Rationale for Implementation of Warm Cardiac Surgery in Pediatrics

Yves Durandy1,2*
1 Perfusion Department, CCML, Le Plessis Robinson, France, 2Intensive Care Department, CCML, Le Plessis Robinson, France

Cardiac surgery was developed thanks to the introduction of hypothermia and cardiopulmonary bypass in the early 1950s. The deep hypothermia protective effect has been essential to circulatory arrest complex cases repair. During the early times of open-heart surgery, a major concern was to decrease mortality and to improve short-term outcomes. Both mortality and morbidity dramatically decreased over a few decades. As a consequence, the drawbacks of deep hypothermia, with or without circulatory arrest, became more and more apparent. The limitation of hypothermia was particularly evident for the brain and regional perfusion was introduced as a response to this problem. Despite a gain in popularity, the results of regional perfusion were not fully convincing. In the 1990s, warm surgery was introduced in adults and proved to be safe and reliable. This option eliminates the deleterious effect of ischemia–reperfusion injuries through a continuous, systemic coronary perfusion with warm oxygenated blood. Intermittent warm blood cardioplegia was introduced later, with impressive results. We were convinced by the easiness, safety, and efficiency of warm surgery and shifted to warm pediatric surgery in a two-step program. This article outlines the limitations of hypothermic protection and the basic reasons that led us to implement pediatric warm surgery. After tens of thousands of cases performed across several centers, this reproducible technique proved a valuable alternative to hypothermic surgery.

Keywords: cardiopulmonary bypass, warm perfusion, warm blood cardioplegia, microplegia, pediatric cardiac surgery

INTRODUCTION

Perfusion is a typical case of experience-based medicine, and there is no agreement on even such basic factors as priming volume and composition, temperature on bypass, type of cardioplegia and re-dosing intervals, non-pulsatile or pulsatile perfusion. The dogma on the imperative need for hypothermic protection in pediatric cardiac surgery should be discussed in the light of modern anesthesia cardiac surgery and recent cardiopulmonary bypass components. This article aims to present the limitations of hypothermic perfusion and the reasons that led us to implement warm pediatric cardiac surgery.

EVOLUTION OF THE DOGMA ON HYPOTHERMIA PROTECTIVE EFFECT DURING CARDIAC SURGERY

In the 1950s, two major breakthroughs led to the initiation and development of open-heart surgery: systemic hypothermia and cardiopulmonary bypass. In 1950, Bigelow introduced systemic...
hypothermia with the goal of lowering oxygen requirements, allowing organs exclusion from the circulation for the period necessary for surgery (1, 2). Systemic hypothermia was the only way to obtain a bloodless operating field, allowing intracardiac repair under direct vision. In 1952, Lewis first applied systemic hypothermia (28°C) and a 5.5 min inflow occlusion to close an atrial septal defect. At the same time, the technology of extracorporeal circulation reached the stage of clinical application, and in 1953, Gibbon used the Gibbon-IBM heart–lung machine to close an atrial septal defect. This was the first open-heart surgery with cardiopulmonary bypass. Initially, the two techniques were used separately. In the 1960s, topical hypothermia around 28–29°C with circulatory arrest was mainly used in Novosibirsk in the treatment of ventricular septal defect, atrioventricular canal, and tetralogy of Fallot (3), while cardiopulmonary bypass with normothermia was mainly used in North America (4, 5).

The two innovations were soon combined, and the alteration in systemic temperature was simplified by the addition of a heat exchanger on the bypass circuit (6). Systemic hypothermia was enhanced by topical hypothermia for myocardial protection (7), and by cold cardioplegia in the 1970s (8, 9). There was no real consensus on the optimal temperature needed for the treatment of simple and complex cardiopathies. Moderate hypothermia (30°C) was used very successfully in 337 patients with tetralogy of Fallot (10), but more severe hypothermia was regarded as superior for organs protection allowing an optimal safety margin. Deep hypothermia with circulatory arrest was introduced in the 1960s and later popularized in complex pediatric cases (11–14).

It was commonly admitted that the benefits of hypothermia outweighed its drawbacks, and brain protection during circulatory arrest was indeed a major concern.

