CEREBRAL PROTECTION STRATEGIES IN AORTIC ARCH SURGERY

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Abstract

Review

Surgery of the aortic arch requires circulatory arrest. During this period, the brain is prone to ischemic and irreversible damage. To protect the brain for longer and more extensive surgery, different cerebral protection strategies have been developed and studied. However, optimal cerebral protection during aortic arch surgery remains technically challenging. Nowadays, three strategies are particularly used for cerebral protection. These three strategies include: deep hypothermic circulatory arrest, retrograde cerebral perfusion and selective antegrade cerebral perfusion. Hypothermic circulatory arrest is essential to operating on the aortic arch. This technique can be adjuncted with either retrograde or selective antegrade cerebral perfusion for longer and more complex surgeries. The mentioned techniques provide cerebral perfusion while the systemic circulation is arrested. Added neuroprotective effects of retrograde cerebral perfusion remain elusive. Selective antegrade cerebral perfusion seems to be a more physiological strategy with better clinical results. In this article, these three most common cerebral protection strategies and their relative advantages and disadvantages are described.

KEYWORDS: Hypothermic circulatory arrest, retrograde cerebral perfusion, selective antegrade cerebral perfusion

> *There is no disease more conducive to clinical humility than aneurysms of the aorta.*
>
> *– Sir William Osler, 1961*

Introduction

An aneurysm, from the Greek word: *ανεύρυσμα*, meaning dilation or to dilate, is an outward bulging of a blood vessel, caused by a localised weak spot of the vessel wall. This might be the result of an acquired disease (e.g. atherosclerosis) or a hereditary condition such as Marfan syndrome. Due to a local increase in blood pressure and a weakened area of the vessel wall, the aneurysm can increase in size and eventually rupture, potentially leading to significant bleeding and subsequent death [1]. Although aneurysms can occur in every blood vessel, they are most often found within the arteries supplying the brain (circle of Willis) and the aorta. Aneurysms of the aorta can be subdivided into thoracic aortic aneurysms (TAA) and abdominal aortic aneurysms (AAA). Figure 1A shows a normal thoracic aorta and figure 1B illustrates a TAA. Small to medium sized TAAs are conservatively treated but are closely monitored for further expansion. Bigger (end diastolic diameter more than 5.5 cm) or symptomatic TAAs require surgical or endovascular treatment [2]. Surgical treatment of ascending and/or arch TAAs is usually performed through open chest surgery (median sternotomy) where the diseased (dilated) part of the aorta is removed and replaced with a synthetic tube graft (figure 1C)[3]. When the disease affects the descending thoracic aorta, a thoracotomy approach is most commonly used where the aneurysm is repaired in the same manner. Surgery of the aortic arch presents a unique risk given the mandatory period of cerebral ischemia, requiring adequate cerebral protection. The brachiocephalic arch vessels must be disconnected to repair these types of aneurysms, thus interrupting the cerebral blood flow. Up to this point, three main cerebral protection strategies have been used in patients undergoing this type of extensive aortic arch surgery. These three strategies include: deep hypothermic circulatory arrest (DHCA), retrograde cerebral perfusion (RCP) and uni- or bi-lateral antegrade cerebral perfusion (ACP). This article aims to provide an overview of the mentioned strategies, discussing their history, clinical technique and relative advantages and disadvantages.

