Retrograde perfusion and true reverse brain blood flow in humans

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Abstract

Objective: Reversal of brain blood flow is necessary for retrograde cerebral perfusion (RCP) to have any metabolic benefit, but RCP is commonly used with little clinical evidence of the true incidence of reverse brain blood flow and impact. S-100B is exclusive to the brain and spinal cord and released during hypothermic circulatory arrest (HCA). True reverse brain blood flow (tRBBF) during RCP may be determined by demonstrating an excess of S-100B in the effluent blood from the common carotid artery compared to blood entering the brain.

Methods: Simultaneous blood samples were drawn from the jugular bulb and left common carotid artery during RCP at 5 min intervals in ten patients undergoing aortic surgery, utilizing HCA and subjected to blood gas, glucose and S-100B quantification. RCP was instituted at maximum pressure of 25 mmHg. Trans-cranial Doppler (TCD) continuously monitored the middle cerebral artery velocity (MCAV).

Results: The mean HCA and RCP durations were 31 min (20±50 min). Reversal of MCAV was demonstrated in only 6/10 cases (mean, 6 cm/s). Veno-arterial (V-A) extraction of oxygen and glucose occurred in all cases (P < 0.001), with the mean effluent pO₂ falling to 14 mmHg. V-A S-100 gradients greater than 5% were demonstrated in 8/10 cases and correlated with higher oxygen extraction (P < 0.01). In patients with and without MCAV reversal, the S-100 gradients were 1.7 and 0.3 μmol/l, respectively (P < 0.01).

Conclusions: tRBBF occurred in nearly all patients. MCAV reversal appears to be a specific but insensitive guide to reverse perfusion. The desaturation of effluent blood is not a reliable guide to true brain perfusion, and despite RCP, the brain remains ischaemic.

Keywords: Retrograde cerebral perfusion; S100 protein; Trans-cranial Doppler

1. Introduction

Retrograde cerebral perfusion (RCP) has been used as a putative brain protective adjunct to hypothermic circulatory arrest (HCA) in aortic surgery [1]. Theoretically, RCP may provide substrate supply and catabolite removal. In order to do so, true reverse brain blood flow (tRBBF) is required.

The issue of de-saturated blood from the common carotid arteries during RCP has been interpreted as evidence of brain metabolic extraction. If metabolic support is provided by RCP, then this infers that ischaemia during HCA is not absolute and that HCA duration could be safely extended. However, venting of deoxygenated blood from the extracranial arteries during RCP may not be confirmation of brain oxygen consumption. As blood may also flow to the upper limbs, extracranial tissue and lower body via the azygos vein during RCP via the superior vena cava (SVC), non-brain tissue may be responsible for oxygen extraction [2].

Antegrade brain blood flow can be directly measured in animals using a number of methodologies, including laser flow Doppler, direct maxillary vein and internal carotid cannulation. These techniques are all highly invasive and are not applicable to clinical RCP monitoring [3–6].

In canine models, true reversal of brain blood flow has been described with demonstrable metabolic benefit [7]. However, the techniques used to institute RCP are not clinically applicable, and they bypass the jugular venous valves known to be present in almost all patients [8]. In the baboon, RCP via the SVC produces no significant reverse brain blood flow or metabolic benefit [6].

In humans, the demonstration of tRBBF during RCP is an important issue, and if tRBBF does occur, then it is important to determine its incidence and its ability to meet the metabolic demands of the ischaemic brain during HCA [9].

The S100B protein is a large, charged, dimeric protein, made up of two β-subunits with a combined molecular weight of 22 000 kDa [10]. It is found almost exclusively in astrocytes. S100B has been used as a marker of brain...
injury after stroke, trauma, intra-cranial haemorrhage and other neurological diseases [11, 12].

A large gradient of S100B protein between the cerebral spinal fluid (CSF) and blood is produced during cardiopulmonary bypass (CPB), which is as great as 20 μg/l [13, 14]. S100B is continuously released into the blood during CPB, and following HCA, all patients have elevated serum levels at the end of bypass [15, 16].

The high CSF–blood gradient and continuous release of S100 protein may allow the identification of true reverse cerebral blood flow. Afferent blood, traversing the brain circulation, would be expected to partially equilibrate with CSF levels. We, therefore, hypothesized that the determination of a trans-cranial afferent–efferent S100B gradient during RCP would be indicative of tRCBF. Further, we postulate that such a gradient may correlate with the occurrence of reversal of middle cerebral artery flow and trans-cranial oxygen extraction.

