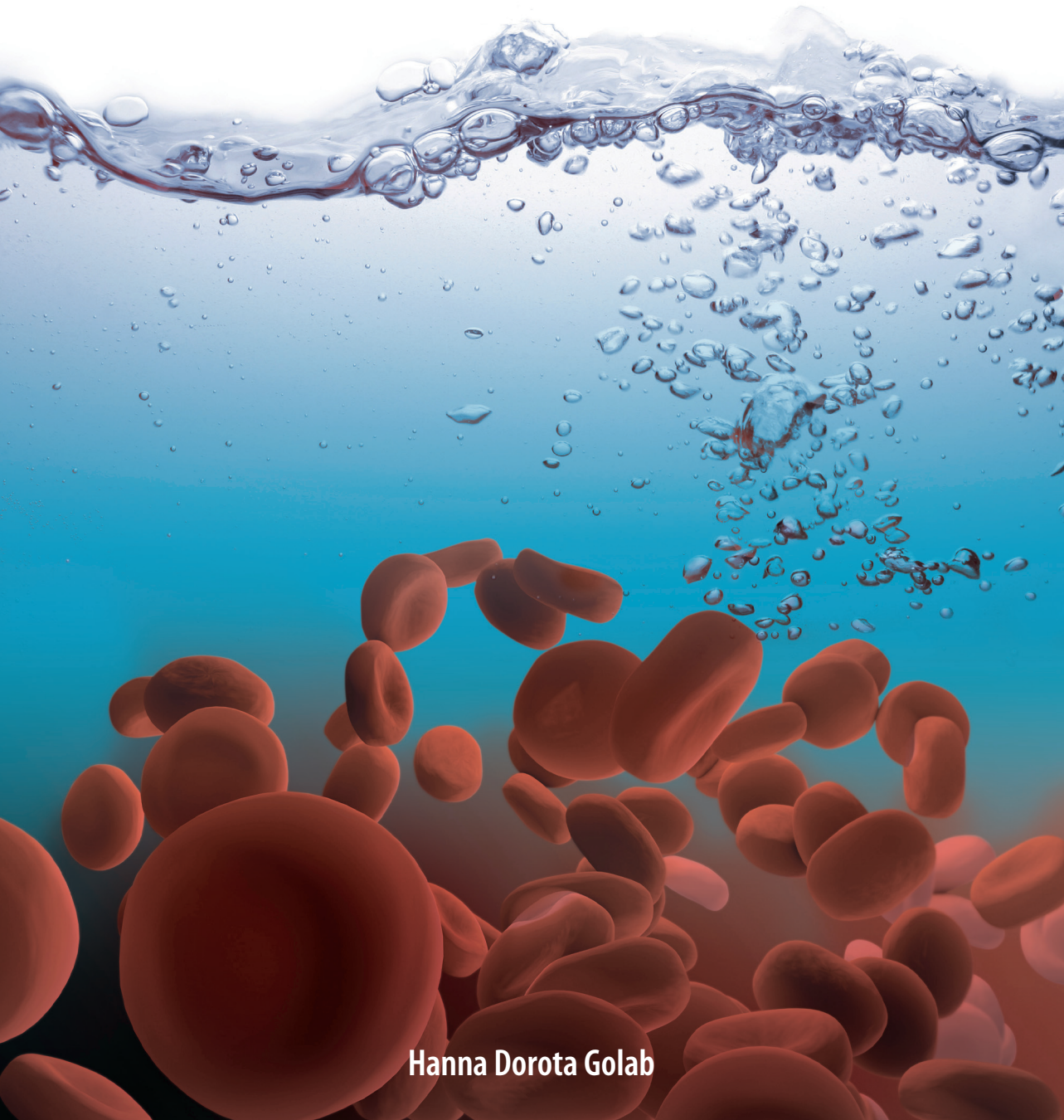
INNOVATIONS IN PEDIATRIC CARDIOPULMONARY BYPASS
A CONTINUOUS PROCESS OF QUALITY IMPROVEMENT



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INNOVATIES IN PEDIATRISCHE CARDIOPULMONALE BYPASS
EEN CONTINU PROCES VAN KWALITEITSVERBETERING

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CONTENTS

Chapter 1

General introduction

Cardiopulmonary bypass (CPB) is defined as a technique that temporarily replaces the function of the heart and lungs, maintaining an adequate blood circulation and oxygen content of the body during surgery of the heart and great vessels.

The current practice of cardiopulmonary bypass was achieved through the efforts of a numbers of individuals who believed that artificial cardiopulmonary support could replace the body's own circulatory and respiratory systems. Collaborative efforts of physiologists, chemists, physicists, engineers, and physicians led to design and development of synthetic devices that could effectively sustain patients who required corrective surgical procedures of treatable lesions of the heart, lungs or other vital organs.

In 1937, Gibbon reported the first successful total cardiopulmonary bypass of an animal (cat) with the use of heparin, a Dale-Schuster-type pump, and a vertical rotating cylinder oxygenator [1]. However, it was not until 1951 that cardiopulmonary bypass was applied in a patient, enabling an unobstructed view of intracardiac lesions. In Minneapolis on the 5th of April 1951, Dennis and his associates performed the first total cardiopulmonary bypass in a 6-year old patient with an endocardial cushion defect [2]. Unfortunately, the patient could not be weaned from the bypass and died on the table because of cardiac failure. Gibbon, who considered to be the "father of cardiopulmonary bypass", together with his wife Mary refined the work of Dennis and successfully performed on the 20th of May 1953 in Philadelphia the closure of an atrial septal defect in an 18-years old patient [3]. This moment marked in the history of cardiopulmonary bypass the beginning of the "applied technology period" that lasted from 1950 to 1970. The "refinement period" has followed and lasts until present [4].

Cardiopulmonary bypass is still an unavoidable prerequisite for complete repair or palliation of many congenital cardiac defects. The current policy in cardiac surgery is to perform a complete repair of congenital heart defects early in life, preferably in neonate and infant patients, before the heart and other organs adapt and change according to the abnormal physiology. In the past 30 years, mortality after pediatric cardiac surgery in Europe and the United States decreased from greater than 50% to less than 2% [5]. This exceptional reduction was achieved through improvements in CPB, and the evolution of diagnostic and surgical techniques as well as perioperative care. However, the exposure of the young and small patients to the CPB still may result in major morbidity and represents a serious challenge for all involved healthcare professionals.

Attempts to reduce postoperative mortality and morbidity related to CPB contain a continuous process of quality improvement (CQI) concerning perfusion technique. Different aspects of quality improvement can be recognized: product improvement, process improvement and people based improvement. The concept of CQI was introduced in the 1920s by Shewhart. Working in the Bell Telephone Laboratories on methods to improve quality and lower costs, he developed the concept of control with regard to process variation [6]. CQI has been used in the manufacturing world more extensively

than in healthcare, despite of being equally well applicable to processes in medicine. Control of process variation includes the observation of a phenomenon, the isolation of influential variables, and changing the process. If a change proves to be beneficial, it will be implemented. If it does not result in advancement, new solutions are explored. Moreover, the CQI concept emphasises strongly that there is always the next area to improve [7].

On institutional level, since many years, perfusionists in the ErasmusMC have been applying the guidelines of CQI into CPB technique. Firstly, the specific CPB registry was developed to automatically collect relevant perfusion and patient data. Secondly, audits of existing data were performed to recognize CPB risk factors and areas of improvement. The evidence-based process innovations, in terms of employed materials and strategies, were introduced and subsequently the results were evaluated. All those efforts were taken to model the CPB strategy to become as beneficial as possible for pediatric patient.

Recently, worldwide healthcare professionals recognized the need of evidence–based perfusion and quality improvement in the field. That led to the formation of the International Consortium for Evidence-Based Perfusion (ICEBP) in October 2006. The mission of the Pediatric Process Improvement Subcommittee of the ICEBP is to "develop, foster, and promote process improvement in the delivery of perfusion services for neonatal, infant and pediatric patients. The objectives of this committee include the development of pediatric practice guidelines and a registry specific to pediatric perfusion. Additionally, the Committee has started collaboration with other congenital heart disease societies such as the World Society for Pediatric and Congenital Heart Disease."[8, 9].

Background on cardiopulmonary bypass

Cardiopulmonary bypass provides a complex set of nonphysiologic circumstances under which patients are subjected to severe physiologic alterations. The systemic inflammatory response syndrome, also named postperfusion syndrome, is recognized as the most deleterious effect of CPB. Its multifactorial etiology is associated with generalized activation of the immune system [10, 11], direct tissue trauma and ischemia-reperfusion injury to the vital organs [12]. Consequently, capillary leak, acute lung injury, coagulopathy and multiorgan failure may occur to some extend in the postoperative period. In neonates and infants, those deleterious effects of CPB are often more pronounced than in adults. One of the reasons is immaturity of vital organs, as well as coagulation and the endocrine system [13]. Additionally, due to the higher metabolic demands, neonates and infants require higher perfusion flow rate per body surface area and this may produce higher sheer stress on the blood cell components. Another negative factor is an extreme disproportion between the CPB circuit size (surface area and volume) in relation to patient size. This results in significant dilution of clotting factors, red blood cells and plasma proteins. As compensation, homologous blood products are transfused

that may exacerbate the inflammatory response [14]. Finally, surgical corrective techniques for some of congenital heart defects still require deep hypothermia with low flow perfusion rates or even circulatory arrest to allow repair and to facilitate adequate exposure [15].

In the last two decades, technological development and intensive clinical research on CPB helped to establish basic guidelines to enhance the outcome for neonatal and infant patients. An effort has been made to ameliorate the adverse CPB effects related to hypothermia used purposely during the bypass [16]. Technical improvements of the CPB circuit and evolution of the surgical skills allowed for temperature strategy changes, the reduction of depth of hypothermia from moderate (± 28 ° C) to mild (± 32 ° C) or to normothermia in most pediatric cardiac procedures [17].

Continuous product improvement has resulted in a miniaturized CPB circuit, tailored to the size of the patient. Manufacturers of circuit elements (oxygenators, arterial filters, ultrafiltration devices) downsized the new models without compromising on the safety and performance quality. Additionally, new pediatric dedicated heart-long machines with pole-mounted pump-heads gave the opportunity to redesign the customary circuits to reduce the volumes and contact surface area and therefore diminished hemodilution and inflammatory response [18].

Another technological innovation that has been successfully introduced as a routine treatment into pediatric CPB is the use of coating materials on the circuit surface. Primarily, heparin- bounded coating layers were designed to allow the reduction of heparinization level during CPB. Its biocompatible quality recognized in clinical studies stimulated further development of different materials with specific bio-neutral qualities [19]. Although the clinical relevance of the biocompatible coatings in neonatal and infant CPB is still a point of discussion [20] the results from clinical studies showed a significant decrease of cytokine and interleukin level in plasma when CPB circuit was coated [21].

Furthermore, conventional ultrafiltration and modified ultrafiltration during- and post-bypass gained lately on popularity as a powerful anti-inflammatory and anti –hemodilutinal strategy. This was possible due to the availability of a wide range of small pediatric hemoconcentration devices [22, 23].

Miniaturization of the CPB circuit and optional use of hemofiltration facilitate a basis for substantial reduction of homologous blood products transfusion during CPB [24].

Additionally, intraoperative blood salvage, that proved a very effective strategy to reduce perioperative transfusion demand in adult patients [25], was introduced into pediatric cardiac surgery. The feasibility of this step depended on the development of a small, high quality salvage system [26]. Not only blood loss during surgery was collected into the cell saving device, also the residual volume of CPB circuit could be processed. In that manner the total blood loss was reduced, requirement for homologous red blood

cell concentrate was diminished and retransfusion of unprocessed residual volume containing inflammatory mediators was avoided [27].

Despite of miniaturization of the bypass circuit and diminishing of the CPB related hemodilution, the composition of the priming solutions is still studied as an important aspect of CPB quality improvement process. The post CPB capillary leak with an undesirable extravasation of the fluids and postoperative weight gain are documented and studied in neonates and infants undergoing CPB [28]. Lowered plasma colloid osmotic pressure (COP) during CPB is pointed as the culprit of the fluids shift and postoperative oedema [29].