The physiology of brain is unique: while this organ accounts for about 2% of the body weight, its blood flow is 13% of the cardiac output, and its oxygen consumption is 20% of the total body oxygen consumption at rest (15). There is no doubt that hypothermia decreases brain oxygen consumption, and it is commonly admitted that this decrease is 6–7% for every degree below 37°C. Consequently, safe periods of circulatory arrest were estimated, but without agreement on the predicted safe duration. From one study to another, it varied from 40 to 60 min for systemic temperature of 20–22°C, to 29 min at 15°C (16–18). This lack of precision was made even worse by the inconsistency of temperatures recorded at various sites. In a study using electroencephalogram assessment of electrocerebral silence as an objective measure of brain function, the authors demonstrated that temperatures from nasopharynx, esophagus, and rectum were inaccurate in predicting the cessation of brain electrical activity. Electroencephalogram silence was observed with nasopharyngeal temperatures varying from 10.1 to 24.1°C and rectal temperatures varying from 12.8 to 28.6°C (19). The safe duration of circulatory arrest is not the only uncertainty in the management of deep hypothermia and the choice between pH-stat versus α-stat strategy is an endless debate (20–26). In the past, despite hypothermic brain protection, neurologic complications were frequent. Postpump chorea was strongly associated with deep hypothermia and circulatory arrest and the prognosis was guarded (27, 28). Much more frequent were post circulatory arrest clinical seizures, with an incidence of around 6–10% (29, 30) but three times more when seizures were diagnosed via continuous electroencephalographic monitoring (31). There is some evidence that neonatal seizures are a good surrogate marker of long-term neurologic outcome (32). As survival rate improved for congenital heart surgery, long-term neurodevelopmental delays were observed in patients treated with deep hypothermia. The dogma of brain hypothermic protection during circulatory arrest became progressively discussed, and antegrade selective cerebral perfusion was introduced to overcome the side effects of circulatory arrest with profound body hypothermia (33–35). The term cerebroplegia was used for cerebral perfusion with 6–10°C blood, while the body was perfused with moderate systemic cooling of around 26°C. Pediatric surgeons accepted to implement this technique for hypoplastic left heart syndrome first stage palliation or aortic arch surgery (36, 37). The benefits were disappointing compared to circulatory arrest, and several works failed to find any positive effect of antegrade cerebral perfusion (38–41). The appropriate hypothermic brain perfusion rate and pressure for neonates remain unknown. Many studies assessed hypothermic perfusion using oxygen delivery or oxygen saturation as a marker of perfusion quality. In fact, high oxygen saturation during hypothermic perfusion may indicate impaired oxygen transfer from blood to tissue rather than normal or over-perfusion (42). Besides, optimizing oxygenation does not mean "the more, the better," and any excessive blood flow can be detrimental, carrying the risk of cerebral edema and intracranial hemorrhage (43).

The mechanisms of hypothermic brain protection are still to be elucidated and decades after its implementation, the management of patients during hypothermia and rewarming is far from uniform. This is, at least in part, due to the lack of clear evidence about the optimal management.

The physiology of the heart is quite unique too. Being a muscle, its myocardial oxygen consumption is mainly related to its activity. At rest, the coronary blood flow represents 5% of cardiac output, while its oxygen consumption is 11% of the total consumption (15). Hypothermic myocardial protection during cardiac surgery is more questionable, as hypothermia increases oxygen consumption per beat, the decrease in oxygen consumption observed being due to bradycardia. It has been estimated that myocardial oxygen consumption, normalized for heart rate, more than doubles when temperature decreases from 37 to 22°C (44, 45). Furthermore, the decrease of myocardial oxygen consumption of an arrested heart is little influenced by temperature and, in dogs, there is an overlapping between myocardial oxygen consumption of a normothermic contracting empty heart and a heart during hypothermic (11°C) arrest (46).

Hypothermic protection of other organs including kidney, liver, gut, lungs, muscle, skin, and endocrine glands is even more questionable. Hypothermia depresses renal blood flow, glomerular filtration, osmolar clearance, and maximum tubular excretory capacity (47, 48). Glomerular filtration rate and renal plasma flow decrease by 40% at 32°C and 70% at 27°C (49). The blood flow of liver, gut, and pancreas is reduced during hypothermia, with a decrease in liver metabolic and excretory functions. There is some concern about the role of hypothermia in the increase in gut permeability and loss of mucosal integrity observed
following cardiopulmonary bypass. These gastrointestinal changes underline the risk of endotoxin or bacteria translocation from the gut to the blood (50, 51). The mechanical effects of hypothermia on lungs have been studied in sheep. A significant decrease in compliance was observed in animals subjected to hypothermia, while compliance was stable in animals subjected to anesthesia alone or normothermic bypass (52). The effects on soft tissue were rapidly established, as the first case of lethal subcutaneous fat necrosis was published in 1953 in a four-and-a-half-month-old boy operated on for a tetralogy of Fallot (53).

A few cases of this rare complication have been published with a more favorable evolution (54). Endocrine function is altered during hypothermia, the most frequent manifestation being a decrease in insulin production with hyperglycemia (55).

Apart from organ dysfunction, reversible platelet dysfunction (56), depressed immune system (57), and pH and PCO₂ modifications (58) have been related to hypothermia. There is also reasonable suspicion that increased endothelial permeability and edema may contribute to organ malperfusion during cooling and rewarming (59, 60).

The side effects of hypothermia are all reversible, and there is no doubt that hypothermic perfusion has been essential to the development and success of cardiac surgery. However, following hypothermia, the delay between normalization of temperature and normalization of organ function and metabolic drawbacks is likely to vary from one case to the other. This is particularly true for neurologic impairment, which may even persist in grown-up children (61), but possibly also for immune function, contributing to a higher risk of postoperative infection (62), and coagulation impairment, with its consequences (bleeding and transfusion) carrying their own risk (63, 64).

**BRAIN WARM ISCHEMIA: A MISUNDERSTOOD RISK**

A common opinion is that during normothermic, 5- to 10-min circulatory arrest, brain changes and neuronal death are irreversible. This is not totally in agreement with the observations in dogs, which can stand up to 30 min of circulatory arrest without permanent brain damage, provided blood is removed from the brain before the arrest (65), nor with observations made on humans following prolonged circulatory arrest. In such cases, hypoxia should affect all the brain with symmetrical destruction while, in fact, the destruction of large areas on one side co-occurs with unaffected corresponding areas on the opposite side (65). This is not in agreement with a recent experimental work on pigs, demonstrating that brain recovery following 30-min warm ischemia depends on the quality of reperfusion. The poorest outcomes, including brain edema and extensive cerebral infarct, were observed with “uncontrolled reperfusion,” while pulsatile “controlled reperfusion” resulted in minimal brain edema and no brain infarction. Uncontrolled reperfusion was defined as normal blood reperfusion by the pig heart, and controlled perfusion was performed via a mechanical pump with a high flow (66). This experimental work could contribute to explain the superior results observed with extracorporeal membrane oxygenation rescue versus conventional cardiopulmonary resuscitation. In one work on in-hospital cardiac arrest in pediatric patients, 11/27 patients (41%) were survivors, 10 of them having good neurologic outcomes (67).

