Preliminary Report

Cerebral protection using retrograde cerebral perfusion during hypothermic circulatory arrest

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Background: Retrograde cerebral perfusion through the superior vena cava (SVC) has been proposed to protect the brain from ischaemic injury during profound hypothermic circulatory arrest (PHCA). Its contribution to cerebral protection is unclear. Furthermore, the addition of anaesthetic or vasodilating agents to the SVC perfusate to enhance brain protection, has never been described.

Methods: In three patients undergoing repair of the ascending aorta utilizing PHCA, the upper body was retrogradely perfused with cold (16°C) blood through the SVC by the cardiopulmonary bypass pump. Electroencephalographic activity was monitored using a computerized electroencephalographic monitor (Cerebro Trac 2500, SRD). Perfusion pressure was measured at a port in the cannula connector. Etomidate or thiopentone was injected into the SVC perfusate to arrest reappearing electroencephalographic activity. Nitroglycerin or nitroprusside was injected into the perfusate to increase retrograde flow and maintain a constant perfusion pressure.

Results: During PHCA periods of up to 61 min, recurrent electroencephalographic activity was abolished by the retrograde administration of small boluses of etomidate (total 50 mg) or thiopentone (total 500 mg). Nitroprusside (100 µg) and nitroglycerin (2 µg·kg⁻¹·min⁻¹) increased retrograde flow from 220 to 550 and 660 ml·min⁻¹, respectively, while maintaining perfusion pressure (25–26 mmHg). Recovery from anaesthesia and surgery was uneventful, with no adverse neurological sequelae.

Conclusion: Injection of anaesthetic agents into the retrograde SVC perfusate during PHCA, can suppress reoccurring electroencephalographic activity and retrograde injection of vasodilators can facilitate an increase in perfusion. It is suggested that both may augment brain protection.

Objectif : La perfusion cérébrale rétrograde par la veine cave supérieure (VCS) pourrait protéger le cerveau de l'ischémie pendant l'arrêt circulatoire en hypothermie profonde (ACHP) mais cette hypothèse n'est pas prouvée. En outre, on n'a jamais rapporté non plus que les agents anesthésiques ou vasodilatateurs ajoutés au liquide de perfusion de la VCS amplifiaient la protection cérébrale.

Méthodes : Au cours d'une réparation de l'aorte ascendante sous ACPH, on a perfusé la partie supérieure du corps de trois patients par voie rétrograde avec du sang froid (16°C) par la VCS à l'aide d'une pompe de circulation extracorporelle. Un moniteur informatisé (Cerebro Trac 2500, SRD) a servi à monitorer l'activité électroencéphalographique. La pression de perfusion était mesurée par un orifice situé sur la canule. L'activité électroencéphalographique était interrompue par l'injection dans le liquide de perfusion de la VCS d'étomidate et de thiopental. Le nitroprussiate et la nitroglycérine étaient ajoutés au perfusé afin d'augmenter le flux rétrograde et maintenir constante la pression de perfusion.

Résultats : L'administration rétrograde de petits bolus d'étomidate (total 50 mg) ou de thiopental (total 500 mg) a aboli la reprise de l'activité électroencéphalographique pendant 61 min d'ACPH ou moins. Le nitroprussiate (100 µg) et la nitroglycérine (2 µg·kg⁻¹·min⁻¹) ont accru le flux rétrograde de 220 à 550 et à 660 ml·min⁻¹ respectivement, tout en maintenant la pression de perfusion constante (25–26 mmHg). La récupération anesthésique et chirurgicale s'est déroulée sans problèmes ni séquelles neurologiques.

Conclusion : L'injection d'agents anesthésiques dans le liquide de perfusion rétrograde de la VCS pendant l'ACPH peut supprimer la reprise de l'activité électroencéphalographique. L'injection rétrograde de vasodilatateurs peut favoriser l'augmentation de la perfusion. Ces deux interventions pourraient accroître la protection cérébrale.