Deep hypothermia with circulatory arrest

The use of deep hypothermia with circulatory arrest (DHCA) was first described in the 1960s and used for the repair of aortic arch arteriovenous fistulas [4]. Griepp and Stinson (1975) reported the first 'actual' case series using DHCA as a cerebral protection technique to repair aortic arch aneurysms. They operated on four patients replacing variable portions of their thoracic aorta with a prosthetic tube graft [5]. Hypothermic circulatory arrest, which was introduced more than 30 years ago, still serves as the basis for surgeries on the aortic arch. This protection technique works by cooling the patient down to dramatically decrease their cerebral metabolism. Studies on canine brains have been done to illustrate the physiologic effects of DHCA [6]. Although the brain takes up only two percent of the human body weight, it uses twenty percent of the total body oxygen consumption and receives fifteen to twenty percent of the circulating blood volume [7]. This is because the brain uses oxygen and glucose at a much higher rate than other organs. Neurons use excessive amounts of adenosine triphosphate (ATP) as their main energy source. This ATP is produced by oxygen-dependent glucose metabolism. Unlike liver cells or muscle cells, the brain cannot store the produced glucose as glycogen. Thus, when the brain does not receive enough glucose or oxygen, neuronal function immediately becomes impaired. The brain does however, have a compensation mechanism by making small changes in the cerebral blood flow, called 'autoregulation' [8]. This homeostatic mechanism is a negative feedback loop that works by vasodilation or vasoconstriction of the small cerebral arterioles to change the total cerebrovascular resistance [9].

To understand by which mechanisms hypothermia protects the brain one must understand two important pathways of ischemic neural injury:

1. When the brain does not receive adequate amounts of oxygen, ATP will be synthesised using anaerobic glycolysis. Anaerobic glycolysis does not produce enough ATP to maintain normal neuronal function [10]. At the same time, anaerobic glycolysis produces lactic acid, lowering the intracellular pH. The combination of energy depletion and accumulation of any produced waste products within the brain will quickly lead to cell damage and necrosis [11].
2. Calcium ions (Ca^{2+}) play a big part in neuronal cell damage. N-methyl-D-aspartate (NMDA) channels get activated by hypoxia through the

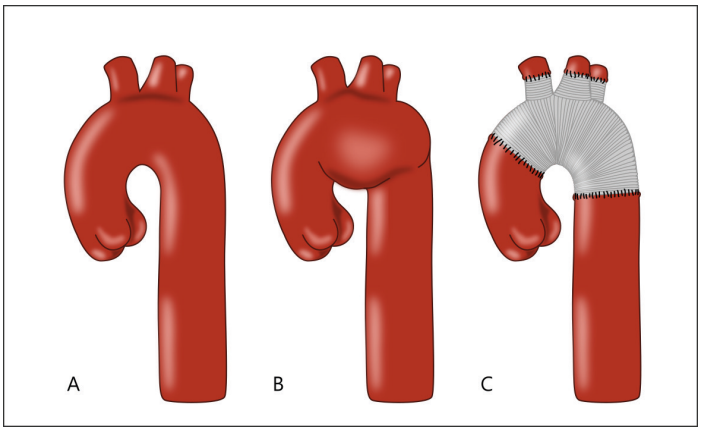

Figure 1: A. *Normal aorta* ***B.*** *Aneurysm of the aortic arch* ***C.*** *Repaired aortic arch.*

release of excitatory neurotransmitters, like glutamate. Activation of the NMDA receptors results in the opening of ion-channels, by which calcium ions can easily enter the cells and accumulate. Imbalance in calcium ions eventually leads to the activation of intracellular proteases and mitochondrial dysfunction resulting in neuronal cell death [11].

Deep hypothermia inhibits both pathways by significantly slowing down the cerebral metabolic rate for glucose and oxygen [10]. Cerebral metabolism slows down by five to seven percent for every single degree Celsius drop in body temperature. At a core temperature of 18 degrees Celsius the metabolic rate of the human body is only 12 to 25% of that at normal temperature, dramatically decreasing the oxygen demand of neurons [12]. Hypothermia also reduces the release of excitatory neurotransmitters resulting in far less NMDA receptors being activated, significantly reducing the amounts of intracellular calcium [11].