There is, of course, no study establishing the safe limit of brain warm ischemia in man, and data have only been gathered from experience. Unexpected recoveries were observed following treatment of massive hemorrhage with deliberate circulatory arrest using induced ventricular fibrillation. Normothermic arrests up to 14 min were observed without sequelae (68). There is some evidence that the time to irreversible brain damage following normothermic brain ischemia is not necessarily as short as commonly admitted. Ischemia–reperfusion effects could be influenced by the quality of reperfusion and anticoagulation avoiding thrombosis in small brain vessels during circulatory arrest.

During full flow warm oxygenated blood perfusion, brain perfusion is controlled by auto-regulation. In case of an incident requiring circulatory arrest longer than the “classical” safe limit, controlled reperfusion should be used to obtain full recovery of the neurologic function. The new challenge is therefore to compare the inherent risks of hypothermic brain perfusion or hypothermic circulatory arrest against the inherent risks of warm perfusion.

**WARM CARDIAC SURGERY, THE ADULT EXPERIENCE**

Continuous whole body warm perfusion with oxygenated blood is one way to avoid the deleterious effects related to ischemia–reperfusion. This option, used in the early years of cardiac surgery (4, 5), was then abandoned until 1989, when a 64-year-old woman was operated on for mitral valve surgery with 33°C perfusion and 37°C continuous cardioplegia infusion. Due to cardiac rupture, the cross clamp time was 393 min. This patient was easily weaned off bypass without inotropic support or intra-aortic balloon pump, but died 17 h later from recurrence of arterio-ventricular separation (69). Following this impressive result, a randomized study on 1,732 coronary bypass surgery patients, classified into warm group (n = 860) and cold group (n = 872), failed to demonstrate any advantage of hypothermic brain protection, and serial creatine kinase MB fraction levels were significantly lower in the warm group (70, 71).

The constraint imposed by continuous cardioplegia infusion, be it antegrade or retrograde, was overcome in 1995. Intermittent antegrade warm blood was compared to cold blood cardioplegia in two groups of coronary artery bypass graft patients. The warm group showed improved outcomes in term of immediate hemodynamics and peak concentration of creatine kinase myocardial-specific isoenzyme. The incidence of myocardial infarction and stroke was lower in the warm group, albeit not reaching significance (72, 73). Warm perfusion and intermittent warm blood cardioplegia was implemented by other groups, confirming the feasibility, safety, and benefits of the technique (74–77). A meta-analysis failed to demonstrate any difference related to perfusion temperature in the incidence of stroke and deterioration of the
neuropsychological function following cardiopulmonary bypass (78). The lack of difference between cold and warm perfusion could be due to the fact that the period at higher risk of embolization occurred at the beginning and the end of bypass, when patients of both groups were normothermic. It is noteworthy that warm adult surgery, introduced 20 years ago, is used worldwide and that the risk of bypass circuit mechanical incident-related brain ischemia is more than exceptional. Intermittent warm blood cardioplegia was mainly used in coronary artery bypass graft and re-dosing intervals of 15 min or less were more than sufficient to perform a distal anastomosis. However, there was some concern regarding the maximum safe time to re-dosing. In the literature, the safe time to re-dosing increases progressively with increased experience in warm surgery. It was 5 min in 1992 (79), 10–15 min in 1995 (73–75), 30 min in 2000 (80), or even more. Single shot warm blood cardioplegia was used for aortic clamp time between 29 and 47 min (81).

IMPLEMENTATION OF WARM PEDIATRIC SURGERY A TWO-STEP SHIFT

We found several aspects attractive in warm perfusion and with recent oxygenators circuits and cannula, in experienced hands, the need for circulatory arrest was no longer essential. In the early 1990s, we thus shifted from cold to warm perfusion. Continuous warm blood cardioplegia being unrealistic in pediatric patients, the first step of our protocol combined warm perfusion with cold blood cardioplegia. The prime was heated to 37°C and the heater–cooler unit was set to 37.5°C during the whole bypass time. Such a protocol was not totally satisfactory, but we learned that warm perfusion was feasible and safe and observed a number of positive outcomes. As expected, time on bypass, a classical risk factor in pediatric cardiac surgery, decreased. The endless debate on the best pH management during hypothermic perfusion was avoided, as well as the risk of hyperthermic brain injury during rewarming (82). Convulsion, a manifestation usually related to deep hypothermia, was no longer observed, preventing long-term neurological impairment (32, 83, 84), and myocardium rewarming between cardioplegia re-dosing was limited by the interposition of a mattress perfused with cold water.