In addition, results of clinical studies established that during CPB the level of most stress hormones raises and that hypothermia during the bypass enhances this effect [30, 31]. The insulin level in plasma can be decreased as well as a peripheral response to this hormone, therefore the plasma glucose level may rise [32]. On the other hand, the glycemic control in the perioperative period, aiming at avoidance of hyperglycemia by maintening normal glucose levels, may be a risk for hypoglycaemia and adverse outcomes [33].

Aim and the structure of the thesis

The aim of this thesis was to investigate the results of specific innovations that were tested and implemented to contain advers effects of neonatal and infant CPB in an attempt to reduce CPB related morbidity and to improve patient outcome.

In Chapter 2, we studied the clinical relevance of the temperature management during CPB on clinical outcome in pediatric patients undergoing correction of ventricular septal defect.

The effects of CPB circuit reduction and processing of the residual volume after the bypass were retrospectively studied in Chapter 3. The results of this retrospective audit encouraged the prospective trial on further circuit reduction and adjuvant perioperative blood salvage in neonates and infants (Chapter 4). The consequences of stepwise circuit miniaturization as a prerequisite for a bloodless neonatal and infant cardiopulmonary bypass are presented in Chapter 5. Chapter 6 reviews different strategies and future possibilities to achieve fully bloodless cardiopulmonary bypass in neonates and infants.

We recognized and retrospectively studied the risk factors for the occurrence of low COP during the CPB in Chapter 7. Subsequently, in a prospective study (Chapter 8) we examined in a randomized fashion the impact of different COP regulatory strategies on postoperative weight gain, fluid balance and clinical outcomes.

In Chapter 9, we present results of the retrospective data audit related to the intraoperative glycemia control strategy.

Chapter 10 contains the general discussion and conclusions to this thesis as well as the recommendations concerning innovative CPB strategy for pediatric patients.

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Chapter 2

The effect of temperature management during cardiopulmonary bypass on clinical outcomes in pediatric patients undergoing correction of ventricular septal defect

Golab HD, Wijers MJ, Witsenburg M, Bol Raap G, Cruz E, Bogers AJJC.

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ABSTRACT

Background: Moderate hypothermia of 28 °C is widely accepted in cardiac surgery with cardiopulmonary bypass (CPB). Recently however, several studies suggested that normothermic or "tepid" bypass techniques may improve the clinical outcomes for patients undergoing cardiac operations.

Methods: To assess the effect of bypass temperature management strategy in pediatric patients undergoing correction of ventricular septal defect, 26 patients with body weight under 10 kg were randomly assigned to two treatment groups: Group 1, mild hypothermia , patients cooled to nasopharyngeal temperature of 32 °C during the bypass; or Group 2, moderate hypothermia of 28 °C. Clinical parameters were recorded and blood samples were obtained just before, during and 24 hours after operation.

Results: All the population characteristics and intraoperative variables were similar in the two groups. Hematologic data after CPB and protamine administration revealed a significantly ($p<0.05$) longer activated partial thromboplastin time in the 32 °C group, however the difference in blood loss did not reach significance.

Conclusion: Our study shows that both perfusion temperatures equally well facilitated CPB for this type intracardiac surgery.

INTRODUCTION

Until recently, intracardiac repair in pediatric cardiac surgery was mostly performed with moderate (27 - 30 °C) to profound (< 25 °C) systemic hypothermia. The exceptions to this rule were short procedures for which only mild (30 - 32 °C) hypothermia was used.

Systemic hypothermia reduces tissue metabolic rate and oxygen demand and is used to protect the myocardium and the brain against potential ischemic insult [1-3]. Furthermore, it enhances protection of the other organs. Systemic hypothermia allows to lower the arterial blood flow and promotes better conditions in the operation field as well as less blood trauma occurrence. Hypothermia also causes marked changes in the peripheral circulation, hormonal body response and alterations in organ function. Generalized inflammatory response, involving the complement, coagulation, kallikrein and fibrinolytic cascades, is often a dominant feature of hypothermic bypass [4-6]. Undoubtedly, hypothermia has its positive as well as negative aspects during cardiopulmonary bypass (CPB). Therefore, normothermic CPB with warm cardioplegia in adult cardiac surgery is becoming increasingly popular [7]. In pediatric heart surgery, technical developments and enhanced surgical skills also allow reduction of depth of hypothermia in most of the procedures. Still comparatively few publications have addressed the issues raised by maintenance of mild or moderate hypothermia during pediatric bypass.

The aim of this study was to compare clinical results between two groups of pediatric patients, operated with short aorta occlusion times and mild or moderate hypothermic CPB.

MATERIALS AND METHODS

Patients

The study population comprised 26 consecutive pediatric patients who underwent closure of ventricular septal defect (VSD) with use of a Gore - Tex® patch. Only children with body weight under 10 kg and without concomitant heart disease were included. Exclusion criteria were: respiratory insufficiency with need of respiratory support, kidney failure, liver failure and neurological impairment. Patients were equally randomized into two groups: Group 1, mild hypothermia (nasopharyngeal temperature ≥ 32 °C during CPB); Group 2, moderate hypothermia (nasopharyngeal temperature ≥ 28 °C during CPB). The same surgeon performed all operations. The study was conducted according to the regulations of the hospital medical ethical committee. Informed parental consent was obtained for all patients.

Anesthesia

Patients were premedicated with 0.3 mg/kg midazolam suppositorium 1 hour before induction of anesthesia. Induction of anesthesia was done by inhalation (halothane or sevoflurane) or intravenously (midazolam, pavulon, fentanyl). Patients were intubated with a nasal - endotracheal tube and ventilated with a minute volume of 10 ml/kg/min. Heart rate, ECG, arterial and right atrial blood pressure, nasopharyngeal and rectal temperature were continuously measured. A bladder catheter was inserted to monitor urine production during and after the operation.

Cardiopulmonary bypass

All patients were operated upon with CPB and cardioplegic arrest. In all patients the ascending aorta was cannulated with either an 8 or 10 Fr standard straight-tip cannula, depending upon patient size. In all cases, venous return was provided by bicaval cannulation of the superior and inferior caval veins with angled metal tip 12 Fr cannulae.

CPB circuit consisted of a membrane oxygenator with integrated venous-cardiotomy reservoir, roller pump with silicone tubing and an arterial line filter. The circuit was primed with Ringer's solution and whole blood to achieve an intraoperative hematocrit of 28% during the bypass period. During CPB nonpulsatile pump flow with rates of 1.8 to 2.4 L/min/m^2 was maintained adequate to metabolic needs of the patient. In-line monitoring of arterial oxygen tension (PaO_2) and venous oxygen saturation (SvO_2) provided conditions for alpha-stat strategy during the whole period of bypass.

Anticoagulation of the patient and the CPB circuit were achieved with initial patient heparin dose of 300 IU / kg body weight and prime heparin dose of 4.2 IU/ml total prime volume. Assessment of anticoagulation during operation was done by measurement of the kaolin activated clotting time (ACT). The ACT values were maintained ≥480 sec by administration of additional heparin when necessary. After discontinuation of the CPB heparin was neutralized by protamine chloride with standard dose of 4 to 5 mg/ kg body weight. Adequacy of protamine reversal was ascertained with the use of heparin-protamine titration.

No aprotinin was administrated to patients in the study population.

Patient mean arterial blood pressure was maintained between 30 - 65 mmHg during the bypass. Continuous recording of the pump flow, arterial blood temperature along with patient nasopharyngeal and rectal temperatures, oxygen and air flow, PaO_2, SvO_2, arterial line pressure as well as patient pressures, was provided by "Odis" - perfusion registration system [8, 9]. Myocardial preservation was achieved by antegrade administration of cold (4 °C) St.Thomas Hospital cardioplegic solution delivered by gravity at the dose of 10 - 15 ml/kg of body weight after application of the aortic cross-clamp. No topical cooling was used.

All patients were weaned from bypass with infusion of dopamine 2 μg/ kg/ min and nitroglycerin 1 μg/ kg/ min.

Measurements and calculations

In both groups arterial and venous blood gas samples were obtained before bypass, during CPB after 5 min - 20 min - and at the end (± 50 min). The last sample was obtained after administration of protamine chloride. During CPB oxygen consumption index (VO_2 I) and systemic vascular resistance (SVR) were calculated as follows:

$$SVR = \frac{\text{mean arterial pressure - central venous pressure}}{\text{cardiac output}} \times 80 \text{ [dynes sec cm}^{-5}\text{]}$$

VO_2 I =cardiac index x {(art. saturation - ven. saturation) x haemoglobin content x 2.32} [ml/min m^2]

Coagulation factors: platelet count, fibrinogen, activated partial thromboplastin time (APTT), thrombin time (TT) and were measured before the bypass, after protamine chloride administration and 24 hours after the operation.

Other measured and recorded variables include occurrence of electrical activity (ECG) during the aortic cross-clamping, spontaneous cardiac conversion after releasing of the clamp and existence of any kind of the rhythm disturbances. In addition, the amount of administrated blood products, diuresis, blood loss, length of the respiratory support and stay in the intensive care unit (ICU) were recorded.

Intraoperative post-correction epicardial echocardiography [10] was carried out with colour-Doppler studies to assess left-to-right shunting by echo-contrast injection into the left atrium. After 24 hours post-operative left ventricular function was determined by echocardiography and follow-up was completed at the discharge visit.

Data analysis

All values are presented as mean ± standard deviation (SD) of the mean. Two-way analysis of variance (ANOVA) for repeated measurements was used for comparison between the groups at specific points in time. p - Values were obtained for the overall group effect. Other data were compared by unpaired t - test between the two groups. p -Values ≤ 0.05 were considered statistically significant.

RESULTS

There were no significant differences in the baseline data between the two groups (Table 1).

Table 1. Characteristics and perfusion data of the study population.

	Group 1 (32 °C)	Group 2 (28 °C)	P - value
Age (mo)	3.5 ± 1.6	5.0 ± 3.2	NS
Weight (g)	4250 ± 817	4958 ± 1245	NS
Height (cm)	56.8 ± 15.8	60.0 ± 4.5	NS
BSA (m^2)	0.27 ± 0.03	0.30 ± 0.05	NS
Calc. Pump Flow (ml/min)	641 ± 83	713 ±116	NS
Mean Pump Flow (ml/min)	592 ± 12	597 ± 129	NS
CPB time (min)	54.5 ± 2.0	56.1 ± 16.0	NS
Crossclamp time (min)	31.5 ± 2.0	31.4 ± 15.0	NS
Cardioplegic solution (ml)	65 ± 30	65 ± 18	NS

All values reported as mean ± SD; BSA – body square area; Calculated pump flow =BSA (dm^2) x 24 (ml/min/dm^2); CPB - cardiopulmonary bypass; Mean pump flow – mean flow during CPB; NS – not significant

Mean nasopharyngeal (N) and rectal (R) temperatures after 5 min on CPB were not significantly different (Group 1; N: 32.5 ± 0.0 R: 33.0 ± 0.1 vs. Group 2; N: 31.9 ± 0.0 R: 33.2 ± 0.1 °C, NS). After 20 min on bypass a significance occurred (Group 1; N: 31.6 ± 0.0 R: 32.3 ± 0.1 vs. Group 2; N: 29.2 ± 0.0 R: 30.9 ± 0.0 °C with $p = 0.008$ and $p = 0.01$, respectively). After 50 min on CPB and rewarming being in progress rectal temperature in Group 2 was still significantly lower (Group 1 R: 34.0 ± 0.1 vs. Group 2 R: 33.2 ± 0.0 °C, $p = 0.02$), but nasopharyngeal temperatures were similar in the groups (Group 1; N: 35.8 ± 0.1 vs. Group 2; N: 35.3 ± 0.0 °C, NS, Figure 1).

Hemodynamic parameters measured and calculated during CPB revealed no significant differences between recorded mean arterial pressure (Figure 2), on the other hand the overall cardiac index was significantly higher in mild hypothermia group (Group 1; 2.43 ± 0.2 vs. Group 2; 2.16 ± 0.2 L/min/m^2, $p = 0.02$, Figure 3).

During CPB, the moderate hypothermic group had significantly higher overall systemic vascular resistance (Group 1; 1164 ± 389 vs. Group 2; 1703 ± 420 dyne sec cm^{-5} Group 1, $p = 0.04$, Figure 4). Oxygen consumption was not significantly different in both groups at the time of measurements (Figure 5).