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PROFOUND hypothermic circulatory arrest (PHCA) is used in adults for the repair of dissection or aneurysms of the ascending aorta or aortic arch.^{1,2} Core temperature is lowered slowly during cardiopulmonary bypass (CPB) to approximately 16°C in order to reduce cerebral energy requirements. The development of an isoelectric electroencephalogram (EEG) indicates a maximum reduction in cerebral metabolism.³ However, increased cerebral ischaemic time is associated with increased incidence of adverse neurological sequelae.⁴ Therefore, retrograde cerebral perfusion (RCP) through the superior vena cava (SVC) has been proposed to facilitate cerebral protection during PHCA.⁵⁻⁸ In this method, cold, oxygenated blood is retrogradely pumped by the CPB pump to the upper body through a SVC cannula. The blood returns to the surgically opened aorta through the carotid and subclavian arteries, and is collected by the sump tube to the CPB pump. Since some of the infused perfusate may be diverted to alternative low resistance vascular beds,⁹ the extent of cerebral perfusion and the efficiency of neural tissue oxygenation are unclear.

In an attempt to potentiate RCP efficacy, we have used the SVC perfusate as a route to administer anaesthetic agents and vasodilators to our patients' cerebral circulation. Our initial experience in three patients forms the basis for this report.

Case reports

The first patient was a 78-yr-old, male, heavy-smoker with chronic obstructive lung disease, recent inferior wall myocardial infarction and ongoing angina pectoris. Coronary angiography disclosed three vessel disease and he was anaesthetized for coronary artery bypass grafting. Ascending aortic and right atrial cannulation was employed for CPB. Flow rate was 2.2 L·m⁻²·min⁻¹ and the patient was cooled to rectal and oesophageal temperatures of 30°C and 28°C, respectively. Distal anastomoses were completed first. Following application of the partial occlusion clamp on the ascending aorta, for construction of the proximal vein graft anastomoses, massive subadventitial bleeding was detected around the clamp and iatrogenic dissection was diagnosed. Patient #2 was a 61-yr-old man with untreated systemic hypertension who underwent repair of a DeBakey type I dissection of the aorta. The third patient was a 78-yr-old man with mild to moderate renal failure, who underwent resection of an aneurysm of the ascending aorta and the aortic arch complicated by severe aortic insufficiency. None of the patients had previous stroke, transient cerebral ischaemic attacks, diabetes mellitus or symptoms of peripheral vascular disease.

The three patients were monitored similarly with: ECG, direct radial arterial and central venous pressures, pulse oximetry, capnography and oesophageal and rectal temperatures. In preparation for PHCA, a two channel computerized EEG monitoring (Cerebro Trac 2500, SRD, Shorashim, Israel) was prepared to assess cerebral activity. This monitor performs real-time spectral analysis of the two EEG channels by converting the complex, irregular EEG data to power spectra by fast Fourier transformation from each cerebral hemisphere. The scalp EEG was recorded with standard adhesive disk electrodes, located bilaterally in a fronto-mastoid configuration. Special attention was given to verify that their impedance did not exceed 5KΩ. The monitor automatically adjusts the amplitudes at the range of 1–200 μvolts with determination of the range of spectral edge frequency (SEF) to 0–30Hz (SEF indicates the frequency below which 90–95% of the EEG is contained). Clinically, this quantitative parameter was used concurrently with the qualitative evaluation of the EEG itself for the assurance of burst suppression and EEG quiescence. An example of a Cerebro Trac tracing of a patient undergoing PHCA and RCP is shown (Figure).

Anaesthesia was induced and maintained in the three patients with fentanyl and midazolam, supplemented with enflurane. Muscle relaxation was achieved with pancuronium.