When intermittent warm blood cardioplegia was proved to be reproducible, efficient, and safe in the adult population, we implemented this technique in pediatrics. The second step combining warm perfusion and cardioplegia started in April 2001. Warm blood cardioplegia was in fact microplegia. Warm oxygenated blood was diverted from the oxygenator or from the origin of the arterial line via a roller pump. Downstream the roller pump, the arresting agent was added via an electrical syringe pump. The ratio of blood to arresting agent was 60:1 and the cardioplegia was sucked back into the circuit. The hydric balance of microplegia was negligible, limited to the few milliliters of arresting agent (85). The arresting agent was similar to St. Thomas I, which is composed of potassium, magnesium, and procaine. The re-dosing interval was 15 min, and we did not observe any hyperkalemia. Our initial experience with this new protocol was satisfactory. We compared retrospectively the last 950 patients operated on with warm perfusion and cold blood cardioplegia and 1,400 patients operated on with warm perfusion and intermittent warm blood microplegia. Spontaneous resumption of sinus rhythm was 99% in the warm group versus 77% in the cold group, and intensive care length of stay was under 48 h in 86 versus 75%. Four groups of frequent cardiopathies were selected to compare time to extubation and postoperative troponin levels: ventricular septal defect, tetralogy of Fallot, complete atrioventricular septal defect, and arterial switch operation. In each group, the results were significantly enhanced following warm surgery. Among the selected patients, mortality was comparable: 5 out of 364 (1.4%) in the warm group versus 5 out of 255 (1.9%) in the cold group. Following this study, we compared risk stratification in our unit to risk assessment from the Aristotle basic complexity score. Patients under 10 kg were included in the study, 38 had prolonged aortic cross-clamp time defined as a cross clamping time exceeding 90 min (group 1), and 196 had shorter cross clamp time (group 2). In terms of mortality and prolonged hospital length of stay, our results compared favorably to the data from the Society of Thoracic Surgeons and European Association for Cardio-Thoracic Surgery database. Interestingly, blood lactate level, a biomarker of perfusion quality, was at 2.5 mmol during bypass, peaked at 2.6 mmol/L on arrival to ICU in group 1 and reached 1.4 mmol/L 20 h later (86). This level was far lower than those associated with complicated postoperative courses described in the literature (87, 88).

The results obtained with warm surgery in our unit proved reproducible. The benefits of warm perfusion on immediate outcomes were confirmed through low requirement for inotropic and short time to extubation, low lactate production, adequate urine output, minimal drainage from the chest drains, short ICU and hospital stay (89). When compared to hypothermic perfusion, warm perfusion was associated with reduced oxidative stress (90). A study comparing arterial switch operation with either cold or warm surgery confirmed the benefits of warm perfusion on postoperative lactate blood levels, time to extubation and length of stay in ICU (91). Myocardial protection assessed on myocardial biopsies confirmed the superiority of warm blood microplegia, while early and late neurodevelopmental status, following warm perfusion, were equivalent to those observed during mild hypothermia (92). The absence of benefits of low temperature over warm perfusion on brain protection became ever more evident. Of note, several European units switched from cold to warm surgery, and none decided to shift back to hypothermia (89–94).

The growing experience in intermittent warm blood microplegia consolidated a significant body of evidence to support the good tolerance of warm myocardial ischemia. The issue was, as it has been for adults, to determine the maximal safe time to re-dosing. We progressively increased time to re-dosing from 15 to 35–40 min without any drawbacks (95–97). This slow drift was done over 10 years and was due to the frequent “2 min” delay requested by the surgeon. In a study assessing Troponin T following 35–40 min re-dosing intervals, we compared 4 groups of patients: 46 patients had cardiac surgery without aortic cross clamping (group 0), 81 patients had one cardioplegia injection (group 1), 31 patients had two injections (group 2), and 7 had 3 injections (group 3). There was no significant difference in
Troponin T levels between group 0 without myocardial ischemia and group 1 with 28.30 ± 8.84 min cross clamp time. In group 2 (65.71 ± 9.70 min cross clamp time), troponin was 2.17 ± 2.29 μg/L and in group 3 (114 ± 13.71 min cross clamp time), the level was 3.79 ± 3.00 μg/L. These blood levels of troponin compare favorably to those from patients receiving cold crystalloid cardioplegia (87, 88, 98). The main limitation of our study is the small number of long-term aortic cross clamp time.

Twenty years from the implementation of warm perfusion, and 15 years after we shifted to warm surgery, thousands of cases have been performed every year, mainly in Europe. The safety, efficiency, and advantages are widely acknowledged by surgeons who adopted this approach. We have been using the technique for all types of cardiopathies, including interruption of the aortic arch without or with transposition of the great arteries or total pulmonary anomalous venous return. During aortic arch repair, the arterial line was divided in two via a Y-type connector. The upper part of the body was perfused through the brachiocephalic artery and the lower part through the descending aorta or the femoral artery. Small femoral cannulas were specifically designed for neonates. We did not experience any of the drawbacks of femoral cannulation and immediate postoperative arterial Doppler demonstrated the permeability of the femoral artery. Many surgeons are less enthusiastic and prefer the comfort of circulatory arrest for complex cases. There is no discussion about the fact that cardiac surgery is teamwork and that the quality of surgical care is of utmost importance. The final decision in the operating room belongs to the surgeon. However, warm surgery is not a “point of no return”: in case of need, hypothermia can be instituted rapidly, especially in low-weight babies.