Venous oxygen saturation remained relatively steady in each group during the CPB period and there was a significant difference between the groups only at the 5 min bypass time (Group 1; 75% vs. Group 2; 66%, $p = 0.01$, Figure 6).

Atrial electrical activity (P wave) during aortic cross clamping was observed in 4 patients in Group 1 and in one in Group 2 ($p= 0.04$). No action was taken in any of these situations.

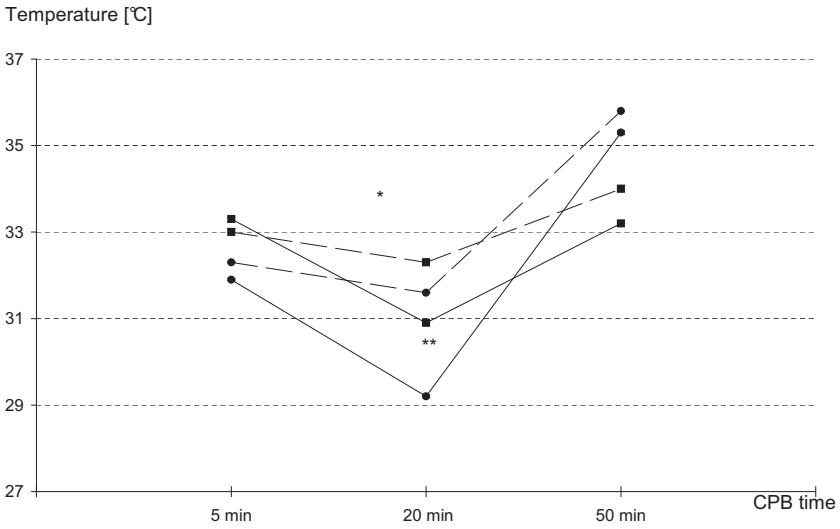

Figure 1. Changes of temperature during cardiopulmonary bypass.

Group 32 °C - N

Group 32 °C - R

Group 28 °C - N

Group 28 °C – R

*p = 0.01

**p = 0.0008

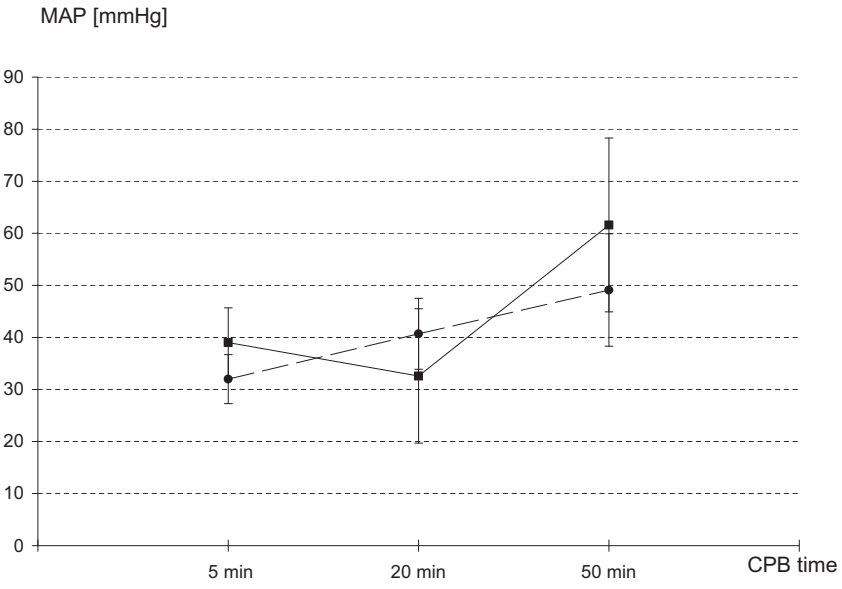

Figure 2. Mean arterial pressure during cardiopulmonary bypass.

Group 32 °C

Group 28 °C

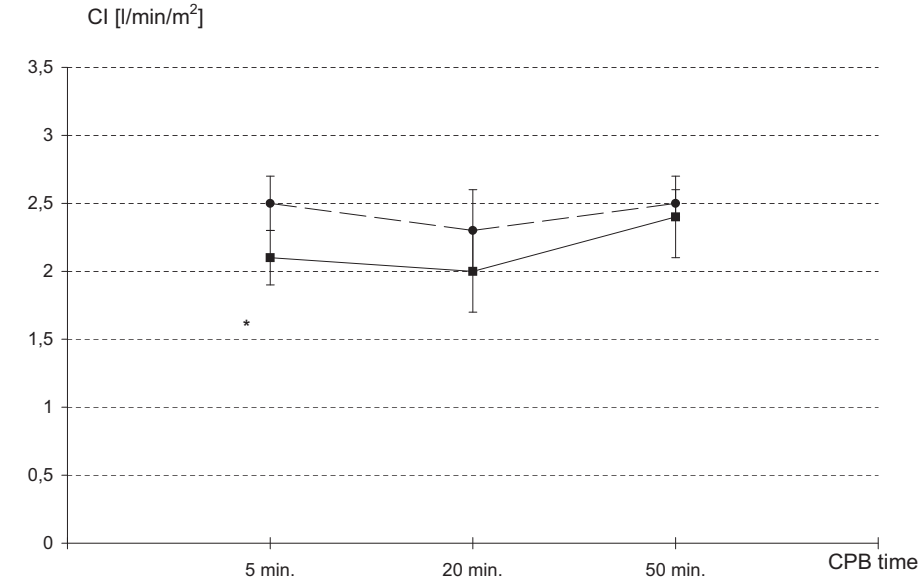

Figure 3. Cardiac Index during cardiopulmonary bypass.
Group 32 °C
Group 28 °C
* p = 0. 0006

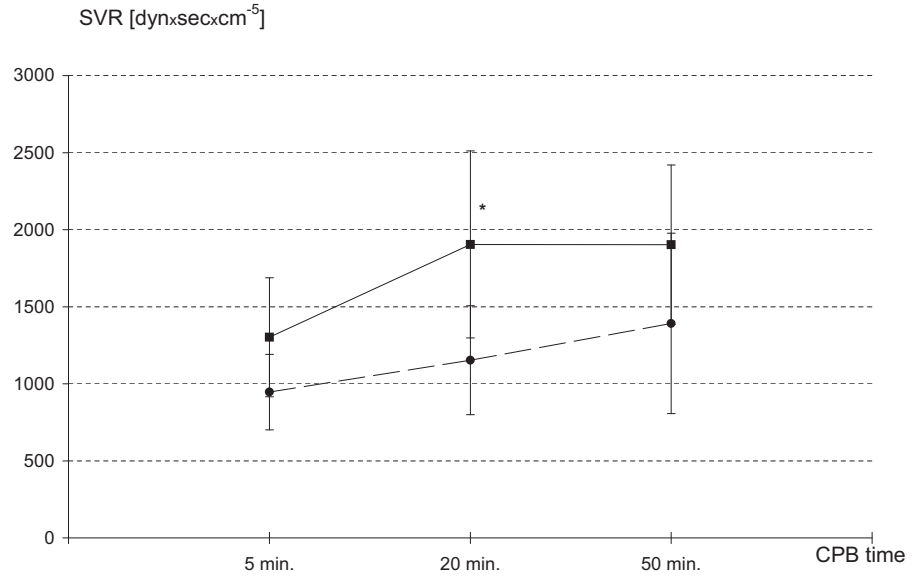

Figure 4. Systemic vascular resistance during cardiopulmonary bypass.
Group 32 °C
Group 28 °C
* p = 0. 01

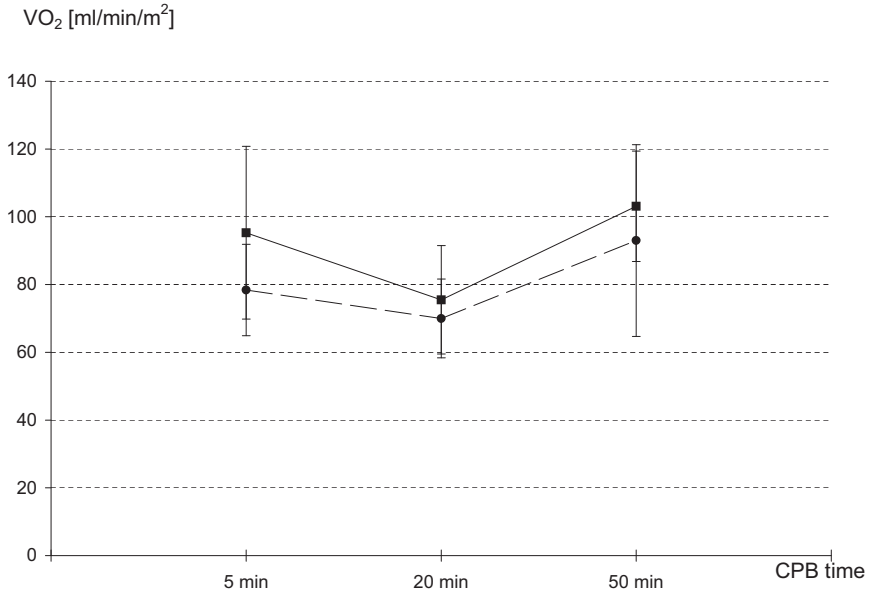

Figure 5. Oxygen consumption during cardiopulmonary bypass.
Group 32 °C
Group 28 °C

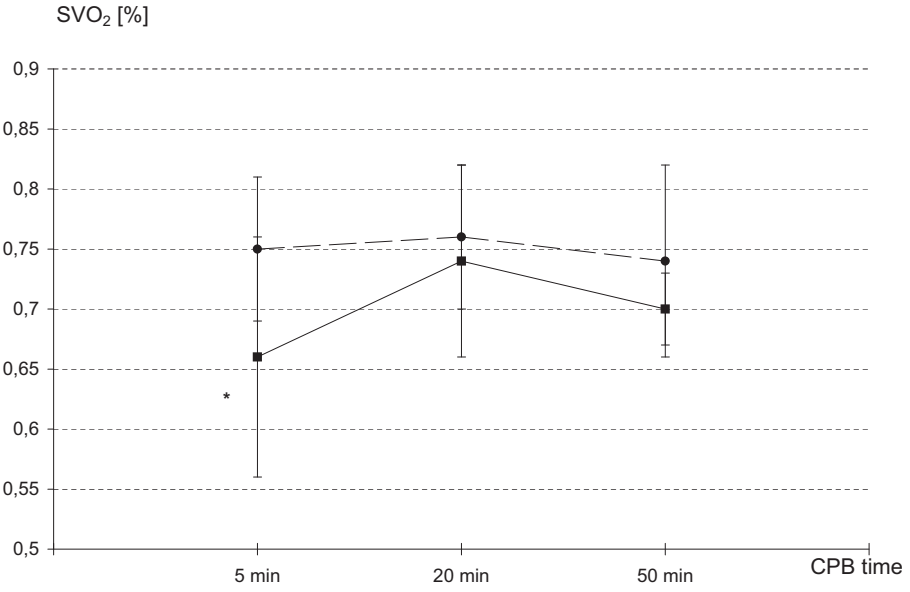

Figure 6. Oxygen saturation in venous blood during cardiopulmonary bypass.
Group 32 °C
Group 28 °C
* p = 0. 01

All patients in both groups converted spontaneously to sinus rhythm after aorta declamping. AV block was temporally observed in 2 patients in Group 1. The external pacing was applied before sinus rhythm returned.

Initial dose of heparin used before the start of CPB was not significantly different between both groups (Group 1; 1222 ± 290 vs. Group 2; 1500 ± 409 IU, NS). During CPB two patients from Group 1 and one from Group 2 required additional heparin to sustain ACT ≥480 sec. Standard protamine dose given in compliance with protocol was not significantly different. In each group, 4 patients required additional protamine (Group 1; 2.2 ± 3.4 mg vs. Group 2; 2.4 ± 3.5 mg, NS). Pre-operative measurement of coagulation factors as well as base line ACT in both groups were not significantly different. After administration of protamine the ACT values were still higher if compared with base line values, but did not show any significant difference between groups; whereas, APTT values (Group 1; 55 ± 18 vs. Group 2; 41 ± 3 s, p = 0.045) were significantly higher in mild hypothermia group (Table 2).

Table 2. ACT values and plasma coagulation factors pre- and post CPB.