The right femoral artery, right atrium and SVC were directly cannulated in the three patients. In the first patient, the femoral arterial cannula was added during CPB, to allow removal of the aortic cannula for repair of the dissection. In the second and third patients, it was placed for the initiation and maintenance of CPB. The SVC cannula was used for RCP. Although its tip was palpated at the junction of the SVC and the innominate vein, probably down stream to the jugular venous valve, this valve was probably made incompetent by the central venous line. The heads and necks of the three patients were packed with crushed ice, and the patients were cooled to rectal temperatures of 15–18°C over 60 min. Anaesthetic agents were administered during cooling through the arterial cannula of the CPB pump and PHCA was commenced. The SVC was retrogradely perfused with cold (16°C) blood, oxygenated by the membrane oxygenator of the CPB circuit (filter size – 20 μm). Perfusion pressure was measured at a port in the SVC cannula connector. The effluent desaturated blood returning through the arch vessels was sucked from the opened aorta and returned to the cardiomy reservoir. Activated clotting time longer than 480 sec was maintained with heparin. Identical techniques of EEG monitoring, retrograde cerebral perfusion and

FIGURE Cerebro Trac tracing of a patient undergoing profound hypothermic circulatory arrest (PHCA) and retrograde cerebral perfusion (RCP).

Raw electroencephalographic and real time computerized spectral analysis tracings are presented during each stage of the surgery (baseline-during cardiopulmonary bypass, systemic cooling, RCP, rewarming, and normal temperature). Spectral edge frequency (SEF) is indicated according to the scale in the upper part of the figure. Systemic cooling to 18°C and small doses of thiopentone administered during cardiopulmonary bypass, produced the typical burst suppression pattern, which was later transformed to complete electrical silence. Reoccurring electroencephalographic activity during the arrest period was abolished by the administration of small boluses of thiopentone to the retrograde perfusate to restore electroencephalographic silence.

retrograde injection of drugs were used in all three patients. Drugs were injected to the SVC circuit, but proximal to the bubble detector and bubble trap devices.

Patient #1

Burst suppression and SEF of 0–4 Hz were evident in the Cerebro Trac following cooling and small boluses of etomidate (total 20 mg), prior to initiation of circulatory arrest. After the onset of PHCA (15°C rectal), perfusion of the upper body through the SVC was ini-

tiated, with a flow of 300 ml·min⁻¹, to maintain a perfusion pressure of 25 mmHg. Twelve minutes after the onset of PHCA, EEG activity was noted, with no electrical noise. Etomidate, 8 mg, was administered through the SVC and cerebral electric activity immediately ceased. Six more etomidate boluses, 6–8 mg each (total 50 mg), were required to eliminate recurrence of electrical activity during the 60 min of PHCA.

The dissected portion of the ascending aorta was excised and a collagen-impregnated dacron patch was sutured, into which the proximal vein graft anastomoses were inserted. The patient was rewarmed slowly until oesophageal temperature reached 37°C and he was weaned from CPB with dopamine, 8 µg·kg⁻¹·min⁻¹. The post-operative course was uncomplicated. Neurological examination after recovery from anaesthesia and before discharge (13th post-operative day), revealed no adverse sequelae.

Patient #2

Total burst suppression and SEF of 0–2 Hz were evident following cooling and administration of 2 G thiopentone prior to initiation of PHCA (18°C rectal). The addition of nitroglycerin (2 µg·kg⁻¹·min⁻¹) to the SVC perfusate enabled an increase in retrograde flow from 220 to 660 ml·min⁻¹, while maintaining the same perfusion pressure (26 mmHg). Thiopentone, 25–50 mg boluses (total 500 mg), was administered to the SVC perfusate during the 61 min of PHCA to eliminate reoccurring EEG activity.

The dissected part of the ascending aorta, extending from 1 cm above the coronary ostia to the origin of the brachiocephalic artery, was excised and replaced by a collagen-impregnated dacron graft. The patient was rewarmed slowly until oesophageal temperature reached 37°C and was weaned from CPB without pharmacological support. He regained consciousness seven hours after surgery without adverse neurological sequelae. Three days after surgery he sustained an embolic cerebral stroke, manifested by paresis of the left hand, which recovered completely after 10 days. Thorough neurological examination was performed following recovery from anaesthesia, daily after the stroke and before discharge. No deficit was detected either before the stroke or immediately before discharge.