Clinical technique

Patients who are to undergo aortic arch surgery with DHCA are placed on cardiopulmonary bypass (CPB) first. The CPB machine completely replaces the function of the heart and lungs allowing surgeons to operate on an empty and arrested heart. To initiate CPB and prepare patients for DHCA, a two-stage cannula is placed in the right atrial appendage for venous return. The ascending aorta is then directly cannulated for arterial perfusion. If this is not possible, femoral artery cannulation is chosen - unless the patient has severe atherosclerotic disease of the descending aorta and/or iliac arteries. In case of severe atherosclerotic disease, right axillary artery cannulation is used. Retrograde flow towards the brain could dislodge debris in the aorta, potentially leading to embolisation in the brain. Figure 2A illustrates the femoral artery cannulation strategy. As soon as the patient is cannulated, CPB is initiated and cooling is started. Cooling is achieved by pumping cold water through a heater-cooler unit located in the CPB oxygenator. Temperature monitoring of the brain is critical during this phase. Most commonly used sites include esophageal, rectal, bladder, nasopharyngeal, tympanum, pulmonary arterial and skin temperature. Most reliable sites seem to be nasopharyngeal, bladder and tympanum [13]. Patients are cooled until establishment of electrocerebral silence, this usually (60% of the cases) occurs at a core temperature of 18 degrees Celsius or after a cooling period of 30 minutes [14]. All patients will reach complete EEG (electroencephalogram) silence at a nasopharyngeal temperature below 12.5 degrees Celsius or after a cooling period of 50 minutes or longer [15]. A two to three degrees Celsius gradient is maintained between the arterial inflow temperature and the venous return temperature to ensure even cooling. As the temperature of blood decreases, Boyles law states that the solubility of gases in blood increases. Arterial blood gas measurements show reduced PaO_2, $PaCO_2$ and an alkalosis when patients are cooled down, requiring the need for accurate pH management. Two strategies: alpha-stat and pH-stat are most commonly used [16]. For pH-stat acid base management, the patient's pH is kept constant and is temperature corrected. In alpha-stat acid-base management, the ionisation state of the amino acid histidine is maintained – this strategy does not correct for any changes in temperature [17]. After sufficient cooling the circulation is arrested, and the aortic arch is repaired [18]. When CPB is resumed after the period of deep hypothermic circulatory arrest, rewarming commences [19]. Rewarming has to happen slow and careful. The perfusion needs to be kept at a gradient of not more than ten degrees Celsius above the measured core temperature to avoid a mismatch between the total body oxygen demand and oxygen delivery [20].

Safety and limitations

Safe duration of DHCA was considered to be 35 to 40 minutes at a core temperature of 20 degrees Celsius [21]. These insights have changed and currently there is no agreement on the safe duration of DHCA. Several studies have shown durations as short as 20 to 25 minutes to be associated with poor neurologic outcomes after surgery [22, 23]. Other authors have reported aortic arch interventions can be safely performed at DHCA times of up to 50 minutes [24]. Complications of DHCA include: cerebral damage (stroke or transient neurologic deficits), post-ischemic hypothermia, impaired autoregulatory mechanisms and blood-brain barrier damage [25]. To increase the duration of the circulatory arrest for more complex aortic repairs and less neurological complications, antegrade selective or retrograde cerebral perfusion have been introduced as additions to DHCA. In this way, the brain is not only protected, but also perfused during surgery.

Retrograde cerebral perfusion

Retrograde cerebral perfusion (RCP) provides retrograde perfusion of the brain using the venous circulation. This protection strategy provides some sort of metabolic support during circulatory arrest and prolongs the safe limits of DHCA. In addition, RCP has the potential added benefit of back-flushing air emboli and debris from the cerebral circulation. These effects are based on the premise that the cerebral venous vasculature is completely free of valves. However, a cadaver study done by de Brux *et al.* has shown valves to be present within the internal jugular veins [26]. RCP was first routinely used by Ueda *et al.* in thoracic aortic surgery to lengthen the safe operating time [27].