	Group 1 (32 °C)	Group 2 (28 °C)	P value
Pre CPB			
ACT (sec)	127 ± 16	132 ± 9	NS
APTT (sec)	48 ± 11	51 ± 17	NS
APTT ratio	1.6 ± 0.4	1.7 ± 0.6	NS
TT (sec)	19 ± 7	16 ± 2	NS
Fibrinogen (mg/dl)	220 ± 70	220 ± 50	NS
Platlets count (x1000/mm^3)	287 ± 55	315 ± 78	NS
Post CPB			
ACT (sec)	144 ± 35	141 ± 23	NS
APTT (sec)	55 ± 18	41 ± 3	NS
APTT ratio	1.5 ± 0.1	1.4 ± 0.1	NS
TT (sec)	15 ± 2	15.9 ± 3	NS
Fibrinogen (mg/dl)	160 ± 30	180 ± 40	NS
Platelets count (x1000/mm^3)	177 ± 61	183 ± 50	NS

All values reported as mean ± SD; ACT – activated clotting time; APTT – activated partial thromboplastin time; APTT ratio - patient's APTT/ normal population APTT; NS – not significant; TT – thrombin time

There was no difference in diuresis, blood loss and the amount of blood products used during the period of 24 hours post CPB (Table 3). Additionally, the mean duration of post - operative ventilatory support, as well as the highest percentage of oxygen used in inspiratory fraction (FiO_2 %) and applied positive end expiratory pressure (PEEP) were similar (Table 4). The mean duration of stay at the ICU by patients in both groups was not significantly different.

Intraoperative epicardial echocardiography revealed a residual VSD with insignificant leakage of contrast in 2 patients from Group 1 and 3 patients from Group 2. At discharge 2 patients in Group 1 displayed a hemodynamically insignificant residual VSD as well as 1 patient in Group 2. No residual VSDs were observed on subsequent follow-up visits. Intraoperative post-correction epicardial echocardiography assessed left ventricular function in all patients as normal. Echocardiographic examination after 24 hours estimated left ventricular function as "diminished" in 3 patients in Group 1 and 1 patient in Group 2, nevertheless at discharge all the patients' regained normal left ventricular function.

Table 3. Urine production and blood balance in 24 hours after CPB.

	Group 1 (32 °C)	Group 2 (28 °C)	P - value
Urine output (ml)	345 ± 44	350 ± 111	NS
Blood loss (ml)	109 ± 106	95 ± 24	NS
Homologous blood (ml)	175 ± 39	145 ± 53	NS
FFP (ml)	63 ±117	106 ± 90	NS

All values reported as mean ± SD; CPB – cardiopulmonary bypass; FFP – fresh frozen plasma; NS – not significant

Table 4. Postoperative use of the respiratory support.

	Group 1 (32 °C)	Group 2 (28 °C)	P - value
Respiratory supp.(h)	22.8 ± 18	16.5 ± 19	NS
Highest FiO_2 (%)	48.8 ± 11	46.0 ± 10	NS
PEEP (cm H_2O)	3.5 ± 0.8	3.7 ± 1.0	NS

All values reported as mean ± SD; FiO_2 – inspiratory fraction of oxygen; NS – not significant; PEEP – positive end expiratory pressure

DISCUSSION

Use of moderate (28 °C) systemic hypothermia improves operating conditions and allows lower arterial flow rates. This, in turns, reduces collateral coronary circulation and contributes to myocardial protection as well as protection of other vital organs. Therefore, moderate hypothermia is widely carried out, although the effects of skin and perhaps muscle ischemia related to this temperature and the increased sympathetic effects may balance out any potential advantages [11]. Another effect of hypothermia is that blood viscosity increases so that use of appropriate hemodilution is required to reduce the systemic vascular resistance during CPB [12]. Hypothermia together with hemodilution disturbs coagulation and fibrinolitic cascades, therefore is assumed to be responsible for enhanced blood loss during and after operation [13]. In certain operations, the selection of CPB temperature is dependent on the complexity of the operation; for example, deep

hypothermia during circulatory arrest. Therefore, questions may be raised as to what the best temperature is in case of short (under 1 hour of CPB time) surgical procedures for small pediatric patients with body weight under 10 kg. [14]. According to the surgeon's opinion, use of moderate (28 °C) or mild (32 °C) hypothermia during correction of the ventriculr septal defect had no influence on the technical complexity of the operation.

The hemodynamic data obtained from both groups showed no differences in adequacy of the CPB. Mean arterial pressure and venous oxygen saturation were kept constant during the bypass without any difficulty, although patients from Group 1 (32 °C) required significantly higher cardiac index to achieve this. On the other hand Group 2 (28 °C) had significantly higher overall systemic vascular resistance during the CPB, which might be caused by moderate hypothermia. Oxygen consumption in the two groups was not significantly different, which can be explained by the negligible differences of patient's temperatures during long time on CPB.

Myocardial protection in both groups was the same and there was spontaneous return of sinus rhythm in all the cases. In Group 1 (32 °C) twice atrio- ventricular block occurred, which had to be resolved by temporarily use of pacemaker. Those adverse events could be related to less adequate myocardial protection, but also could be associated with the surgical procedure itself. There were no clinical consequences of these events and the echocardiographic control of the left ventricular function showed no difference between the patients from both groups. Kidney function assessed by urine output and lung function assessed by duration of ventilation support did not differ in both groups.

The amount of heparin and protamine used showed no difference in the two groups. Postoperative, after administration of protamine, both groups still had prolonged ACT values and significantly lower plasma fibrinogen concentration when compared to the " base line " values, but Group 1 (32 °C) also had significantly longer APTT in comparison to Group 2 (28 °C). Mean blood loss was least in the moderate hypothermia group but the difference did not reach significance. Hematologic data suggested increased fibrinolitic potential in the mild hypothermia group [15].

CONCLUSIONS

Our study documented no difference in organ preservation depending on type of hypothermia, mild or moderate, used during the reconstruction of VSD in pediatric patients. The chosen temperatures did not impair adequacy of CPB. There was no difference in technical complexity of the operation. Moreover, the clinical outcome of the patients did not depend on the type of hypothermia. There was suggestion of more activation of fibrinolitic potential in the 32 °C group.

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Chapter 3

Effects of cardiopulmonary bypass circuit reduction and residual volume salvage on allogeneic transfusion requirements in infants undergoing cardiac surgery

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ABSTRACT

Background: Cardiopulmonary bypass in children may cause severe hemodilution and can lead to excessive perioperative blood loss and high transfusion requirements. Minimization of cardiopulmonary bypass circuit and salvage of red blood cells from the residual volume after the procedure are widely utilised to reduce allogeneic transfusion. We evaluated the effectiveness of those measures introduced in infant cardiac surgery in our institution.

Methods: This retrospective observational study included 148 consecutive infants between 1 to12 months of age, with a body weight less than 10 kg, who underwent an elective cardiac operation between 1997 and 2005. Patients were divided into three groups defined by the circuit prime volume; 700 mL (Group 1), 450 mL (Group 2) and 330 mL (Group3). In Group 1 residual volume after perfusion was discarded and in Group 2 and 3 was processed in cell saving device. Analyzed variables were: perioperative blood loss, urine production, transfusion of homologous blood products and cell salvage product, and haematology data.

Results: Reduction of the circuit volume significantly diminished use of red blood cells concentrate from 1.6 units to 0.8 units ($p<0.0001$) and fresh frozen plasma from 1.3 units to 0.4 units ($p<0.0001$). Utilization of the cell salvage product reduced significantly ($p=0,023$) the postoperative need for homologous blood transfusion.

Conclusions: Reduction of cardiopulmonary bypass circuit together with cell salvage from the residual volume of hart-lung machine proved to be effective in reducing of homologous blood transfusion in infant cardiac surgery.

INTRODUCTION

Cardiopulmonary bypass (CPB) during open-heart surgery remains a non-physiological technique that may cause severe hemodilution and an acute inflammatory body response [1,2,3,4]. In children, who undergo cardiac surgery, this alone can lead to excessive perioperative blood loss and high transfusion requirements. Additionally, nowadays smaller and younger patients are undergoing more complex procedures and there is strong evidence of enhanced blood loss and blood transfusion associated with these patients [5-8]. Awareness that allogeneic blood may transmit known and unknown pathogens and cause alloimmunization on future transfusion and pregnancies, stimulated development of new blood conservation policies.

Use of smaller CPB circuits and perioperative salvage of red blood cells (RBC) diminished some of the adverse effects of CPB and consequently reduced transfusion demand. Despite recent advances in technology, the majority of neonates and infants still require perioperative transfusion of different homologous blood components [9,10,11]. In the past decade, an effort was made in our institution to reduce the exposure of pediatric patients to homologous blood products. First, we minimized the extracorporeal circuit used during CPB and secondly, a cell saving device was routinely used to process residual blood from the extracorporeal circuit. The present study evaluates the effects of those blood conservation measures.

MATERIAL AND METHODS

Population

From January 1997 to March 2005, 166 consecutive infants between 1 to 12 months of age, with body weight of less than 10 kg, underwent an elective cardiac operation with CPB at the Erasmus University Medical Center, Rotterdam. During this period, three different types of CPB circuits were used; each specific type was solitary utilized within the defined period. For the purpose of the retrospective study patients were assigned into three groups according to the type of CPB circuit and how the residual volume after CPB was processed. Excluded were patients who had preoperatively known clotting disorders, patients on systemic anticoagulant drugs preoperatively, re-do procedures with perioperative cell salvage and postoperative reexplorations. Patients with aorta occlusion time longer than 90 minutes were also excluded from the study to homogenize the patient's groups according to the type and complexity of the operation.

In Group 1(patients operated from 1997 to 1999), the CPB system consisted of a Cobe VPCML flat-sheet membrane oxygenator with hard-shell reservoir (Cobe, Denver, CO),

with a priming volume 450 mL. The total priming volume of the CPB system was 700 mL. The residual volume of the system was discarded after the procedure.

In Group 2 (patients operated from 2000 to 2003), a Polystan Safe Mini hollow-fibre membrane oxygenator with hard-shell reservoir (Maquet Cardiopulmonary, Hirrlingen, Germany) was used, with a priming volume 160 mL. The total priming volume of the CPB system was 450 mL. Residual volume after the procedure was processed by HaemoLite 2 plus (Haemonetics, Bothwell, UK) cell-saving device with a pediatric centrifugal bowl of 100 mL. Red blood cell concentrate obtained through cell salvage was postoperatively transfused to the patient.

Group 3 (patients operated from 2004 till March 2005), had a Capiox Baby Rx hollow-fibre oxygenator with hard-shell reservoir (Terumo, Tokyo, Japan), with priming volume 60 mL. The total CPB system volume was reduced to 330 mL. The residual volume was as in Group 2, processed under the same conditions by the cell-saving device.

All the CPB systems utilized a roller pump with ¼" silicone tubing (Raumedic REHAU, Muri, Switzerland), a D736-40 Micron (Dideco, Mirandola, Italy) arterial filter and PVC ¼" arterial and venous tubing. None of the CPB systems was coated.

Patients gender, cardiac anomaly, age, body weight (BW), body surface area (BSA), CPB time, aorta cross-clamp time (AoX) and time at the Intensive Care Unit (ICU) were noted.

Anesthesia, Anticoagulation and Cardiopulmonary Bypass

All patients received standard anesthesia with midazolam, pancuronium bromide (Organon, Oss, The Netherlands) and fentanyl (Janssen-Cilag, Tilburg, The Netherlands). Anticoagulation was established with an initial bolus 300 IU/kg BW of porcine heparin (Leo Pharmaceutical Products, Weesp, The Netherlands). Additional heparin was administrated to maintain activated clotting time higher than 480 sec during the whole procedure. Initial protamine hydrochloride dose was 5 mg/kg BW (ICN Pharmaceutic, Zoetermeer, The Netherlands). Control of the heparin neutralization was performed with the HepCon HMS device (Medtronic HemoTec, Englewood, CO) and if necessary an extra protamine was given.

The CPB prime contained always red blood cells (RBC), fresh-frozen plasma (FFP) and Ringer's Solution (Baxter, Utrecht, The Netherlands) or Gelofusine (B. Braun, Melsungen, Germany). The amount of RBC product added to the priming was calculated to achieve a hematocrit of 0.28 L/L during CPB. The prime was completed with 0.5 g/kg BW mannitol (NPBI, Emmer, The Netherlands), 0.5 g/kg BW human albumin (Sanquin CLB, Amsterdam, The Netherlands), 4.2 IU heparine / mL priming volume and 2-5 ml $NaHCO_3$ 8.4% (Fresenius Nederland, s'Hertogenbosch, The Netherlands).