When coupled to warm surgery, pulsatile perfusion generates a peripheral pulse detectable with an oximeter. As expected, during pulsatile warm perfusion, pulse oximetry values were equivalent to values measured with a co-oximeter. Several commercially available monitors display not only saturation but also a numerical value known as the perfusion index, a relative assessment of the pulse strength. This index is influenced mainly by the amount of blood at the monitoring site and not by the level of oxygenation and there is some evidence that it accurately reflects peripheral perfusion (99, 100). We routinely monitor peripheral saturation and perfusion index, peripheral saturation and perfusion index being likely to reflect saturation and perfusion quality of end organs. Furthermore, we use peripheral saturation to adjust FiO₂ at the lowest level needed to reach a saturation of 98%, avoiding the potential deleterious effect of hyperoxia. In cyanotic patients, it was suggested that controlled reoxygenation decreased myocardial damage, oxidative stress, and cerebral and hepatic injury when compared to hyperoxic bypass (101). During aortic arch surgery, bilateral ear lobe sensor should display identical saturation and pulsatile index. Ear-lobe probe measures oximetry of the distal part of the external carotid artery and, in young patients, is likely to be a strong predictor of brain blood saturation. This simple tool could be a valuable alternative to monitoring of regional cerebral oxygenation via near-infrared spectroscopy. Studies comparing the two techniques are underway.

Beside the medical advantages, warm perfusion and intermittent warm blood microplegia are also cost-effective. The microplegia circuit is simple and therefore inexpensive and the arresting agent costs but a few euros. Furthermore, the negligible hydric balance of microplegia is a positive factor for blood conservation and contributes to reduce blood transfusion. For all these reasons, warm surgery was implemented by European teams in many humanitarian surgery missions. During missions, warm surgery is the perfect answer to the need for inexpensive and simple procedure, short time on bypass, and short intensive care length of stay, allowing more cases to be performed.

The main objection raised by opponents to warm surgery is the absence of safety margin in case of incident, requiring circulatory arrest lasting more than a few minutes. This is true, and if a surgeon experienced such incident during cold perfusion, he would probably better not implement warm surgery. However, after decades of application and tens of thousands of cases performed in numerous centers, we can confirm that the accidental risk is not a valuable reason to be afraid of warm surgery.

It is always challenging to choose a way opposite to the “gold standard” and the implementation of warm pediatric cardiac surgery was initially done against the opinion of the medical community. Nowadays, the results of pediatric cardiac surgery are so good that the number of patients needed to demonstrate the benefit of warm perfusion on mortality makes such a single center study utopian. Furthermore, cardiopulmonary bypass is only one element in the management of a patient. Cardiac surgery is a teamwork, the results of which depend on everyone involved in diagnosis, surgery, and intensive care including all the doctors, technician, and nurses from the medical staff. However, when a technique is simple, reproducible, safe, efficient, and cost-effective, and when no one changed his mind after choosing to implement it, it suggests that the approach makes sense. We can hardly imagine that full flow warm oxygenated blood brain perfusion could be worse than circulatory arrest or deep hypothermic regional cerebral perfusion. It is difficult to conceive that the good results observed in short-term outcomes on myocardial and brain functions could worsen over time, and we do hope that longitudinal studies will, in a next future, demonstrate the quality of long-term results of warm surgery.

**AUTHOR CONTRIBUTIONS**

The author confirms being the sole contributor of this work and approved it for publication.

**REFERENCES**

1. Bigelow WG, Callaghan JC, Hops JA. General hypothermia for experimental intracardiac surgery; the use of electrophrenic respirations, an artificial pacemaker for cardiac standstill and radio-frequency rewarming in general hypothermia. *Ann Surg* (1950) 132:531–9. doi:10.1097/00000658-195009000-00018

2. Bigelow WG, Lindsay WK, Greenwood WF. Hypothermia; its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperatures. *Ann Surg* (1950) 132:849–66. doi:10.1097/00000658-195011000-00001

3. Karaskov AM, Litasova EE, Vlasov YA. A documentary on the life and work of Eugenij Nikolaevich Meshalkin. *Circ Pathol Cardiac Surg* (1999) 1:4–11.
du Plessis AJ, Jonas RA, Wypij D, Hickey PR, Rivelli J, Wessel DL, et al. Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardio pulmonary bypass in infants. *Theor. Cardiovasc. Surg* (1997) **11**:991–1000; discussion **11**:1001-9.

Abdel Aziz KA, Mendoza A. Is pH-stat or alpha-stat the best technique to follow in patients undergoing deep hypothermic circulatory arrest? *Interact Cardiovasc Thorac Surg* (2010) **10**:271–82. doi:10.1515/ICTS.2009.214130

Medlock MD, Cruse RS, Winek SJ, Geiss DM, Hornnas DL, Schultz DL, et al. A 10-year experience with postpump chorea. *Ann Neurol* (1993) **34**:820–6. doi:10.1002/ana.40340611

Wong PC, Barlow CF, Hickey PR, Jonas RA, Castaneda AR, Farrell DM, et al. Factors associated with chooreoathetosis after cardiopulmonary bypass in children with congenital heart disease. *Circulation* (1992) **86**(Suppl):I118–26.