Patient #3

Total burst suppression and SEF of 0 Hz were evident following cooling and administration of 1.45 G thiopentone, prior to initiation of PHCA (17°C rectal). The administration of nitroprusside (100 µg bolus) into the SVC perfusate, enabled an increase in retrograde flow from 220 to 550 ml·min⁻¹, without

change in perfusion pressure (25 mmHg). The EEG remained isoelectric during the 31 min of PHCA.

The patient underwent composite graft replacement of the aortic valve, ascending aorta and arch, with reimplantation of the coronary ostia into the graft. He was rewarmed slowly until oesophageal temperature reached 37°C and was weaned from CPB with dopamine support of 13 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. He regained consciousness on the first postoperative day without adverse neurological sequelae. Neurological examination after recovery from anaesthesia and before discharge (13th postoperative day), did not reveal adverse sequelae.

Discussion

These case reports demonstrate that, in adult patients undergoing aortic surgery utilizing PHCA with RCP, pharmacological effects can be realized by drug administration into the retrograde SVC perfusate. The administration of anaesthetic agents and/or vasodilators into the retrograde perfusate, respectively, suppressed EEG activity (which presumably reflects brain metabolism), and augmented retrograde flow. This suggests that both the brain and the cerebral circulation may be amenable to pharmacological manipulation during PHCA.

The risk of cerebral injury during PHCA can be reduced by systemic¹⁰⁻¹³ and topical^{12,13} cooling, pharmacological brain protection ("cerebroprotection"),^{2,13-16} and RCP.⁵⁻⁸

Animal experiments have demonstrated a direct correlation between cerebral or systemic temperature and histopathological cerebral damage resulting from temporary global cerebral ischaemia.^{10,11} Cooling humans to 27°C during CPB decreased cerebral metabolic rate to < 25% of pre-bypass value.¹⁷ Cooling dogs to 14°C diminished energy requirements to 7% of baseline.¹⁸ However, as cerebral ischaemic time increases, a higher incidence of neurological deficits becomes apparent despite the presence of hypothermia.⁴

Anaesthetic agent administration prior to circulatory arrest may further reduce cerebral electric activity and energy requirements.^{2,13,16,19-21} Thiopentone is the most commonly used neuroprotective anaesthetic agent^{2,19} though its potential myocardial depressant effect may prove deleterious to patients with significant myocardial dysfunction or severe ischaemic heart disease. Etomidate, in contrast, has minor myocardial effects,²² while possessing effective neuroprotective properties. It considerably reduces cerebral metabolic rate and regional blood flow (the former by 50% more than the latter),²¹ and depresses EEG activity.²³ However, the use of etomidate for brain protection has not been validated by randomized studies.²⁴

Retrograde perfusion of the upper body via the SVC during PHCA has been introduced in recent years in an attempt to improve brain protection,⁵⁻⁸ since profound hypothermia and current "cerebroprotection" cannot abolish cerebral metabolic demands. Some metabolism is necessary for the maintenance of cellular integrity, even at profound hypothermia. In addition, cerebral cooling may not necessarily be homogenous and regional areas of increased temperature and higher metabolism may exist.^{25,26} These "hot spots" and their surrounding areas of brain are at a greater risk from ischaemic damage. Although RCP could not maintain aerobic metabolism in dogs, it has been demonstrated to preserve tissue concentrations of adenosine triphosphate, which rapidly decreased during PHCA without retrograde perfusion.⁶

The mechanisms by which RCP protects the brain are not completely understood. These may include: maintaining the hypothermic state and the associated decrease in cerebral metabolism by ongoing cerebral perfusion with cold perfusate; providing substrates for the maintenance of residual cerebral metabolic function; removing waste products and; flushing out emboli that might have reached the brain.⁸ Retrograde SVC perfusate may reach the brain if the internal jugular venous valves are naturally incompetent or are made incompetent by central venous catheters, or through azygos and vertebral plexus venous connections.⁹