Nonpulsatile CPB, with mild hypothermia of 28 °C to 32° C, was performed with blood flow rates between 1.8 L/min/m^2 to 3.2 L/min/m^2 to maintain venous oxygen satura-

tion above 70% and mean arterial pressure between 40 to 60 mmHg. In accordance with our infant CPB protocol no modified ultrafiltration was used and no aprotinin was administrated in any of the cases.

Administrations of RBC products and additional crystalloids or colloids during CPB were at the discretion of the perfusionist, based upon the working volumes and hematocrit levels. Cardioplegic cardiac arrest was obtained by antegrade infusion of 10-15 mL/kg BW St. Thomas Hospital Solution I á 4 °C (Apotheek ErasmusMC, Rotterdam, The Netherlands). Laboratory tests, urine production, blood loss and blood products transfusion

Hemoglobin concentration (Hb), hematocrit (Ht) and platelet count (Thr) were measured one day before the operation, at the start and end of the operation, during the CPB at the 5 min on bypass and at the end of the CPB, and after 24 hours postoperatively. Urine production and blood loss was noted at the end of the operation and as the total volume collected at the ICU.

Blood loss in the operation room (OR) represented the sum of blood loss calculated from swabs, discarded suction volumes and the chest drains output. Postoperative blood loss was calculated as the total loss from the chest tubes during the ICU stay.

In Group 1, an additional blood loss was the discarded residual volume from the CPB circuit (RES). In Group 2 and 3 residual volumes were processed by a cell saving device. Discarded plasma fraction separated during the cell saving and a minimal RES were than accounted for a blood loss. The decision to transfuse blood products was based upon measured blood loss, patient clinical status and laboratory tests. In general, acyanotic patients were transfused to maintain a hemoglobin level of 6.0 mmol/L. Platelet transfusion was considered if the platelet count at the end of CPB was less than 100 x 10^9/L. The volume of blood products transfused in the OR, including blood products added to the circuit prime and during the CPB, and administrated at the ICU was noted.

Data analysis

Continuous data are presented as mean ± standard error of the mean, categorical data are presented as proportions. Continuous independent data were compared with one-way analysis of variance ANOVA and Bonferroni (in case of equal variances) or Tamhane T2 (in case of unequal variances) post-hoc corrections were applied to the p values for multiple comparisions. Categorical data were compared with the chi-square test. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 13.0 statistical software (SPSS, Chicago, IL).

RESULTS

Demographics and CPB

A total of 148 consecutive infants fulfilling the inclusion criteria were enrolled in this study. Fifty-two patients were selected into Group 1, 54 patients in Group 2 and 42 in Group 3. Thirteen patients were excluded due to an aorta occlusion time longer than 90 minutes. Five patients with re-do procedures were also excluded. The same surgical team performed all the operations. Postoperatively there were no complications, no re-explorations and all patients survived. Population and CPB data are presented in Table1.

Table 1. Population and CPB data.

Variable	Group 1	Group 2	Group 3	
	n = 52	n = 54	n = 42	P value
	Mean ± SE	Mean ± SE	Mean ± SE	
Gender (female/male)	27/25	28/26	17/25	0,76
Age (mo)	6,2 ± 0,4	5,5 ± 0,3	4,4 ± 0,4	0,004[ab]
Weight (kg)	6,2 ± 0,3	5,7 ± 0,2	5,3 ± 0,2	0,001[ab]
BSA (m2)	0,35 ± 0,02	0,33 ± 0,01	0,31 ± 0,01	<0,001[a]
CPB time (min)	76 ± 4	91 ± 6	91± 4	0,03[ab]
Cross-clamp time (min)	43 ± 3	51 ± 2	58 ± 3	<0,001[ab]
ICU time (hours)	33 ± 3	31 ± 2	22 ± 0,4	0,001[b]
Anomaly - correction				
ASD - closure	4	2	0	
VSD - closure	9	11	16	
AVSD - correction	19	19	14	
F4 - correction	11	11	4	
Other	9	11	8	

[a] p=ns Group2 vs. Group 3; [b] p=ns Group 1 vs. Group 2; ASD - atrial septal defec; AVSD – atrioventriculair septal defect; BSA - body surface area; CPB-cardiopulmonary bypass; F4 – tetralogy of Fallot; ICU - Intensive Care Unit; SE - standard error of the mean VSD – ventricular septal defect

Laboratory tests results, urine production and blood loss

Measurements of hemoglobin concentration (Hb), hematocrit (Ht) and platelet count (Thr) are presented in Figures 1, 2 and 3. There were no significant differences with regard to Hb and Ht values measured the day before operation and pre-perfusion. At the end of the operation, Group 2 compared to Group 3 had significantly lower values of Hb (p=0,006) and Ht (p=0,023). After 24 hours at the ICU there were no significant differences between the groups.

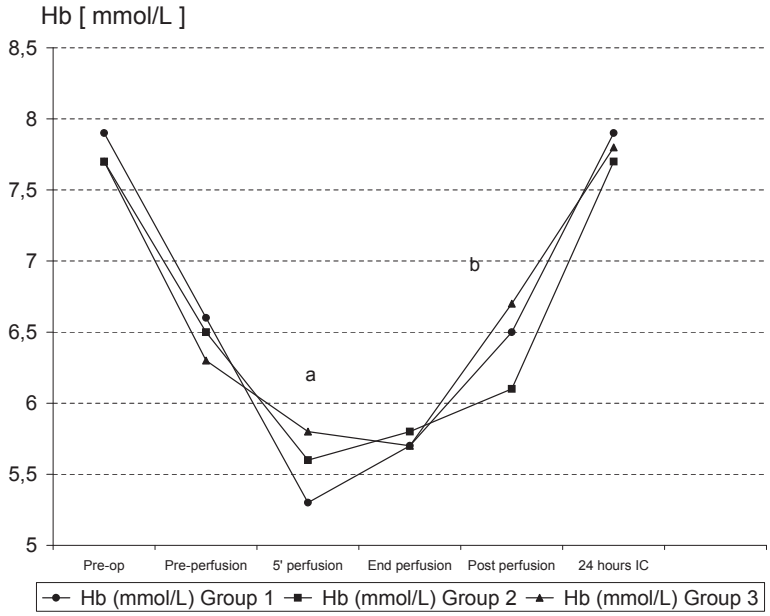

Figure 1. Concentration of hemoglobin in pre-, per- and postoperative period.
Hb – haemoglobin; [a] p<0.0005 Group 1 vs. Group 3; [b] p=0,006 Group 2 vs. Group 3

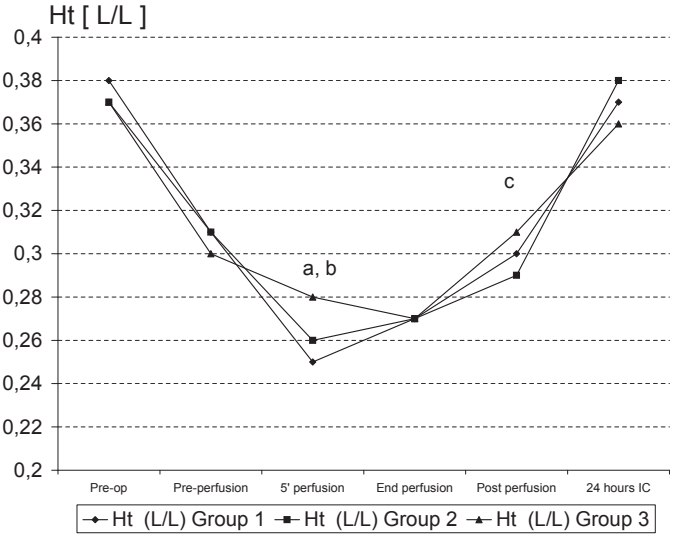

Figure 2. Hematocrit levels in pre-, per- and postoperative period.
Ht – hematocrit; [a] p<0.0005 Group 1 vs. Group 3; [b] p=0.016 Group 1 vs. Group 2; [c] p=0.023 Group 2 vs. Group3

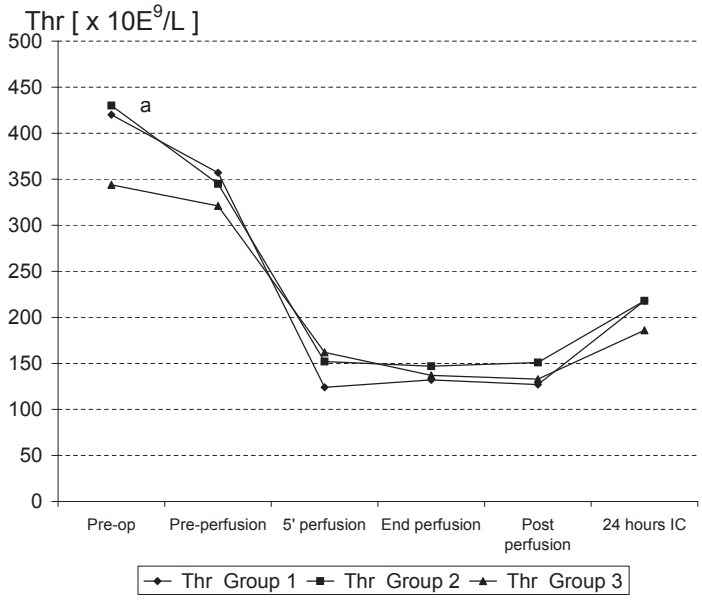

Figure 3. Platelets count in pre-, per- and postoperative period.
Thr – thrombocytes; [a] p=0.021 Group 1 vs. Group 3; [b] p=0.006 Group 2 vs. Group 3

Table 2. Urine output during and post –operation.

Urine output	Group 1	Group 2	Group 3	
mL/kg/h	n = 52	n = 54	n = 42	P
	Mean ±SE	Mean ±SE	Mean ±SE	value
OR	8 ± 1	6 ± 1	7 ±1	0,54
ICU	6 ± 0,2	3 ± 0,2	4 ± 0,2	<0,001[a]

[a] p =ns Group 2 vs. Group 3; ICU – Intensive Care Unit, OR – operation room, SE – standard error of the mean

The platelet count the day before operation was significantly lower in the Group 3 compared to the Group 1 (p=0,021) and 2 (p=0,006), but already preoperatively was not significantly different. Urine production and blood loss are presented in Table 2 and 3 respectively. Postoperatively, Group 1 had significantly higher urine output than both other groups. There were no significant differences in the blood loss.

Blood products transfusion

The amount of homologous blood products and cell salvage product transfused in the OR and the ICU are presented in Table 4. Significantly more allogeneic RBC (p<0.0001) was used in the prime and during CPB in Group 1 (1.6 units) compared to Group 2 (1.1 units) and 3 (0.8 unit). Group 2 required significantly more RBC in the prime (p<0.0001) and during the bypass (p=0.024) than Group 3.

Table 3. Blood loss in OR and ICU.

	Group 1	Group 2	Group 3	
	n = 52	n = 54	n = 42	P
	Mean ±SE	Mean ±SE	Mean ±SE	value
Blood loss (mL/kg)				
OR	13 ± 1	14 ± 2	16 ± 1	0,49
ICU	14 ± 1	17 ± 2	21 ± 3	0,08
Total OR+ICU	27 ± 2	30 ± 3	37 ± 4	0,08
Blood loss (mL)				
Intraoperative	82 ± 7	75 ± 10	80 ±7	0,82
Postoperative	84 ± 9	92 ± 11	104 ± 15	0,47
Total OR+ICU	166 ± 10	168 ± 17	184 ± 17	0,69
RES + CS	654 ± 11	362 ± 23	212 ± 13	0,005 [ab]

[a] p= 0.0002 Group 1 vs. Group 3, [b] p=0.02 Group 2 vs. Group3; CS – cell saver, ICU – Intensive Care Unit, OR – operation room, RES – residual volume, SE – standard error of the mean

Table 4. Homologous and cell saver product transfusion volumes.