Ebihara A, Fenchel GM, Bender HW Jr. Incidence and prognosis of seizures in infants after cardiac surgery with profound hypothermia and circulatory arrest. *JAMA* (1984) **252**:3165–7. doi:10.1001/jama.1984.0350020071035

Rappaport LA, Wypij D, Bellingier DC, Helmers GS, Holm GL, Barnes PD, et al. Relation of seizures after cardiac surgery in early infancy to neurodevelopmental outcome. *Boston Circulatory Arrest Study Group. Circulation* (1998) **97**:773–9. doi:10.1161/01.CIR.97.8.773

Helmers SL, Wypij D, Constantinou JE, Newburger JW, Hickey PR, Carrazana EJ, et al. Perioperative electroencephalographic seizures in infants undergoing repair of complex congenital cardiac defects. *Electroencephalogr Clin Neurophysiol* (1997) **102**:27–36. doi:10.1016/S0003-4697(96)70078-8.

Clancy RR, McGaurn SA, Wernovsky G, Gaynor JW, Spray TL, Norwood WI, et al. Risk of seizures in survivors of newborn heart surgery using deep hypothermic circulatory arrest. *Pediatrics* (2003) **111**:592–601. doi:10.1542/peds.111.3.592

Guilmet D, Roux PM, Bacht J, Gouodt B, Tawil N, Diaz F. A new technic of cerebral protection. Surgery of the aortic arch. *Presse Med* (1986) **15**:1096–8.

Kazui T. Update in surgical management of aneurysms of the thoracic aorta. *Rinsho Kyobu Geka* (1986) **6**:7–15.

Bacht J, Guilmet D, Gouodt B, Dreyfus GD, Deleuendecker P, Brodaty D, et al. Antegrade cerebral perfusion with cold blood: a 13-year experience. *Ann Thorac Surg* (1998) **67**:1874–8. doi:10.1016/S0003-4975(97)00411-7

Pigula FA, Nemoto EM, Griffith BF, Sweers RD. Regional low-flow perfusion provides cerebral circulatory support during neonatal aortic arch reconstruction. *J Thorac Cardiovasc Surg* (2000) **119**:331–9. doi:10.1016/S0022-5223(00)70189-9

Asou T, Kado H, Imoto Y, Shiokawa Y, Tominaga R, Kawachi Y, et al. Selective cerebral perfusion technique during aortic arch repair in neonates. *Ann Thorac Surg* (1996) **61**:1546–8. doi:10.1016/0003-4975(96)00002-5

Goldberg CS, Bove EL, Devaney EJ, Mollen E, Schwartz E, Tindall S, et al. A randomized clinical trial of regional cerebral perfusion versus deep hypothermic circulatory arrest: outcomes for infants with functional single ventricle. *J Thorac Cardiovasc Surg* (2007) **133**:880–7. doi:10.1016/j.jtcvs.2006.11.029

Hoffman GM, Stuth EA, Jaquiss RD, Vanderwal PL, Staudt SR, Toshbrosny TJ, et al. Changes in cerebral and somatic oxygenation during stage I palliation of hypoplastic left heart syndrome using continuous regional cerebral perfusion. *J Thorac Cardiovasc Surg* (2004) **127**:223–33. doi:10.1016/j. jcts.2003.08.021

Sistino J, Atz AM, Ellis C Jr, Simpson KN, Ikonomidis JS, Bradley SM. Association between method of cerebral protection during neonatal aortic arch surgery and attention deficit/hyperactivity disorder. *Ann Thorac Surg* (2015) **100**:663–70. doi:10.1016/j.athoracsur.2015.04.119

Mahar VL, Ilangovan S, Cuisson R, Patil J, Dockter S, Rizzo V, et al. Does antegrade cerebral perfusion protect the brain during deep hypothermic circulatory arrest? *J Pediatr Surg* (2005) **40**:510–5. doi:10.1016/j. jps.2004.11.043

Dexter F, Hindman BJ. Theoretical analysis of cerebral venous blood hemoglobin oxygen saturation as an index of cerebral oxygenation during hypothermic cardiopulmonary bypass. A counterproposal to the “luxury perfusion” hypothesis. *Anaesthesia* (1995) **50**:405–12. doi:10.1111/j.1365-2044.1995.tb10021.x

Politio A, Ricci Z, Di Chiara L, Giorni C, Iacolla C, Sanders SP. Cerebral blood flow during cardiopulmonary bypass in pediatric cardiac surgery: the role of transcranial Doppler – a systematic review of the literature. *Cardiovasc Ultrasound* (2006) **4**:47–58. doi:10.1186/1476-7120-4-47
Association of complications with blood transfusions in pediatric cardiac surgery patients. **Pediatr Infect Dis J** (2009) 28(5):459–62. doi:10.1097/00001223-200905000-00012

67. Huang SC, Wu ET, Chen YS, Chang CI, Chiu IS, Wang SS, et al. Extracorporeal membrane oxygenation rescue for cardiopulmonary resuscitation in pediatric patients. **Crit Care Med** (2008) 36:1547–53. doi:10.1097/01.CCM.0b013e318170b6b2

68. Ulsey JR. Pathophysiology and Techniques of Cardiopulmonary Bypass. (Vol. II). Baltimore: Williams & Wilkins (1983). 37 p.