2. Material and methods

The study was approved by the Local Research Ethics Committee of South Birmingham Health Authority, and all patients gave informed consent. Ten patients undergoing aortic surgery using HCA and RCP were studied. Aortic root and ascending replacement was performed in six patients, hemiarch replacement in three, and total arch replacement in one.

Standardized anaesthesia, CPB, HCA and RCP techniques were used, as previously described [17]. During RCP, the inferior vena caval line was clamped, allowing the pressurization of the inferior vena cava via the azygos collaterals.

A right retrograde jugular bulb line was inserted for pressure monitoring and blood sampling, and its position checked later by a skull X-ray in the intensive care unit. Following cooling on CPB, HCA was initiated at a nasopharyngeal temperature of 15°C. RCP was instituted with the patient in the Trendelenberg position via the SVC, limiting the jugular bulb venous pressure to 25 mmHg, with the pressure manometer zeroed at the angle of the jaw.

Trans-cranial Doppler (TCD) (SciMed 862, Fishponds, Bristol, UK) monitoring of the right middle cerebral artery velocity (MCAV) was performed in all patients using a 2 MHz probe, with the focus at 5 cm and an acquisition width of 1 cm. The probe was positioned to gain the optimum signal before the start of bypass, and fixed in place with a head band. Continuous recording of the MCAV trace was captured on VHS video tape. The mean MCAV was noted immediately before HCA, and during RCP.

Arterial blood samples were drawn at the start of CPB, just before HCA and at the end of CPB. During the RCP period, blood samples from the jugular bulb line and directly from the common carotid artery using a 15 cm soft, flexible cannula were taken at 5 min intervals. The whole blood samples were subjected to blood gas analysis on a Stat Profile 9 (Nova Biochemical, USA). pH, pCO2 and pO2 were measured at 37°C, and later corrected for temperature using standard formulae [18].

Serum was obtained by centrifuging blood at 6000 rev/min for 5 min. S100B levels were measured using a dual site monoclonal chemiluminescent assay (LIA-MAT 100, Sangtec, Cambridge Life Sciences, Bury St Edmunds, UK) in pairs calibrated with the control samples supplied. This assay has a co-efficient of variation of 5%. The efferent serum S100B protein levels were subtracted from the afferent level. A value greater than 5% of the afferent level was taken as the true difference, in accordance with the limitations of the assay.

The data were analyzed on an IBM-compatible personal computer using standard two-tailed t-tests.

3. Results

In the ten patients studied, the mean bypass, HCA and RCP durations were 216, 32 and 30 min, respectively. One patient died from primary myocardial failure, and one patient suffered permanent neurological deficit manifest by sensory loss over the left maxillary division of the trigeminal nerve.

During RCP, veno-arterial oxygen and glucose extraction occurred in all cases. The effluent SO2 fell from 99.94 ± 0.01 to 68.17 ± 4.6% (P < 0.0001), the pO2 fell from 226 ± 22.6 to 9.5 ± 2.9 mmHg (P < 0.001), and the glucose from 7.7 ± 0.9 to 6.9 ± 0.8 mmol/l (P < 0.001; Fig. 1; ± SEM).

Overall, there was a significant gradient of S100B, (afferent, 3.0 μg/l; effluent, 6.0 μg/l; P < 0.001). A V-A S100 gradient of greater than 5% occurred in 8/10 cases.

In one patient, MCAV data could not be obtained because of an inadequate acoustic window. In the remainder, the pre-HCA mean MCAV was 10 ± 1.4 cm/s. MCAV reversal, with a mean velocity of 6.02 ± 3.5 cm/s was detected in six patients. In patients with and without MCAV reversal, S100B gradients were 1.73 ± 0.56 and 0.31 ± 0.6 μg/l,
respectively ($P < 0.01$; Fig. 2). The effluent $pO_2$ was lower in those patients with a significant $S100$ (V-A) gradient (Fig. 3).

4. Discussion

Surgery requiring HCA has a high incidence of brain injury, and there is an undoubted need for improved brain protection [19,20]. RCP has been used as an adjunct to assist HCA in many institutions, yet no prospective randomized trials have been performed. Moreover, there is no definitive evidence that materially significant, tRBBF occurs.

