Normothermic cardiopulmonary bypass and myocardial cardioplegic protection for neonatal arterial switch operation

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Abstract

Objective: Hypothermic cardiopulmonary bypass (CPB) associated with cold myocardial protection is commonly used to perform neonatal cardiac surgery. Hypothermia is usually chosen to preserve the brain in case of failure of oxygen delivery whatever it may result from. Nowadays, there is a growing number of evidence demonstrating that hypothermia induces deleterious effects, which may culminate in organ dysfunctions. In 2001, we started a protocol where the heart and the body were no longer cooled, in all the procedures, including the arterial switch operation (ASO), except those with aortic arch reconstruction. Methods: Because data on the neonatal arterial switch operation were prospectively gathered in our unit (and included fine biochemical analysis of myocardial damage), we have compared two consecutive populations of arterial switch operation to sort out the impact of normothermic CPB and normothermic cardioplegia. Results: The results show that warm cardiopulmonary bypass associated with warm cardioplegia is feasible for ASO, and that most of the operative data are similar to hypothermic switch operation to sort out the impact of normothermic CPB and normothermic cardioplegia. Results: The results show that warm cardiopulmonary bypass associated with warm cardioplegia is feasible for ASO, and that most of the operative data are similar to hypothermic bypass. None are worse. Among the postoperative data, the cardiac troponin I (cTnI) time course showed significantly lower values in the normothermic group after 24 h ($4.46 \text{ ng ml}^{-1}$ vs $6.17 \text{ ng ml}^{-1}$ ($p = 0.027$)), time to extubation is improved ($32 \pm 6.17 \text{ h}$ vs $30 \pm 6.17 \text{ h}$ ($p = 0.02$)) and consequently the cost of surgery. Conclusion: Normothermic cardiopulmonary bypass is feasible for ASO and seems to allow a faster recovery time.

Keywords: Cardiopulmonary bypass; Normothermia; Congenital heart disease; Neonates; Arterial switch

1. Introduction

Hypothermic cardiopulmonary bypass (CPB) associated with cold myocardial protection is commonly used to perform neonatal cardiac surgery. The rationale for using this technique is to preserve the brain in case of failure of oxygen delivery whatever it may result from. In addition, hypothermic bypass helps complete cold myocardial protection by delaying myocardial rewarming and maintaining a low metabolic state. Nowadays, there is a growing body of evidence demonstrating that hypothermia induces deleterious effects, which may culminate in organ dysfunctions [1—5]. Furthermore, the protective effect of hypothermia on the inflammatory reaction and neurological recovery may have been previously exaggerated, as convincingly suggested by recent reports. The inflammatory reaction induced by CPB seems to be delayed rather than diminished by hypothermia [6]. Finally, when hypothermic bypass is associated with a circulatory arrest, long-term follow up has shown impaired neuro-developmental outcome [7]. Therefore, normothermic CPB, already commonly used in adult cardiac surgery, has been progressively extended in our paediatric practice [8,9].

Hypothermic cardioplegia has the same effects on the heart. Hypothermia delays recovery of mechanical function of the myocardium (the most important determinant of oxygen consumption) and reduces basal metabolism. This reduction, however, has only a minimal impact on oxygen need. Less known is the deleterious effect of hypothermia on the myocardium. Reactivity of the microcirculation seems to be impaired after deep hypothermia and possibly also many cellular functions. In 2001, we started a different perfusion protocol where the heart and the body were no longer cooled. The protocol was rapidly extended to most of our operations, including the arterial switch operation, when there was no need for an aortic arch reconstruction. The arterial switch operation has always been specially analysed in our unit with a prospective determination and gathering of fine biochemical markers of myocardial damage. This gave us the opportunity to finely compare two populations undergoing arterial switch
repair; one operated on with hypothermia and the other
operated on with normothermia. During the duration of
the study, the perfusion protocol was the only parameter that was
modified, and this allowed us to obtain two comparable groups
of patients and determine the impact of normothermia on
myocardial and body damage.