Clinical technique

CPB is achieved by cannulating the femoral artery, axillary artery or direct cannulation of the aneurysm. Bi-caval cannulation (both the superior and inferior vena cava are cannulated) is used to allow retrograde flow, while maintaining venous drainage from the inferior vena cava. Figure

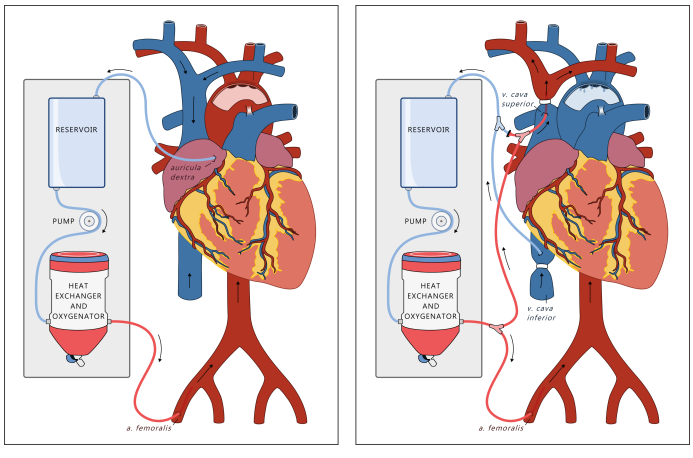

Figure 2: A. *Cannulation for deep hypothermia* ***B.*** *Retrogade cerebral perfusion*

2B illustrates this cannulation strategy. After initiating CPB, cooling of the patient is started. The circulation is arrested after EEG silence is achieved. Nasopharyngeal and rectal temperatures are constantly monitored, pH is controlled using pH-stat or alpha-stat for optimal acid-base management and proper heparinisation is monitored with activated clotting times (ACT). Myocardial protection is achieved in the standard fashion using antegrade and/or retrograde cold diluted blood with added hyperkalemic cardioplegic solution. The bypass circuit allowing RCP includes several Y-connectors: one connected to the cannula in the superior vena cava, splitting the arterial and venous tubes, and one placed in the arterial line (figure 2B). Once the circulation is arrested, arterial blood is routed only through the cannula in the superior vena cava. Flow is adjusted to maintain a proximal venous pressure of around 20 to 25 mmHg, providing a flow rate ranging from 150 to 500 ml/min. Back bleeding from the brachiocephalic vessels confirms retrograde flow, when this obstructs the surgeons vision, RCP flow is briefly reduced. After completing the aortic arch repair, CPB is restarted, RCP is discontinued and rewarming of the patient is started [28].

Safety and limitations

The hypothetical neuroprotective mechanisms of RCP where promising, however, several clinical and laboratory studies have shown that these mechanisms remain controversial. Aforementioned, de Brux *et al.* have shown valves to be present within the internal jugular veins, requiring higher perfusion pressures (up to 40 mmHg) [26]. High perfusion pressures could lead to cerebral edoema, especially when RCP is continued for longer periods of time [29]. The effectiveness in brain preservation of RCP is mainly attributed to the continued cerebral cooling via the venoarterial and venovenous collateral circulations [30]. The technique or mechanism of cerebral protection using RCP remains elusive, requiring the need for an alternative technique [31].

Selective antegrade cerebral perfusion

The most routinely used cerebral protection technique today, was first used in 1957 by DeBakey *et al.* for the resection of an aneurysm of the aortic arch [32]. The patient survived but results of the technique in the following years were very disappointing. ACP was completely abandoned after Griepp *et al.* showed that aortic arch repair is safely possible with DHCA alone [5]. Over time when expertise in aortic surgery increased it became apparent that adjunctive cerebral protection techniques might offer more complete and complex aortic repairs along with better neurological outcomes. Since the effects of RCP remained controversial, selective antegrade perfusion revived.