The presence of de-saturated blood flowing from the carotid arteries during clinical RCP suggests brain metabolic extraction. However, as all the blood flowing from the cephalic vessels could have come from extra-cranial sources, the effective tRBBF could be insignificant.

In this study, using a trans-brain $S100B$ gradient as evidence of tRBBF, we have demonstrated that tRBBF occurs in the majority of patients. Secondly, the reversal of the MCAV signal appears to correlate with the $S100$ gradient, inferring that MCAV monitoring may be a specific, but relatively insensitive, real-time index of tRCBF. We have also found that despite the evidence of tRBBF, the metabolic impact of RCP is slight.

The assessment of tRBBF during RCP in humans is problematic. Previously, using the brain perfusion agent, 99m-Technetium-labelled $n$-hexamethyl propylene amine oxime ($[^{99m}\text{Te}]$HMPAO), we have been able to produce images of radioactive blood flow into the head and brain during RCP [17,21] with the blood filling through the internal jugular vein and dural sinuses.

Although radio-labelled blood entered the brain in three out of 13 patients, the slow rise in the time-activity curves was compatible with the markedly reduced flow rate compared to antegrade perfusion. In addition, tRBBF could not be precisely differentiated from arterIALIZATION of the brain venous capacitance vessels that contain up to 70% of the brain blood volume. However, this study clearly demonstrated that blood could enter the brain past the valves of the internal jugular vein in some patients, but collateral vessels may be more important. As radio-imaging using brain perfusion agents can not be performed routinely in clinical practice, less invasive monitoring techniques are required.

Ganzel et al., using near infra-red spectroscopy (NIRS), reported a slowing of the normal decline in the regional saturation ($rSO_2$) with the use of RCP during HCA [22]. This result is disappointing. Since 70% of the total brain blood volume is venous, tRBBF should arterialize this space and result in a higher $rSO_2$ than normal. Additionally, the path-length of the NIRS beam is unknown. It is critical to the calculation of $rSO_2$ and usually it is assumed to be constant [23]. However, changes in the CSF or blood volume during CPB, HCA and RCP will change its value and may lead to false results. Thus, the $rSO_2$ before and during HCA and RCP may not be comparable.

Direct measurements of the cortical cerebral blood flow have been made in a few patients using a sub-dural laser Doppler, but this requires a craniotomy [24]. During RCP, cortical flows of 10% of that immediately before the start of HCA have been reported. However, the technique is not quantitative, and the efficacy of the technique to measure brain blood flow during HCA has not been validated.

TCD is a simple, common and safe brain blood flow monitoring technique, and has been used in many studies of moderately hypothermic CPB [25]. During RCP, Ganzel et al. reported reversal of MCAV with some modification of the standard commercial apparatus [22]. However, MCAV reversal has not been correlated with tRBBF by any previous study, and hence, the significance of signal reversal is unknown.

It is possible that MCAV reversal may arise from blood bypassing the brain capillary beds during RCP via known veno-arterial shunts [26], and this phenomenon would much reduce the specificity of TCD as a tRBBF monitor.

Other methods of assessing brain blood flow, such as $^{133}$Xe, Kety–Schmidt and [18] oxygen-positron emission imaging...
tomography (PET) techniques, have not been applied to study tRBBF and may be impractical during RCP. Moreover, in dogs, Fukae and Furuzawa [3,27] reported a maldistribution of brain blood flow during RCP, with poorer flows in the cortex compared to the medulla. Therefore, the simple determination of flow during RCP may not be a reliable guide to its metabolic impact. Thus, the development of a reliable non-invasive technique to detect tRBBF during RCP is a desirable first step in assessing its impact.

S100B protein has potential as a marker of brain perfusion. In cardiac surgery, S100B is released into the serum in association with CPB and HCA [28]. Serum S100B protein levels rise within 5 min of the start of bypass, and rose continuously up to the end of bypass in all patients studied [29]. Thus, even after short periods of bypass, there is a large ECF–blood S100 gradient, as evidenced by the high CSF levels (up to 20 μg/l) [14].