2. Methods

The arterial switch operation has always received
particular attention in our unit. A data bank was prospec-
tively created, which included many postoperative bio-
chemical parameters. In 2001, we changed our perfusion protocol
and introduced normothermic CPB with normothermic
cardioplegia. The last 20 neonates, with simple d-TGA,
operated with the traditional hypothermic CPB and cold
cardioplegia were compared with the first 20 neonates
operated on with our new protocol. All operations were
performed between October 2000 and October 2001 on
children less than 7 days of age. The children were referred
to us from France and overseas French territories and
operated consecutively by the same team using the same
technique.

2.1. Common approach

Induction of anaesthesia was performed with sevoflurane,
alfentanil and vecuronium, and maintenance of anaesthesia
was done with continuous infusions associating alfentanil and
midazolam (2 mcg kg\(^{-1}\) min\(^{-1}\)). All the patients underwent
the procedure with a closed circuit including a Dideco\(^6\) 701
gas exchanger and a centrifugal pump (Medtronic\(^8\) biome-
dicus). They received a high-dose aprotinin regimen,
30,000 KIU kg\(^{-1}\) before CPB and in the priming, followed
by 8000 KIU kg\(^{-1}\) h\(^{-1}\) of CPB. The efficacy of perfusion was
assessed by continuous monitoring of the oxygen venous
saturation which was kept over 70%, continuous haemoglobin
level (Terumo CDI 100\(^6\)) and discontinuous blood gas analysis.
Temperature was measured with rectal, oesophageal and
arterial line probes. CPB is performed at a flow rate around
3 l min\(^{-1}\) m\(^{-2}\) in the normothermic group and 2.7 l min\(^{-1}\) m\(^{-2}\)
in the hypothermic group, using alphastat blood gas
management with a PaO\(_2\) maintained below 150 mmHg.
The haematocrit is targeted to be at least around 44% at the
end of CPB for both groups. At the end of the procedure, low
doses of milrinone (0.3 mcg kg\(^{-1}\) min\(^{-1}\)) and epinephrine
(0.1 mcg kg\(^{-1}\) min\(^{-1}\)) were infused until the first echocardi-
ographic assessment of myocardial contractility.

2.2. Surgical technique

Our technique has already been reported elsewhere
\[10,11\]. Cardiopulmonary bypass was established between
both vena cava and the aortic arch. After cross-clamping of
the aorta, the heart was arrested with infusion of
cardioplegic solution in the aortic root and then intermitt-
tently selectively in the coronary ostia. The aorta and
pulmonary artery were transected. The coronary arteries
were harvested with a button of aortic wall. The defect
created was covered with a single patch of fresh autologous
pericardium. After division of the ductus arteriosus and
extensive dissection of the pulmonary arteries, the pulmonary
bifurcation was translocated anterior to the ascending
aorta. The native pulmonary root was anastomosed to the ascending
aorta and the coronary arteries were reimplemented appro-
priately. The atrial septal defect (ASD) was closed using an
incision in the right atrium. The heart was then deaired, warm
blood cardioplegia given in the neoaortic root and the aortic
cross-clamp removed. The pulmonary bifurcation was recon-
structed on a perfused and beating heart. Cardiopulmonary
bypass was discontinued after haemodynamic and rhythm
stability was achieved. Continued ultrafiltration of blood was
performed during CPB, as previously described by our group
\[12\]. Additional modified ultrafiltration was not performed.

2.3. Hypothermic group

Immediately after initiation of CPB, core temperature was
lowered to approximately 23 and 25 °C. After cross-clamping of
the aorta, an initial dose of warm cardioplegia (induction
cardioplegia) was followed by intermittent infusion of cold
blood (at 8 °C) cardioplegia every 20 min, or sooner when
myocardial activity resumed. Warm blood cardioplegia was
given (hot shot cardioplegia) shortly before the removal of
the aortic clamp. The patient was rewarmed during
reconstruction of the pulmonary bifurcation. Ultrafiltration
of blood was initiated during the rewarming phase and
terminated at the end of CPB.