Clinical technique

The technique of selective antegrade cerebral perfusion (ASCP) is very appealing because it is more comparable with a physiologic flow than the 'no flow' DHCA or the retrograde approaches. The technique is still used as an addition to DHCA, as described before. However, different cooling temperatures are used [33]. There are different cannulation strategies to perform ASCP. The two most commonly used strategies include either direct bi-lateral cannulation of the brachiocephalic vessels using balloon tipped catheters or uni-lateral cannulation of the axillary artery with the use of a side graft sewn to the artery in an end-to-side fashion to allow perfusion of the artery in both directions. A two-stage cannula is placed in the right atrial appendage for venous drainage. Systemic cooling is, as stated before, variable and depends on the anticipated time of the circulatory arrest period. For separate cannulation of the brachiocephalic vessels (figure 3A), the arteries have to be divided and cannulated prior to circulatory arrest [34]. Balloon tipped catheters with individual pressure-monitoring lines need to be used to avoid cerebral hypertension. Optimal protection is achieved by direct perfusion of all three brachiocephalic vessels, not just the innominate artery and left common carotid artery [35]. When cannulating

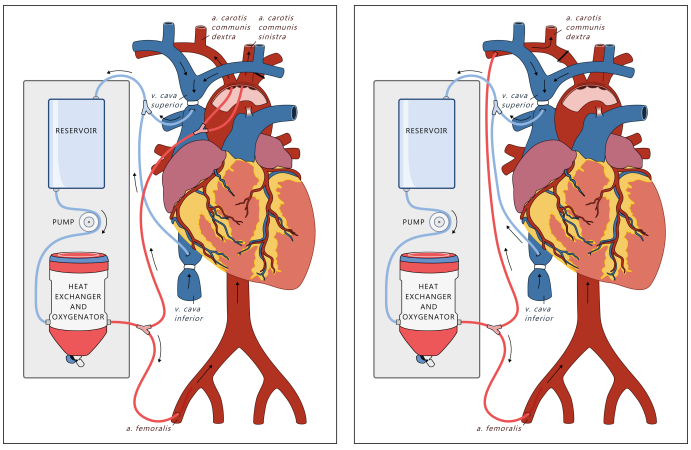

Figure 3: A. *Bi-lateral selective antegrade cerebral perfusion* ***B.*** *Antegrade cerebral perfusion, axillary cannulation*

the axillary artery (figure 3B) - prior to circulatory arrest - the innominate artery is clamped off proximally, selective cerebral perfusion is started and adjusted to maintain a flow rate of 10 ml/kg/min [36].

Safety and limitations

Results using the different cannulation strategies with selective antegrade cerebral perfusion (ASCP) are varied. Dossche *et al.* found hospital mortality to be affected significantly by the choice of cannulation technique used for ASCP. As of today, it remains unclear whether ASCP should be delivered using an uni-laterally or bi-laterally approach. Uni-lateral perfusion using a cannula in the innominate artery resulted in higher mortality rates compared to bi-lateral perfusion [37]. Kazui *et al.* operated on 220 patients using bi-lateral cannulation in the innominate and left common carotid arteries. The left subclavian artery was clamped during ASCP. They found an overall in-hospital mortality of 12.7% and an overall neurologic dysfunction rate of 9.3%, ASCP time did not seem to significantly influence on mortality and neurological outcome [38]. Tanaka *et al.* performed a laboratory study to address important perfusion details such as the optimum perfusion flow rates, pressure and perfusate temperature [39]. From these results, the technique of selective antegrade cerebral perfusion seems to be an extremely useful adjunct to DHCA alone.

Conclusion

Cerebral protection remains a technically challenging asset of aortic arch surgery. Over the years different techniques have been developed and studied to ensure adequate brain protection. Hypothermic circulatory arrest alone is an utmost essential and can be adjuncted with retrograde cerebral perfusion or antegrade cerebral perfusion. The neuroprotective effects of retrograde cerebral perfusion remain elusive. The combination of hypothermic circulatory arrest combined with either uni-lateral or bi-lateral selective antegrade cerebral perfusion is currently considered the optimal protection strategy for aortic arch surgery [40].

Acknowledgements

RAMS would like to thank dr. G. Geuzebroek, Department of Cardiothoracic Surgery, Radboud university medical center, Nijmegen, the Netherlands and L. L. Boer, Department of Anatomy, Radboud university medical center, Nijmegen, the Netherlands, for proofreading and providing feedback on this article.

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