Variabele	Group 1	Group 2	Group 3	p
	n = 52	n = 54	n = 42	value
	Mean ±SE	Mean ±SE	Mean ±SE	
RBC (mL)				
Prime volume	313 ± 5	205 ± 5	167 ± 8	<0.0001
During CPB	117 ± 8	88 ± 7	60 ± 8	<0.0001
OR	38 ± 2	28 ± 7	35 ± 13	0.39
ICU	65 ± 7	45 ± 5	38 ± 8	0.023
Total RBC	533 ± 10	367 ± 12	303 ± 15	<0.0001
CS product (mL)				
OR		105 ± 8	13 ± 5	<0,0001
ICU		35 ± 5	43 ± 8	0.42
FFP (mL)				
Prime volume	383 ± 6	213 ± 11	92 ± 5	<0,0001
During CPB	52 ± 4	85 ± 9	47± 7	<0,0001[a]
OR	53 ± 4	42 ± 7	36 ± 7	0.15
ICU	88 ± 8	69 ± 9	77 ± 9	0.24
Total FFP	576 ± 11	410 ± 20	251 ± 12	<0,0001
Platelets (mL)				
OR	77 ± 12	57 ± 10	13 ± 5	<0,0001[b]
ICU	36 ± 6	20 ± 4	22 ± 6	0.07

[a] p= ns Group 1 vs. Group 3; [b] p=ns Group 1vs Group 2, CS – cell saver; FFP – fresh frozen plasma; ICU – Intensive Care Unit, OR – operation room, RBC-red blood cells; SE – standard error of the mean

The FFP was used in significantly (p=0.0001) larger volume in the prime of Group 1 (1.2 units) versus Group 2 (0.7 unit) versus Group 3 (0.3 unit). The cell saving product, available for Group 2 and 3, was transfused in the OR in a significantly larger volume (p<0.0001) in Group 2 than in Group 3. Platelets concentrate transfusion was significantly higher in de Group1 in the OR (p<0.0001) but at the ICU were no differences between the groups.

Table 5 shows transfusion incidence of homologous blood products (RBC, FFP and platelets) and cell salvage product. In all groups 100% of patients were exposed to the homologous RBC and FFP in the prime of the CPB circuit.

Table 5. Percentage of patients' transfused with homologous blood and cell saver product.

	Group 1	Group 2	Group 3	
Incidence (%)	n = 52	n = 54	n = 42	p value
RBC Prime	100	100	100	ns
FFP Prime	100	100	100	ns
RBC CPB	100	89	79	<0.01
FFP CPB	52	46	71	0.03
RBC OR	100	67	71	<0.001
FFP OR	77	70	71	ns
CS OR		96	24	<0.001
Platelets OR	52	39	17	<0.001
RBC ICU	98	77	58	<0,001
FFP ICU	69	79	95	0.03
CS ICU		61	77	ns
Platelets ICU	54	41	29	0.03

CPB – cardiopulmonary bypass; CS – cell saver; FFP – fresh frozen plasma; ICU – Intensive Care Unit; ns – not significant; OR – Operation Room; RBC – red blood cells

DISCUSSION

This study shows that consequent minimization of the bypass circuit and cell salvage from circuit residual volume were effective measures in reducing the need for homologous blood products transfusion in infants younger than 12 months of age, who underwent an elective cardiac operation in our institution.

Circuit reduction and homologous transfusion requirements

It is undoubtedly true that the volume of the CPB circuit determines the exposure to allogeneic blood products in the majority of children weighting less than 10 kg. In 2005

Boettcher et al. reported results related to transfusion –free cardiopulmonary bypass in Jehovah's Witness patients weighing less than 5 kg and a 2.2-kg neonate [12, 13]. With a dedicated pediatric heart lung machine and small circuits (200 or 190 ml priming volume) they performed safely uneventful non-sanguineous cardiac surgery. The effort to minimize the CPB circuit in our institution was an important step in the blood conservation policy. The CPB circuit volume was consequently reduced from 700 mL (Group 1), to 450 mL (Group 2) and further decreased to the small size of 330 mL (Group 3). This reduction was obtained mainly by use of smaller, new type membrane oxygenators. Priming volume of tubing system and the arterial filter did not change substantially over the years; Group 1 – 250 mL, Group 2 - 290 mL, Group 3 – 270 mL. Use of the conventional "adult" heart long machine and the safety aspects of the system caused this unwanted effect. Smaller CPB circuit was translated into a substantial reduction of the amount of homologous RBC needed in the prime; Group 1 – 313 mL, Group 2 – 205 mL, Group 3 – 167 mL, $p<0,0001$. At the end of CPB patients in all three groups had the same mean hematocrit of 0.27 L/L, but to achieve this Group 1 required 117 mL of RBC, Group 2 - 88 mL and in Group 3 only 60 mL of blood products. In the OR after the cessation of CPB patients in all three groups received comparable amounts of homologous RBC ($p=0.39$). During ICU stay, on the other hand, Group 1 was transfused with significantly more homologous RBC than the other groups ($p=0.029$). The total volume of homologous RBC used in Group 1 was 533 mL (1.9 unit), in Group 2 - 367 mL (1.3 unit) and in Group 3 - 303 mL (1.1 unit). Unfortunately, we did not succeed yet to reduce the exposure to homologous RBC to less than 1 unit per patient.

Requirements of FFP during the intraoperative period revealed that the patients in Group 1 received more homologous plasma than the patients in the other groups, due to the high amount of FFP used in the prime of the CPB circuit and during bypass. Incidence of platelets concentrate transfusion and the amount transfused in the OR were highest in this group, and correlates with the lowest value of platelets count post CPB (trigger for transfusion) and at the end of the operation.

Cell salvage residual volume

Cell salvage of the residual CPB volume was introduced as another blood conservation measure, already successfully used in adult cardiac surgery in our institution [14]. During the ICU stay, cell saving product was transfused in accordance to the patient's demand (incidence 61% - Group 2, 77%- Group 3) and led to reduction of the need for homologous RBC transfusion in Group 2 and 3 compared to Group 1 ($p=0.09$ and $p=0,036$), but did not replace it utterly. The cell salvage product was accepted for transfusion (according to the institution policy) up to 12 hours after it was obtained and this led in some cases to the need for transfusion of homologous RBC later during ICU stay. Hishon et al. [15] demonstrated minimal chemical deterioration and limited microbiologic

contamination in blood salvaged from the CPB circuit and stored at room temperature for an 18-hour period. Therefore, prolongation of acceptable transfusion period for cell salvage product could be beneficial. In the OR 96% patients from Group 2 received cell salvage product versus 24% from Group 3, but this was not translated to a reduction of homologous blood transfusion in the OR. The cell salvage product was available not earlier than at the end of the procedure, a practical limitation to the transfusion.

Comparison between groups

Our study shares that in recent years children who undergo cardiac surgical operation are becoming younger and smaller. The mean age and weight of infants that were operated in our institution decreased steadily over the years of this study, while CPB and aortic cross clamp times increased. This illustrates that younger and smaller children undergo procedures that are more complex. However, ICU stay in the most recent years has declined. The ICU length of stay was significantly longer in Group 1 compared to Group 2 and 3 (33 h vs 31 h vs 22 h respectively, p=0,001) but most likely related to the logistic at the ICU than to the type of the corrections. This requires further study. Pre-perfusion hemoglobin concentration, hematocrit and platelet count, intraoperative and postoperative blood loss were not significantly different between three groups. Slightly higher total blood loss in Group 3, the youngest group, (37 mL/kg BW) compared to Group 2 (30 mL/kg BW) and Group 1 (27 mL/kg BW) was only borderline significant (p=0.08). In this regard our study results were well within the ranges presented by others [6,7].

The mean age differences between three groups were small and all patients were older than 1 month that excluded influence of the immaturity of the coagulation system, mostly associated with age younger than 1 month [8]. In relation to urine production during the OR stay we have found no significant differences between the groups, but postoperatively Group 1 compared to Group 2 and 3 had enhanced urine output (6 mL/kg vs 3 mL/kg vs 4 mL/kg respectively). Although, we have not specific data to validate our hypothesis, use of the Ringer's Solution in the prime of the CPB circuit could be associated with this occurrence.

Study design and limitations

Our project was designed as a retrospective observational study to evaluate the consequences of policy changing through the years in the infant cardiac surgery in our institution. Due to the retrospective character of our study and 8 years time span involved, we were not able to apply a more demanding protocol (for example for retransfusion of cell saving product) and homogenized our study population. In addition, a formal cost-benefit analysis was not possible. We expect that a follow up prospective study, which is already under way, will give more conclusive information on cell salvage product utilization.

CONCLUSIONS

Minimization of the CPB circuit significantly reduced the demand of homologous blood products, both RBC and FFP, during the infant cardiac surgery. This reduction diminished patient exposure to the number of donors with all well-known benefits of this. We also showed the beneficial effect of the cell salvage from residual volume of the CPB circuit. The timing of the cell saving product availability in the OR, the amount of the product and acceptable transfusion period after the operation are of crucial importance for it effective utilization. In conclusion, allogeneic transfusion data and cell salvage data obtained in this study were important for modifying of the clinical practice in infant cardiac surgery in our institution.

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Chapter 4

Intraoperative cell salvage in infants undergoing elective cardiac surgery: a prospective trial

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ABSTRACT

Background: For a long time intraoperative cell salvage was considered to be not applicable in pediatric patients due to technical limitations. Recently, new autotransfusion devices with small volume centrifugal bowls and dedicated pediatric systems allow efficient blood salvage in small children. The purpose of this prospective non-randomized study was to determine the impact of intraoperative cell salvage on postoperative allogeneic blood products transfusion in infant patients undergoing cardiac surgery with cardiopulmonary bypass.

Methods: Two consecutive cohorts (122 patients) were studied. The first cohort underwent between January 2004 and July 2005 procedures with only blood salvage from the residual volume. The second cohort consisted of patients operated on from August 2005 until December 2006, with additional use of intraoperative cell salvage. The following variables were analyzed: peri- and postoperative blood loss, transfusion of homologous blood products and cell salvage product, haematological and coagulation data, measured before, during and after the operation.

Results: Additional intraoperative cell-salvage significantly enhanced the amount of cell saving product available for transfusion (183 ± 56 vs. 152 ± 57 mL, $p = 0.003$) and significantly more patients in this group received the cell saving product postoperatively. Consequently, allogeneic blood transfusion was significantly reduced in volume as well as in frequency. We did not observe any adverse effects of intraoperative cell-salvage.

Conclusions: Intraoperative cell-salvage, employed as an adjuvant technique to the residual volume salvage in infants undergoing first time cardiac surgery with cardiopulmonary bypass, was a save and effective method to reduce postoperative allogeneic blood transfusion. Considering current cell salvage related expense and the cost reduction achieved by diminished allogeneic transfusion, intraoperative cell-salvage in infants demonstrated no economic benefit.

INTRODUCTION

Intraoperative cell salvage (ICS) has been developed and adopted in different fields of surgery as a blood conservation technique to reduce allogeneic transfusion requirements related to excessive blood loss. This technique recovers blood lost in the operative field, purifies it and returns the obtained red blood cells (RBCs) concentrate to the patient. Although there are no doubts about the safety and efficacy of this technique in adult patients undergoing cardiac operation with or without cardiopulmonary bypass (CPB) [1, 2, 3], recent studies questioned the positive impact of ICS on allogeneic transfusion need in other fields of adult surgery [4, 5].

The effectiveness and safety of ICS in small children is not well documented. For a long time ICS was considered to be not applicable in pediatric patients due to the technical limitations to wash and hemoconcentrate small volumes of salvage blood (<300 mL). More recently, new autotransfusion devices allow efficient blood salvage in small children by introducing small volume centrifugal bowls and dedicated pediatric systems.

In infants undergoing cardiac surgery with CPB, transfusion of allogeneic blood products is almost unavoidable, to counteract extreme hemodilution and to compensate for perioperative blood loss [6-9]. Therefore, salvage of red blood cells from the CPB circuit after the procedure is adopted as a practical blood conservation measure to minimize allogeneic transfusion needs. In our institution, this technique is routinely used in children as well as in adult patients [10, 11].

The purpose of this prospective non-randomized study was to determine the impact of ICS, as additional blood conservation technique, on allogeneic blood products transfusion in infant patients undergoing elective cardiac surgery. To assess safety and haematological consequences of ICS perioperative blood loss, haematological and coagulation data were also evaluated.