2.4. Normothermic group

Core temperature was maintained between 35 and 36 °C.
Cardioplegia was obtained by infusion of warm hyperkalaemic
blood every 10 min for 1 min, or sooner when myocardial
activity resumed. Ultrafiltration was used throughout CPB.

2.5. Measurements

Perioperative data were prospectively recorded including
duration of surgery, aortic clamping time, CPB assistance
time, volume of cardioplegic solution, incidence of delayed
ternal closure, time to extubation, length of stay in the ICU
and mortality rate.

Myocardial protection was assessed clinically and bio-
chemically. Spontaneous sinus rhythm recovery, dysrhyth-
mias, electrical shock and potassium level at the end of aortic
clamping and at the end of the procedure were recorded.

Cardiac troponin I (cTnI) was measured before bypass,
30 min after aortic unclamping, 6, 12, 18 and 24 h after the
procedure with the immunoenzyme assay Stratus provided by
Dade\(^6\) (Fig. 3).

2.6. Statistical analysis

Statistical analysis was performed with Epi Info 6.04 Fr
software (CDC Atlanta). Results are expressed as the
mean ± SEM. Intragroup and between groups comparisons
were achieved using ANOVA, followed by Fisher’s t-test when
statistical significance was detected, or with non-parametric
test (Kruskal–Wallis for two groups–Mann–Whitney U-test)
when appropriate. Where information is missing, the number
of non-missing values is given. The criterion of significance was \( p < 0.05 \).

### 3. Results

Groups were similar in known risk factors like age, weight, coronary pattern and associated cardiac anomalies (Table 1). Cardiopulmonary bypass, aortic cross-clamp and assistance on CPB times did not differ between groups (Table 2). The normothermic group received significantly more cardioplegic volume than the hypothermic group (153 ± 27 ml kg\(^{-1}\) vs 128 ± 31 ml kg\(^{-1}\) (\( p = 0.01 \)). The volume of ultrafiltration was not significantly different between the groups, although a little bit higher in the normothermic group (332 ± 103 ml kg\(^{-1}\) vs 275 ± 40 ml kg\(^{-1}\) (\( p = 0.1 \)). The rate of delayed sternal closure was 10% (2/20 patients) and 15% (3/20 patients) in the normothermic and hypothermic group, respectively (\( p = 0.7 \)).

#### 3.1. Clinical outcome

No patient died during hospitalisation or thereafter. The time on mechanical ventilation was significantly shorter in the normothermic group (32 ± 26 h vs 70 ± 69 h (\( p = 0.02 \)) (Fig. 1). The length of stay was also shorter in this group (3.5 ± 1.5 days vs 5.6 ± 3.9 days), although not significantly (\( p = 0.08 \)) (Fig. 2).

All the patients resumed a spontaneous sinus rhythm without need for electrical shock. Two patients showed subsequent arrhythmia: one patient (hypothermic group) presented a transient run of ventricular tachycardia, and the other patient with preoperative atrial flutter (normothermic group) resumed a transient atrial flutter after a short period of sinus rhythm.

#### The cTnI showed significantly lower values in the normothermic group than in the hypothermic group after 24 h (Fig. 3). The time course, however, showed a reduction of the difference on an accumulated scale which no longer reached significance. In spite of the infusion of larger cardioplegic volume, the potassium level did not significantly increase in the normothermic group (3.7 ± 0.6 mmol l\(^{-1}\) vs 4.2 ± 0.8 mmol l\(^{-1}\)).