69. Lichtenstein SV, el Dalati H, Panos A, Slutsky AS. Long-term clamp time with warm heart surgery. **Lancet** (1989) 1(8765):1433–4. doi:10.1016/0140-6736(89)90140-2

70. The Warm Heart Investigators. Randomised trial of normothermic versus hypothermic coronary bypass surgery. **Lancet** (1994) 343:887–93. doi:10.1016/0140-6736(94)91519-9

71. Fremez SE, Tamariz MG, Abramov D, Christakis GT, Sever JY, Sykora K, et al. Late results of the Warm Heart Trial: the influence of nonfateful cardiac events on late survival. **Circulation** (2000) 102(Suppl 3):III33–45. doi:10.1161/01.CIR.102.suppl_3.III-33

72. Calafiore AM, Teodori O, Di Giammarco G, Bosco G, Mezzetti A, Lapenna D, et al. Intermittent antegrade cardioplegia: warm blood vs cold crystalloid. A clinical study. **J Thorac Cardiovasc Surg** (Torino) (1994) 55(Suppl 1):179–84.

73. Calafiore AM, Teodori O, Mezzetti A, Bosco G, Verna AM, Di Giammarco G, et al. Intermittent antegrade warm blood cardioplegia. **Ann Thorac Surg** (1995) 59:398–402. doi:10.1016/0003-4975(94)90834-V

74. Franke UF, Korsch S, Wittwer T, Albes JM, Wippermann J, Kahuza M, et al. Intermittent antegrade warm myocardial protection compared to intermittent cold blood cardioplegia in elective coronary surgery – do we have to change? **Europace** (2003) 5:341–4. doi:10.1016/S1040-1347(02)00828-X

75. Lichtenstein SV, Naylor CD, Feingold H, Cassidy G, Ragno G, Khuri S, Altschule MD. Complicating hypothermic cardiac surgery. **Ann Thorac Surg** (1992) 53:175–81. doi:10.1016/0003-4975(92)00828-X

76. Mehta PS, Naccarelli GV, Berbari EF, Englander D, Hani FE, et al. The intervals of cardioplegia. **Crit Care Med** (1996) 24:163–7. doi:10.1097/00003188-199602000-00053

77. Zimetbaum PJ, Dexter M, Lindan WE, et al. The effect of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. **Ann Thorac Surg** (1999) 68:488–99. doi:10.1016/S0003-4975(99)00572-5

78. Moyer JH. The effect of hypothermia on renal function and renal damage from ischemia. **Clin Lab Invest Suppl** (1970) 49222.x

79. Ehrlich MP, McCullough JN, Zhang N, Weisz DJ, Juvonen T, Bodian CA, et al. Pathophysiology and Techniques of Cardiopulmonary Bypass. (Vol. II). Baltimore: Williams & Wilkins (1983). 37 p.

80. Lichtenstein SV, el Dalati H, Panos A, Slutsky AS. Long cross-clamp time with warm heart surgery. **Lancet** (1989) 1(8652):1443. doi:10.1016/S0140-6736(99)80118-6

81. Moyer JH. The effect of hypothermia on renal function and renal damage from ischemia. **Ann N Y Acad Sci** (1959) 84:424–34. doi:10.1111/j.1749-6632.1959.tb49220.x

82. Sinclair DG, Haslam PL, Quinlan GJ, Pepper JR, Evans TW. The effect of mild perioperative hypothermia on cellular immune responses. **Clin Lab Invest Suppl** (1995) 89:43–51. doi:10.1097/00003359:1995:10000053

83. Buckberg GD, Brazier JR, Nelson RL, Goldstein SM, McConnell DH, Cooper Utley JR. Pathophysiology and Techniques of Cardiopulmonary Bypass. (Vol. II). Baltimore: Williams & Wilkins (1983). 37 p.

84. Ehrlich MP, McCullough JN, Zhang N, Weisz DJ, Juvonen T, Bodian CA, et al. Pathophysiology and Techniques of Cardiopulmonary Bypass. (Vol. II). Baltimore: Williams & Wilkins (1983). 37 p.

85. Lichtenstein SV, el Dalati H, Panos A, Slutsky AS. Long-term clamp time with warm heart surgery. **Lancet** (1989) 1(8652):1443. doi:10.1016/S0140-6736(99)80118-6

86. Mehta PS, Naccarelli GV, Berbari EF, Englander D, Hani FE, et al. The intervals of cardioplegia. **Crit Care Med** (1996) 24:163–7. doi:10.1097/00003188-199602000-00053

87. Zimetbaum PJ, Dexter M, Lindan WE, et al. The effect of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. **Ann Thorac Surg** (1999) 68:488–99. doi:10.1016/S0003-4975(99)00572-5

88. Moyer JH. The effect of hypothermia on renal function and renal damage from ischemia. **Clin Lab Invest Suppl** (1970) 49222.x

89. Ehrlich MP, McCullough JN, Zhang N, Weisz DJ, Juvonen T, Bodian CA, et al. Pathophysiology and Techniques of Cardiopulmonary Bypass. (Vol. II). Baltimore: Williams & Wilkins (1983). 37 p.

90. Lichtenstein SV, el Dalati H, Panos A, Slutsky AS. Long cross-clamp time with warm heart surgery. **Lancet** (1989) 1(8652):1443. doi:10.1016/S0140-6736(99)80118-6

91. Moyer JH. The effect of hypothermia on renal function and renal damage from ischemia. **Clin Lab Invest Suppl** (1970) 49222.x

92. Ehrlich MP, McCullough JN, Zhang N, Weisz DJ, Juvonen T, Bodian CA, et al. Pathophysiology and Techniques of Cardiopulmonary Bypass. (Vol. II). Baltimore: Williams & Wilkins (1983). 37 p.