Optimal retrograde perfusion conditions in humans have not been studied. The retrograde perfusion pressure in our patients was 25–26 mmHg, based on a single animal study.⁷ External jugular venous pressures < 25 mmHg were associated with a decrease in cerebral blood flow, while pressures > 25 mmHg increased intracranial pressure, restricted cerebral perfusion and possibly resulted in brain oedema.⁷ Even under optimal conditions, RCP was suggested to provide only one quarter of the oxygen provided by CPB flow of 1000 ml·min⁻¹.⁷

Although systemic and topical cooling, pre-arrest cerebroprotection and RCP were used in our patients, the reappearance of EEG activity during the arrest period suggests that these measures are inadequate for brain protection during PHCA. Cerebral ischaemic injury could be minimized by a better match between cerebral energy supply and residual metabolic demand. Theoretically, this could be obtained by reduction in cerebral metabolic rate with concomitant increase in cerebral blood flow. Therefore, we administered anaesthetic and vasodilating agents via the retrograde SVC perfusate during the PHCA period. To the best of our knowledge, such an approach has never been reported.

Our first two patients demonstrated that cerebral perfusion can be accomplished in humans using RCP.

Since persistent EEG activity during PHCA may be associated with postoperative neurological dysfunction,²⁷ we believed it was important to achieve prompt burst suppression by retrograde anaesthetic administration. This supports anaesthetic administration via the RCP to improve brain protection during PHCA. Etomidate or thiopentone were introduced to the SVC perfusate, reached neural tissue and re-arrested EEG activity promptly. In the first patient, who had severe myocardial ischaemia, we chose etomidate because of its negligible haemodynamic effects. Thiopentone was chosen for the second patient, since his cardiac performance was normal.

The administration of vasodilating agents into the retrograde SVC perfusate enabled an increase in retrograde flow without necessitating an increase in perfusion pressure. It should be stressed that direct cerebral flow was not measured in any of our patients and it is uncertain whether the brain benefited from the extra flow. Further studies are required to determine the dose-response curve of vasodilators administered by RCP, their possible benefits in terms of cerebral flow at various temperatures and supply-demand ratios, and the possible role of administered CO₂ in improving the distribution of retrograde upper body perfusion in favour of the brain. Patient #1, in whom vasodilators were not used, required a high total dose of etomidate for EEG suppression. It would have been interesting to investigate whether augmented flow could have reduced the required dose.

It is reasonable to assume that more accurate monitoring of brain temperature (e.g., tympanic temperature) or metabolism (e.g., "venous" oxygen saturation of blood returning from the brain through the internal carotid artery) should have used, both before and after retrograde drug administration.

Potential complications of retrograde administration of drugs to the brain include air emboli, drug overdose, pH effects of acidic/alkalotic solutions, hyperosmolar load, "luxury" cerebral blood flow and extracerebral shunting. Cerebral air emboli were avoided by injecting drugs proximal to the bubble detector and bubble trap devices. We believe that cerebral effects of drug overdose, pH and hyperosmolality were avoided by administering small doses of the drugs. If the entire thiopentone bolus of 50 mg had reached the brain, this as a fraction of the usual induction dose, would resemble the fraction of cerebral blood flow out of cardiac output. Moreover, these small boluses were distributed to the entire upper body, and probably to the lower body as well.⁹

Although brain CT was not performed immediately after operation, neurological examination did not reveal deficits in any of the three patients, and it is

unlikely that brain oedema could have resulted from the increased flow. While direct cerebral blood flow should be measured in order to exclude blood shunting from the brain, we avoided retrograde administration of vasodilators having such a potential (e.g., alpha-adrenergic receptor blockers).

In summary, we have shown that anaesthetic agents and vasodilators administered by RCP depress EEG activity and augment retrograde SVC blood flow during PHCA. Retrograde delivery of anaesthetic drugs guided by EEG may allow titration of anaesthetic drug administration during PHCA to the endpoint of constant EEG suppression.

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