None of the patients experienced neurological disorders such as seizures, chore athetosis or motor deficit during the ICU stay. None of them needed peritoneal dialysis for acute renal failure.
4. Discussion

After decades of debates, adult cardiac surgery is nowadays often performed at normothermia [13] whereas routine neonatal CPB is still performed at low temperature [14]. By observing our two groups of patients, we tried to answer the following questions: is it feasible, is it safe and finally is this shift from cold to warm CPB justified in paediatric cardiac surgery?

First, those results and those of other children now reaching more than 2500 patients clearly show that this perfusion protocol is feasible and safe. None of the reported parameters are worse in the normothermic group compared with the hypothermic group. Normothermia, in spite of the more frequent administration of cardioplegia, neither increases the length of the procedure nor the duration of the aortic cross-clamping. Anaesthetic requirements remain unchanged and none of the routine process associated with bypass such as ultrafiltration or aprotinin protocol had to be modified. The results do not show important difference between groups. Nevertheless, the normothermic group presents a quicker recovery as shown by a shorter time of mechanical ventilation, a shorter length of stay in the ICU and a quicker return to the baseline of cTnI. These results are obtained without additional or deleterious effects, particularly with regard to potassium level and arrhythmias. Due to the large standard deviation, in the hypothermic group, the difference in ICU length of stay cannot be expressed as significant although the mean duration in the normothermic group is 3.5 ± 1.7 days versus 5.5 ± 4 days in the hypothermic group. Shorter time to extubation in the normothermic group is one of the findings of the study. Lungs are very sensitive to CPB, and hypothermia could increase the capillary leakage more than normothermia by inducing microcirculatory dysfunction and impairing endothelial responses [15]. Time on bypass is not shorter in the normothermic group probably due to the time for surgical haemostasis after bypass which remains essential in the ASO. The myocardial protection seems to be adequate with regard to spontaneous rhythm recovery, low rate of arrhythmias, lack of low cardiac output syndrome and cTnI time course. The level of inotropic drugs has not been compared in this study due to our protocol using systematically 0.5 mcg kg\(^{-1}\) min\(^{-1}\) of milrinone and 0.1 mcg kg\(^{-1}\) min\(^{-1}\) of epinephrine after the completion of CPB. When paediatric cardiac surgery is performed using hypothermic CPB and when a cardiac arrest is required, the myocardial protection generally depends on a cold cardioplegic solution. It may be more or less sophisticated with cristaloids or blood, with or without additives, with warm induction and/or warm reperfusion. Neonatal hearts may be difficult to protect because of immaturity, cyanosis, hypertrophy of the right ventricle, complex coronary artery pattern and duration of ischaemia to achieve a good repair. When using a normothermic bypass, two methods are available; continuous or intermittent warm cardioplegia.

Continuous warm cardioplegia has already been described for Fallot repair or mitral valve replacement in children [16]. It does not make surgery more comfortable and is at risk of producing excessive hyperkalemia. Intermittent warm blood cardioplegia (IWBC) routinely used in adult patients could be the appropriate choice in this setting. Myocardial protection seems to be dependent on age and degree of cyanosis and is difficult to assess in paediatric cardiac surgery. Despite many unsolved questions, cTnI time course seems to be the best marker of perioperative myocardial injury [17] and therefore is a good surrogate to evaluate strategies of myocardial protection. In ASO, the cTnI time course is particularly interesting because of the absence of ventriculotomy, therefore the cTnI level is a direct marker of myocardial injury. We have monitored cTnI time course in more than 300 arterial switches to identify specific time courses. In ASO for simple TGA, cTnI increases during the early postoperative period, peaks between the 12th hour and the 18th hour to less than 10 ng ml\(^{-1}\) and declines slowly to return to baseline between the second and the third postoperative day without secondary increase. In our study, the results are very similar between cold blood diluted cardioplegia associated with warm induction and reperfusion and IWBC. Both methods seem to provide a good myocardial protection. Nevertheless, the myocardium seems to recover quicker in the normothermic group with IWBC, as shown by the lower cTnI level at 24th hour postoperatively. These results corroborate a recent experimental study reporting an increase in reactive oxygen species during hypothermia [18].