Therefore, during any period of S100 release, measurement of S100B protein in the blood entering and leaving the brain would show higher concentrations in the efferent blood. The diffusion of S100B protein into the blood must occur across the blood brain barrier (BBB) in the capillaries; it is expected that this would accompanied by metabolite exchange if there is a significant S100B gradient between the afferent (jugular bulb) and efferent blood (left common carotid artery (LCCA)).

The sensitivity of using S100 as a brain perfusion marker is theoretically high. At low flows, the blood dwells in the capillaries for longer, and hence, has more time to equilibrate, thereby amplifying the signal (A-V S100 gradient). Thus, for a large range of brain blood flows, the afferent–efferent blood S100B protein difference is maintained, irrespective of the direction of flow. However, the measurement is qualitative, as the rate of brain release of S100B is unknown.

In this study, the detection of a significant trans-cranial S100B gradient implies that true brain perfusion occurs in the majority of patients undergoing RCP. The correlation of the S100 gradient (V-A) with MCAV signal reversal suggests that TCD may be a specific, but perhaps insensitive, tool to monitor RCP. In previous studies, TCD was unreliable in detecting MCAV below an antegrade flow of 30 ml/kg per min in children, although in certain cases, it can detect a signal down to 10 ml/kg per min [30].

However, we also found that S100B gradients were associated with a greater degree of efferent de-saturation (Fig. 3). This implies that a high effluent oxygen content is not in fact an index of greater tRBBF, but reflects extra-cranial shunting. During any brain perfusion, the pO2 of the efferent blood will be in equilibrium with the extra-cellular pO2 supplying the neuronal mitochondria. In this study, the low pO2 content in effluent blood suggests that, despite tRBBF, the contribution of RCP to the brain metabolism is small and the brain remains ischaemic.

Although we found evidence of tRBBF in the majority of patients, the mean efferent pO2 in the LCCA was 9.5 mmHg, significantly lower than the jugular bulb pO2 of 40 mmHg during antegrade CPB. This approximates the critical neuronal mitochondrial pO2 of 5 mmHg, and suggests that the metabolic impact of RCP, even in those with true perfusion, is slight.

One of the limitations of this study is that effluent sampling could be contaminated from extra-cranial sources. We sought to minimize this by placing a long catheter high in the LCCA from within the open aortic arch.

Although some contamination of the blood in the LCCA by extra-cranial sources is inevitable, as the brain has the highest metabolic rate of any tissue in the body, brain effluent blood will have a lower pO2 than that of the extra-cranial tissues. Therefore, if the LCCA blood is a mixture, the LCCA pO2 will be an overestimate of the brain extra-cellular fluid pO2, and hence, the true brain metabolic state during RCP.

The ability to determine tRBBF during clinical RCP is important. Any assumption that the visualization of de-saturated blood from the carotid arteries during RCP signifies significant tRBBF is incorrect. On the contrary, MCAV reversal is a good real-time monitoring method of determining the ability of RCP to generate tRBBF in patients with a satisfactory acoustic window.

However, despite evidence of tRBBF, profound effluent hypoxaemia implies that RCP, as currently used, is metabolically ineffective. Experimental work has suggested that tRBBF can be increased by physical and pharmacological manipulation [31,32]. The effectiveness of such manoeuvres in the clinical situation and the true utility of RCP require appropriate investigation.

References


Appendix A. Conference discussion

Dr H. Borst (Munich, Germany): I think this is quite a provocative paper, confirming what many surgeons working on the thoracic aorta always have been suspecting. What is your practical conclusion from this? Are you still using RCP?

Dr Wong: Yes, we are using RCP in the context of having completed a prospective trial. We are also investigating the possibility of potentiating RCP, since a number of reports suggest that pharmacological manipulation can increase the flow, augmenting perfusion.

Dr Borst: Do you think it has a protective effect in keeping the temperature down, for instance, or in washing out metabolites, debris and things of that sort you always hear about?

Dr Wong: Well, this study doesn’t address that problem, and that will have to be addressed by the study we just recently completed, which is the prospective randomized trial between RCP and HCA only. We have yet to analyze that data fully, but we will be presenting some of our results in the Atlanta meeting of the American Heart Association.

Dr D. Blyth (Durban, South Africa): Could I ask you, do you know of a study that shows anything with regard to uniformity of distribution of blood by this route in the human?

Dr Wong: Not in humans. There are two studies in animals, which suggest that perfusion is mal-distributed, which, if the flow is small, is not an unreasonable result [3,27].