MATERIAL AND METHODS

Population

Between January 2004 and December 2006, 135 consecutive infant patients with a body weight of less than 10 kg underwent an elective, first time cardiac operation with CPB in our institution. All patients were eligible to take part in this prospective observational study. The study was conducted according to the institutional standards and parental informed consent was obtained for all patients. After completion of the study, the Institutional Review Board in retrospect confirmed procedural compliance and a formal approval was waived (MEC 2007-306).

Exclusion criteria were preoperatively known clotting disorders and procedures that required deep hypothermic circulatory arrest (DHCA).

Two consecutive cohorts were studied. The first cohort (control group) underwent procedures with blood salvage from the residual volume of CPB circuit, between January 2004 and July 2005. At that point, additionally to the residual volume salvage, ICS was introduced and used in all infant patients operated on thenceforth. The second cohort (ICS group) consisted of patients operated on from August 2005 until December 2006. The same surgical team performed all the operations.

Anesthesia, Anticoagulation, Cardiopulmonary Bypass and Cell Salvage

Before induction of anesthesia, all patients were monitored with a five-lead, two-channel electrocardiogram, non-invasive blood pressure measurement, and pulse oximetry. After the insertion of a peripheral venous line, general anesthesia was induced with midazolam 0.2 mg/kg, sufentanil 2 mcg/kg and pancuronium 0.15 mg/kg. Patients were nasotracheally intubated and pressure controlled ventilated (PCV) using a Siemens 900C ventilator. Anesthesia was maintained with midazolam 0.1 mg/kg/h and sufentanil 1 mcg/kg/h. Invasive monitoring via a femoral arterial line and an internal jugular central venous catheter was performed, and a Foley bladder catheter and rectal temperature probe were inserted. Before going on CPB all patients received 30 mg/kg iv methylprednisolone, 30 mg/kg iv magnesium sulfate, 1 mg/kg iv furosemide, 40 mg/kg iv cefazoline and 1 mg/kg iv ranitidine.

Anticoagulation was established with an initial bolus 300 IU/kg BW of porcine heparin and additional heparin was administrated to maintain activated clotting time higher than 480 sec during the whole procedure. Initial protamine hydrochloride dose was 4 mg/kg BW. Control of the heparin neutralization was performed and if necessary additional protamine was given.

The CPB circuit consisted of a Capiox Baby Rx hollow-fiber oxygenator with hard-shell reservoir (Terumo, Tokyo, Japan), a roller pump with ¼" silicone tubing (Raumedic RE-HAU, Muri, Switzerland), a D736-40 Micron (Dideco, Mirandola, Italy) arterial filter and PVC ¼" arterial and venous tubing. The CPB systems were not coated. In accordance with our infant CPB protocol no modified ultrafiltration and no antifibrinolitic medication was used.

CPB prime contained homologous red blood cells concentrate (RBCs), fresh-frozen plasma (FFP) and Gelofusine (B.Braun, Melsungen, Germany). The amount of RBCs added to the priming was calculated to achieve a hematocrit of 28% during CPB. The prime was completed with 0.5 g/kg mannitol, 0.5 g/kg human albumin 20% solution, 4.2 IU heparine / mL priming volume and 2-5 mL $NaHCO_3$ 8.4%.

Nonpulsatile CPB, with mild hypothermia of 28° C to 32° C, was performed with blood flow rates between 1.8 L/min/m^2 to 3.2 L/min/m^2 to maintain venous oxygen saturation

above 70% and mean arterial pressure between 40 to 60 mmHg. During CPB α – stat regulation was used. Myocardial protection was achieved with crystalloid cardioplegia.

Administration of RBCs, FFP, crystalloids or colloids during CPB was based upon the system working volumes, target values for hematocrit (not lower than 28% for acyanotic as well as cyanotic patients) and colloid osmotic pressure (not lower than 15 mmHg).

After CPB, residual volume of the circuit was in all cases processed by HaemoLite 2 plus (Haemonetics, Bothwell, UK) cell-saving device with a centrifugal bowl of 100 mL. In the ICS group all blood loss from skin incision to commencement of CPB and then after administration of protamine to skin closure was also salvaged. The HaemoLite 2 plus utilized an automatic protocol with centrifuge speed of 8000 rpm, pump speed of 300 mL/min by filling, washing and transfusing, and pump speed of 150 mL/min by concentrating. Washing volume was 500 mL. All those parameters were not manually interrupted during the study. Only completely filled bowls were automatically processed (in the last cycle the "concentrate" option was used to fill the bowl completely) and accepted for transfusion. In all cases the entire salvage volume was processed. The harvested cell saving (CS) product had a hematocrit of 60%.

Laboratory tests, blood loss and blood products transfusion

The hematocrit (Hct) and platelet (Plt) count were measured one day before the operation, at the start and end of the operation, during the CPB at the 5 min on bypass and at the end. During the postoperative period, measurements were performed at 6 hours and at 24 hours. Fibrinogen (Fib) concentration, prothrombin time (expressed as international normalized ratio, PT ratio) and activated partial thromboplastin time (expressed as APTT ratio to a normalized control value) were measured at the start and end of the operation and 6 and 24 hours postoperatively.

Blood loss was recorded at the end of the operation and at 6 and 24 hours postoperatively.

In the operation room (OR) blood loss represented the sum of blood loss calculated from swabs, discarded suction volumes (control group) or collected volumes (ICS group) and the chest drain output. In the intensive care unit (ICU), the volume of chest tube drainage was counted as blood loss. Post CPB and postoperatively the decision to transfuse RBCs, CS product, FFP or platelet concentrate was based upon the patient's clinical status and laboratory tests. Acyanotic as well as cyanotic patients were transfused to maintain a level of Hct above 30%. The CS product, if available, was always considered first line blood replacement therapy. Institutional transfusion policy allowed transfusion of this product only up to 6 hours and overdue remnants of the CS product were always discarded. Transfusion of FFP was administrated in case of enhanced blood loss and prolonged PT values (PT ratio >1.5). Platelet concentrate was administrated if the Plt count at the end of CPB was less than 100 x 10^9/L.

The volume of blood products transfused in the OR, including blood products added to the circuit prime and during the CPB, and administrated at the ICU was recorded.

Data analysis

Continuous data are presented as a mean ± standard deviation (SD); categorical data are presented as proportions. All data were assessed for normality of distribution and equality of variance. Continuous independent data were compared with unpaired t test and one-way analysis of variance ANOVA (in case of normally distributed data) or Mann – Whitney test (in case of non-normally distributed data). Repeated measures of continuous variables were compared using repeated measures ANOVA. Categorical data were compared with the chi-square test. Pearson correlation test quantified the relation between two variables where appropriate. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 13.0 statistical software (SPSS, Chicago, IL). In order to detect 50% reduction in postoperative RBCs transfusion with a power of 80% and an alpha value of 0.05, 60 patients in each group were required.

RESULTS

Population and CPB data

One hundred twenty two patients completed the study. Twelve patients who underwent DHCA were excluded as well as one patient with delayed sternum closure (1 day after operation). There were no patients with preoperative clotting disorders and no re-thoracotomies were required during the study period. All patients survived. Patient's gender, age, body weight, body surface area, CPB time, aorta cross-clamp time, time at the ICU and cardiac anomaly are presented in Table 1.

In the control group 38% of patients was diagnosed with cyanotic type of congenital heart disease versus 42% in the ICS group (p = 0.76).

Laboratory tests result and blood loss

In the control group, mean Hct values measured the day before operation and before start of the CPB were lower than the ICS group, but results showed no significance (Figure 1). Otherwise, the Hct values were not significantly different between the groups. There was no evidence for preoperative secondary erythrocytosis related to cyanotic type of heart disease (Table 2).

The Plt count was not significantly different between the groups at the times of measurements (Figure 2), as well as the mean values of PT ratio, APTT ratio and Fib concentration (Table 3).

Table 1. Population and CPB data.

	Control	ICS	
Variable	N = 63	N = 59	P value
	Mean ± SD	Mean ± SD	
Gender (female/male)	34/29	26/33	0.27
Age (months)	4.2 ± 2.0	4.1 ± 2.1	0.93
Weight (kg)	4.8 ± 1.6	5.2 ± 1.8	0.19
BSA (m2)	0.29 ± 0.06	0.30 ± 0.07	0.23
CPB time (min)	99 ± 37	99 ± 45	0.92
Cross-clamp (min)	64 ± 32	57 ± 32	0.21
ICU time (hours)	23 ± 5	25 ± 9	0.17
Anomaly - correction			
ASD - closure	0	2	
VSD - closure	9	6	
AVSD - correction	26	21	
F4 - correction	9	12	
TGA - Switch	4	7	
TAPVR - correction	2	3	
PCPC	4	3	
Other	9	5	

ASD - atrial septal defec; AVSD – atrioventriculair septal defect; BSA - body surface area; CPB- cardiopulmonary bypass; F4 – tetralogy of Fallot; ICS – intraoperative cell-salvage; ICU - Intensive Care Unit; PCPC – partial cavopulmonary connection; SD - standard deviation; TAPVR – total anomalous pulmonary venous return; TGA – transposition great arteries; VSD – ventricular septal defect

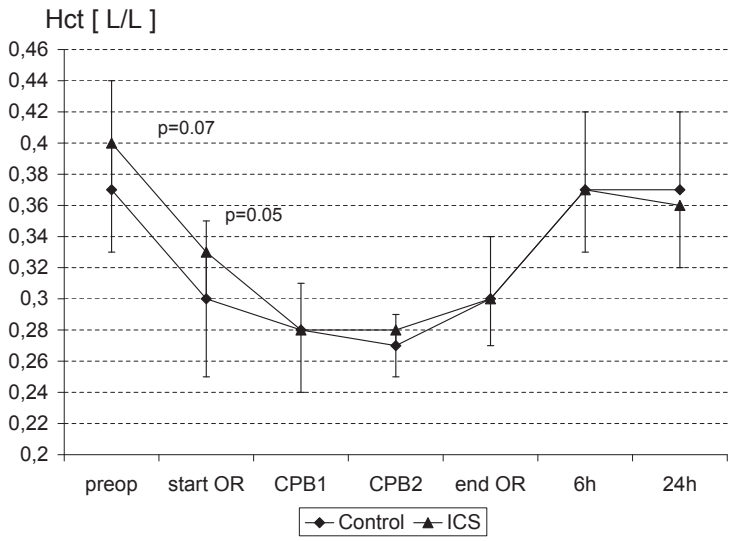

Figure 1. Hematocrit levels in pre-, per- and postoperative period.
CPB – cardiopulmonary bypass; Hct – hematocrit; ICS – intraoperative cell-salvage; OR – Operation Room

Table 2. Preoperative values of hematocrit in cyanotic and acyanotic patients.

	Control	N = 63		ICS	N = 59	
Variable (%)	Cyanotic	Acyanotic	p	Cyanotic	Acyanotic	p
	N = 24	N = 39	value	N = 25	N = 34	value
Hct preop	41 ± 9	36 ± 6	0.03	43 ± 9	38 ± 6	0.02
Hct start OR	32 ± 5	30 ± 5	0.14	36 ± 10	31 ± 6	0.04

ICS – intraoperative cell-salvage; Hct – hematocrit; OR – Operation Room

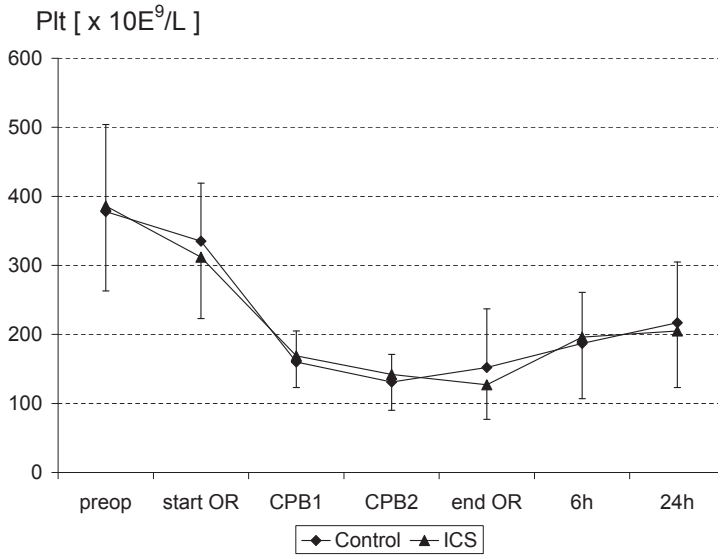

Figure 2. Platelets count in pre-, per- and postoperative period.
CPB – cardiopulmonary bypass; ICS – intraoperative cell-salvage; OR – Operation Room; Plt – platelets count

After 6 hours postoperatively the mean values of Fib concentration were within the normal range, APTT and PT values were normalised at 24 hours. There were no significant differences in terms of a total blood loss (Table 3) at any indicated time.