The incidence of delayed sternal closure is lower in the normothermic group although not significant (10% vs 15%, p = 0.7) but in our group, the indication to delay the sternal closure is based more on low weight (<2.5 kg) and difficult coronary patterns rather than on haemodynamic or echocardiographic data. Results after repair of congenital heart defects are improving and the mortality/morbidity rates are decreasing continuously [10]. Change in cardiopulmonary bypass technique is responsible for this improvement as well as improved surgical and anaesthetic techniques, echocardiography and postoperative care. Modifications to neonatal cardiopulmonary circuits and management have been numerous such as smaller pump, priming and canulae, ultrafiltration, assisted venous drainage, methods to modulate the systemic inflammatory response [19] and better understanding of deep hypothermic circulatory arrest (DHCA) pathophysiology [20]. This change in the approach of neonatal cardiac surgery allowed early corrective surgery even in premature and low birth weight infants. Despite the arising of this advanced technology, bleeding, blood components transfusion, low postoperative cardiac output, delayed sternal closure and impaired neurological outcome are still present and add to the morbidity/mortality rate. The advantages of hypothermia with or without DHCA have been well described. Hypothermia has been used mainly to increase the ischaemic tolerance by reducing the oxygen demand, to protect the brain when the surgical repair required a decrease of CPB flow to dry the operating field. With the development of DHCA and later with the low-flow technique, hypothermia remained actually the only way. In addition, hypothermia avoided spontaneous myocardial rewarming and allowed an adequate myocardial protection. Hypothermia was also designed to cope with any technical problem arising during the procedure (circuit leakage, power failure, etc.). With regard to the incidence of technical problems, this point is much less relevant [21] than before as long as the recommendations for standards of monitoring and alarms are met. After decades of hypothermic CPB, there is a
growing number of evidences that show that temperature management during CPB may influence perioperative outcome. The price to pay for the benefits of hypothermia is particularly high: impaired haemostasis [1], microcirculatory dysfunction, capillary leakage, parenchymal oxygen delivery, endotoxin release, glucose metabolism [2] or myocardial contractility [3]. By reducing oxygen demand, hypothermia is effective in protecting the brain, but it impairs vasomotricity and cerebral oxygen regulation [4] alters energetic metabolism [5], increases intracranial pressure and rewarming may induce neurological injury [22]. With regard to the management of CPB, normothermia makes it more simple and preserves vasomotricity, avoiding vasoactive drugs during CPB. Excessive pulmonary venous return can be managed by reducing the pump flow down to venous oxygen saturation around 70% and does not impede surgery.

Further studies will have to provide answer on bleeding, renal function, and particularly on neuro psychological outcome. A recent study [9] found no difference in the release of brain specific proteins (NSE and S-100 beta protein) between hypothermic and normothermic CPB during repair of congenital heart disease. Another study [23] reports that cortical oxygen extraction is maintained during warm cardiopulmonary bypass at full flow and moderate haemodilution, and cerebral oxygen balance assessed by SjO$_2$ is not impaired during normothermic CPB. In our cohort of ASO, none of the patients experienced clinical or electrical seizures nor motor deficit or choreic movements. Long-term neurological assessment has not been performed yet.

In conclusion, due to the lack of literature about warm neonatal surgery, it is difficult to compare our experience with others. We are aware of the fact that this study has some limitations regarding the methods, but in this setting it is difficult to blind the protocols. Nevertheless we can say that normothermic cardiopulmonary bypass associated with warm cardioplegia is feasible for ASO, and that most of the operative data are similar to hypothermic CPB. Among the postoperative data, extubation time is improved, myocardial protection seems to be better regarding troponin I recovery and there is a trend to reduce the length of ICU stay and consequently the cost of surgery.

References