93. Moyer JH. The effect of hypothermia on renal function and renal damage from ischemia. **Clin Lab Invest Suppl** (1970) 49222.x

94. Ehrlich MP, McCullough JN, Zhang N, Weisz DJ, Juvonen T, Bodian CA, et al. Pathophysiology and Techniques of Cardiopulmonary Bypass. (Vol. II). Baltimore: Williams & Wilkins (1983). 37 p.

95. Lichtenstein SV, el Dalati H, Panos A, Slutsky AS. Long-term clamp time with warm heart surgery. **Lancet** (1989) 1(8652):1443. doi:10.1016/S0140-6736(99)80118-6

96. Moyer JH. The effect of hypothermia on renal function and renal damage from ischemia. **Clin Lab Invest Suppl** (1970) 49222.x

97. Ehrlich MP, McCullough JN, Zhang N, Weisz DJ, Juvonen T, Bodian CA, et al. Pathophysiology and Techniques of Cardiopulmonary Bypass. (Vol. II). Baltimore: Williams & Wilkins (1983). 37 p.
85. Durandy Y, Hulin S. Intermittent warm blood cardioplegia in the surgical treatment of congenital heart disease: clinical experience with 1400 cases. J Thorac Cardiovasc Surg (2007) 133:241–6. doi:10.1016/j.jtcs.2006.10.004
86. Durandy Y, Younes M, Mahut B. Pediatric warm open heart surgery and prolonged cross-clamp time. Ann Thorac Surg (2008) 86:1941–7. doi:10.1016/j.athoracsur.2008.08.004
87. Taggart DP, Hadjinikolas L, Wong K, Yap J, Hooper J, Kemp M, et al. Vulnerability of paediatric myocardium to cardiac surgery. Heart (1996) 76:214–7. doi:10.1136/hrt.76.3.214
88. Lipschutz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, Sacks DB, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation (1997) 96:2641–8. doi:10.1161/01.CIR.96.8.2641
89. Shamsuddin AM, Nikman AM, Ali S, Zain MR, Wong AR, Corno AF. Normothermia for pediatric and congenital heart surgery: an expanded horizon. Front Pediatr (2015) 3:23. doi:10.3389/fped.2015.00023
90. Caputo M, Bays S, Rogers CA, Pawade A, Parry AJ, Suleiman S, et al. Randomized comparison between normothermic and hypothermic cardiopulmonary bypass in pediatric open-heart surgery. Ann Thorac Surg (2005) 80:982–8. doi:10.1016/j.athoracsur.2005.03.062
91. Pouard P, Mauriat P, Ek F, Haydar A, Gioanni S, Laquay N, et al. Normothermic cardiopulmonary bypass and myocardial cardioplegic protection for neonatal arterial switch operation. Eur J Cardiothorac Surg (2006) 30:695–9. doi:10.1016/j.ejcts.2006.07.032
92. Poncelet AJ, van Steenbergh M, Moniotte S, Detalle T, Beauloye C, Bertrand L, et al. Cardiac and neurological assessment of normothermia/warm blood cardioplegia vs hypothermia/cold crystalloid cardioplegia in pediatric cardiac surgery: insight from a prospective randomized trial. Eur J Cardiothorac Surg (2011) 40:1384–90. doi:10.1016/j.ejcts.2011.03.047
93. Corno AF, von Segesser LK. Is hypothermia necessary in pediatric cardiac surgery? Eur J Cardiothorac Surg (1999) 15:110–1. doi:10.1016/S1010-7940(98)00291-7
94. Durandy Y. Warm pediatric cardiac surgery: European experience. Asian Cardiovasc Thorac Ann (2010) 18:386–95. doi:10.11177/0218492310376675
95. Durandy Y, Rubatti M. Warm blood microplegia redosing interval in pediatric surgery. Ann Thorac Surg (2013) 96:2285–6. doi:10.1016/j.athoracsur.2013.06.076
96. Rubatti M, Durandy Y. Prolonged warm ischemia for transfusion-free arterial switch and ventricular septal defect surgery in a 4.5-Kg baby. Perfusion (2012) 27:230–4. doi:10.1177/0267659112437775
97. Durandy YD. Is there a rationale for short cardioplegia re-dosing intervals? World J Cardiol (2015) 7:658–64. doi:10.4330/wjc.v7.i10.658
98. Mildh LH, Pettilä V, Sairanen HI, Rautiainen PH. Cardiac troponin T levels for risk stratification in pediatric open heart surgery. Ann Thorac Surg (2006) 82:1643–8. doi:10.1016/j.athoracsur.2006.05.014
99. De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. Eur J Pediatr (2002) 161:561–2. doi:10.1007/s00431-002-1042-5
100. Hakam N, Dilli D, Zenciroglu A, Aydin M, Okumus N. Reference values of perfusion indices in hemodynamically stable newborns during the early neonatal period. Eur J Pediatr (2014) 173:597–602. doi:10.1007/s00431-013-2224-z
101. Caputo M, Mokhtari A, Miceli A, Ghorbel MT, Angelini GD, Parry AJ, et al. Controlled reoxygenation during cardiopulmonary bypass decreases markers of organ damage, inflammation, and oxidative stress in single-ventricle patients undergoing pediatric heart surgery. J Thorac Cardiovasc Surg (2014) 148:792–801. doi:10.1016/j.jtcs.2014.06.001

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2016 Durandy. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.