover, Germany): Dr. Pagano, there has been some evidence recently for some metabolic support, in addition to driving out emboli and gas from the brain, and this of course would be a very important advantage of this method.

Dr. A. Ergin (New York): Dr. Borst, thank you for the opportunity to discuss this paper. I have been an open-minded skeptic or retrograde cerebral perfusion since its inception. Again I rise to point out the discrepancy between what we know that does not happen experimentally and what we think that happens clinically. In spite of very carefully performed experimental studies, including work from the President’s laboratory, using different animal models and different perfusion markers for the brain, I have yet to see one study that proves without a question that the brain does, in fact, receive clinically adequate blood flow during retrograde cerebral perfusion.

So my question concerns the accuracy of the method that you have used in detecting brain perfusion in your clinical study. Is the spatial resolution of your method such that you can differentiate between true brain perfusion, that is, isotope delivered to tissues per unit of time versus the isotope that sits in the venous pool elsewhere in the cranium, or that slowly accumulates in the brain tissue by passive diffusion.

Dr. Pagano: We used a gamma camera in theater, equipped with a general purpose collimator which gives a good compromise between sensitivity and spatial resolution. We used an agent (99mTc-HMPAO) that acts as a chemical microsphere and is normally used for clinical brain perfusion scanning. It can be used also to quantify cerebral blood flow, but single photon emission techniques are logistically difficult to implement in theater. However, if we look at the time-activity curves for patient number 1, we can see that while the vascular background curve has reached a plateau, the curves for the cerebral hemispheres show continuous accumulation of activity, indicating that metabolic trapping is occurring in the cerebral matter and demonstrating cerebral tissue perfusion. To settle the issue of cerebral metabolic support with retrograde cerebral perfusion, we need other investigations. I think that future research is a field should concentrate on humans, as the variability of results obtained in animals may underline the limitations of these experimental models.

Dr. A. Arbulu (Detroit, Michigan): I think that it is very difficult to assess the metabolic problems in humans. First I would like to make a comment. In the past 3 years we have operated upon 16 patients with retrocerebral perfusion and circulatory arrest. The longest period was in a 79-year-old gentleman who was arrested and in retrocerebral perfusion for 119 min. He had no problems. In all our survivors, we have seen no neurological problem. Of our 16 patients, 10 were elective and we didn’t lose any of these patients; one was a redo patient who died, and then there were five acute dissections, two of these patients died.

Interestingly enough, we had two cases where the distal arch was involved and also the descending thoracic aorta, and we cannulated the left internal jugular vein for retrograde cerebral perfusion, approaching the aneurysm from a left thoracotomy.

My question is, what was the longest time a patient of yours was on circulatory arrest and in retrograde cerebral perfusion? Thank you very much.

Dr. Pagano: In our series the longest circulatory arrest was 60 min.