Blood salvage and blood products transfusion

Results of blood salvage and CS product transfusion are presented in Figure 3.The mean amount of CS product, generated from residual volume of CPB circuit and intraoperative blood loss, in the ICS group was significantly more than in the control group (183 ± 56 mL versus 152 ± 57 mL, p = 0.003). The mean volume of shed blood collected in the autotransfusion device was 66 ± 25 mL, with an estimated mean Hct of 30%. Only in 10 out of 59 patients in the ICS group, collected shed blood had adequate quantity and quality to produce full bowl at the end of the CPB without additional salvage of the CPB residual volume.

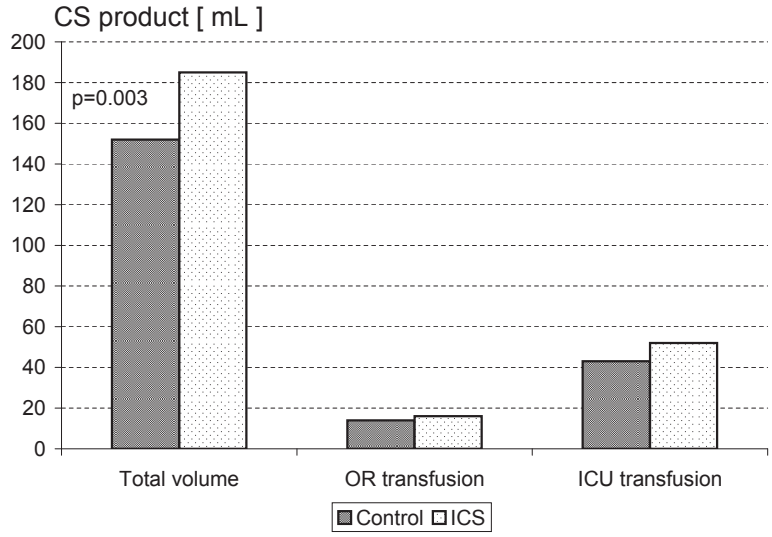

Figure 3. Use of the cell saving product.
CS – cell saving product; ICS – intraoperative cell-salvage; ICU – Intensive Care Unit; OR – Operation Room

In the OR after the cessation of CPB, there was no significant difference in the amount of transfused CS product or allogeneic RBCs between two groups and there was no significant difference in the frequency of transfusion (Table 4 and Table 5). On the other hand, during the first 6 postoperative hours 79% of patients in the ICS group received CS product versus 46% ($p<0.0001$) in the control group. The mean volume transfused was not significantly different between the groups (ICS group: 52 ± 45 mL versus control group: 43 ± 50 mL, $p = 0.32$). Frequency of allogeneic RBCs transfusion in the ICU during the first 6 hours was in ICS group significantly lower than in the control group (27% versus 59%, $p<0.0001$) as well as the mean volume transfused (14 ± 15 mL versus 37 ± 35 mL, $p = 0.008$).

In relation to the FFP and Plt concentrate transfusion, no significant differences between the groups were observed considering volume and transfusion frequency at any time of measurements.

COMMENT

This prospective observational study investigated the effects of ICS on allogeneic blood transfusion in infants, who underwent an elective first time cardiac operation with CPB. Our results demonstrated that ICS significantly enhanced the amount of CS product available for transfusion. In the postoperative period, significantly more patients in the ICS group received CS product, therefore the frequency of allogeneic RBCs transfusion

Table 3. Blood loss, APTT, PT and fibrinogen concentration during the study period.

	Control	ICS	
Variable	N = 63	N = 59	P value
	Mean ± SD	Mean ± SD	
Blood loss (mL/kg)			
End operation	21 ± 13	27 ± 10	0.06
6 hours	13 ± 9	11 ± 8	0.23
24 hours	8 ± 5	7 ± 3	0.08
PT ratio			
Start operation	1.1 ± 0.1	1.0 ± 0.1	0.72
End operation	1.4 ± 0.2	1.5 ± 0.3	0.31
6 hours	1.2 ± 0.3	1.4 ± 0.2	0.26
24 hours	1.0 ± 0.2	1.1 ± 0.1	0.38
APTT ratio			
Start operation	1.4 ± 0.3	1.3 ± 0.2	0.24
End operation	1.9 ± 0.2	1.5 ± 0.2	0.06
6 hours	1.3 ± 0.5	1.0 ± 0.1	0.23
24 hours	1.1 ± 0.2	1.0 ± 0.2	0.34
Fibrinogen (g/L)			
Start operation	2.2 ± 0.7	2.1 ± 0.3	0.41
End operation	1.4 ± 0.4	1.6 ± 0.3	0.33
6 hours	2.1 ± 0.5	2.3 ± 0.3	0.22
24 hours	2.5 ± 0.7	2.3 ± 0.5	0.31

APTT – activated partial thromboplastin time; ICS – intraoperative cell-salvage; PT – prothrombin time; SD – standard deviation

was significantly reduced as well as the mean transfused volume. We did not observe in the ICS group any adverse effects of CS product transfusion in terms of increased postoperative bleeding, derangement of clotting pathway or enhanced transfusion of platelets concentrate and FFP.

Prospective studies addressing the effects of intraoperative cell salvage in adult cardiac surgery have been performed since the late seventies. Results proved that intraoperative and postoperative cell salvage was effective, safe and that autotransfusion of washed cells was not associated with clinically significant derangement of clotting profiles [2, 11], although mechanochemical activation of platelets and leucocytes was found in the salvage blood [12]. Initially, cell salvage of the residual CPB volume was successfully introduced in our institution in adult cardiac surgery. Later on intraoperative cell salvage was subsequently combined with it as a routine blood conservation measure [13]. Availability of the new autotransfusion system, which processes small volumes of blood (100 mL bowl), gave us the opportunity to adapt this technique also in small children

Table 4. Transfusion of blood products.

	Control	ICS	p
Variable (mL)	N = 63	N = 59	value
	Mean ± SD	Mean ± SD	
RBCs			
Prime	170 ± 48	148 ± 47	0.01
CPB	62 ± 50	62 ± 49	0.93
OR	36 ± 33	36 ± 31	0.98
6h ICU	37 ± 35	14 ± 15	0.008
24h ICU	11 ± 9	8 ± 10	0.39
CS			
OR	14 ± 32	15 ± 34	0.82
6h ICU	43 ± 50	52 ± 45	0.32
FFP			
Prime	92 ± 32	88 ± 30	0.45
CPB	52 ± 49	42 ± 37	0.20
OR	34 ± 30	41 ± 37	0.32
6h ICU	59 ± 52	65 ± 47	0.53
24h ICU	19 ± 25	27 ± 29	0.11
Plt. Concentrate			
OR	19 ± 38	15 ± 40	0.59
6h ICU	26 ± 35	22 ± 39	0.78
24h ICU	3 ± 7	1 ± 3	0.46

CPB – cardiopulmonary bypass; CS – cell saving; FFP – fresh frozen plasma; ICS – intraoperative cell-salvage; ICU – Intensive Care Unit; OR – Operation Room; Plt – platelets; RBCs - red blood cells concentrate; SD – standard deviation

undergoing cardiac surgery. Primarily, we investigated the impact of the cell salvage from the residual volume of CPB circuit and the results showed a significant reduction of allogeneic RBCs transfusion in postoperative period [14]. Although, recent studies in infants undergoing surgical correction of craniosynostosis or acetabuloplasty found intraoperative cell salvage effective in limiting allogeneic blood transfusion [15], it is obvious that ICS is not equally useful for all types of surgery. Its effectiveness strongly depends on the ability to collect shed blood from the operating field, the hematocrit of collected blood as well as on the transfusion trigger.

In this study, in infants with a body weight less than 10 kg who underwent cardiac surgery with CPB, intraoperative blood loss collected in the autotransfusion device was in 83% of the cases not sufficient to fill completely the bowl of 100 mL, without additional salvage from the residual volume of the CPB circuit. We did not accept partially filled bowls for further processing to avoid an unpredictable and too low hematocrit

Table 5. Percentage of patients transfused with blood products.

Variable (%)	Control	ICS	
	N = 63	N = 59	p value
RBCs			
Prime	97	98	0.48
CPB	79	87	0.13
OR	70	63	0.49
6h ICU	59	27	<0.001
24h ICU	34	23	0.42
CS			
OR	21	28	0.50
6h ICU	46	79	<0.001
FFP			
Prime	98	100	0.55
CPB	75	75	0.98
OR	70	66	0.53
6h ICU	84	89	0.68
24h ICU	57	62	0.59
Plt. concentrate			
OR	29	21	0.44
6h ICU	39	35	0.63
24h ICU	2	2	0.98

CPB – cardiopulmonary bypass; CS – cell saving product; FFP – fresh frozen plasma; ICS – intraoperative cell-salvage; ICU – Intensive Care Unit; OR – Operation Room; Plt – platelets; RBCs – red blood cells concentrate

[16]. Because of that, the CS product was no sooner available for transfusion until the salvage of CPB residual volume had been completed, usually at the end of the operation. Accordingly, patients in both groups received in the OR transfusion of allogeneic RBCs with a frequency and amount that was not significantly different. In the OR use of the ICS had no effect on allogeneic blood transfusion. On the contrary, during the first 6 hours in the ICU, only 27% of patients from the ICS group received transfusion of allogeneic RBCs compared to as much as 59% of patients in the control group. Patients in the ICS group received on average 14 ± 15 mL of allogeneic RBCs and patients in the control group; 37 ± 35 mL. After 6 hours allogeneic RBCs were routinely administrated in the both groups, because the CS product acceptance for transfusion elapsed after this time. The study of Hishon et al. and Amand et al. [17,18] demonstrated minimal chemical deterioration and limited microbiologic contamination in blood salvaged from the CPB circuit and stored at room temperature for an 18-hour period. Therefore, prolongation

of the acceptable transfusion period for CS product could be beneficial with regard to further reduction of allogeneic blood requirements. Use of the ICS had no consequence for the FFP and platelet concentrate transfusion as well as for the coagulation pathways and Fib concentration changes in the perioperative period.

Additionally, our study results revealed that allogeneic blood was in many cases transfused in the ICU even though there was sufficient amount of CS product available (Figure 3). This phenomenon was considered to be a major study limitation.

Study design and limitations

The study compared two cohorts of patients that underwent operations in different periods, nevertheless there were no differences in perioperative management, CPB and population data as well as the ratio between cyanotic and acyanotic patients in each group.

On the other hand, preoperative laboratory data revealed unexplained lower Hct values in the control group (for cyanotic and acyanotic patients, Table 2). Consequently, significantly more allogeneic RBCs were used in the prime of the CPB circuit and a second unit of allogeneic blood was required for transfusion after the cessation of CPB. This occurred in 48% of patients in control group versus 23% in ICS group ($p = 0.04$). Both groups showed a significant correlation (control group $r = 0.86$, ICS group $r = 0.78$, both $p = 0.05$) between transfusion of a second unit allogeneic RBCs in the OR and use of allogeneic blood during the first six postoperative hours. These findings support the hypothesis that, against the protocol, homologous blood transfusion was continued in the ICU if the previous exposure to the specific unit of blood took place in the OR. Consequently, postoperative use of the CS product was limited (Figure 3). After reconsideration of those findings, the study data on allogeneic RBCs transfusion during the first 6 postoperative hours were recalculated. To correct for this bias, patients who utilized the whole volume of the first unit allogeneic RBCs before the end of the CPB were excluded from the recalculation. Even so, frequency of allogeneic RBCs transfusion in the ICS group was significantly lower than in the control group (23% versus 41%, $p = 0.03$), but difference in the average transfused volume did not show significance (12 ± 11 versus 23 ± 32 mL, $p=0.11$).

We also performed a financial cost-benefit analysis based upon the reduction of allogeneic RBCs transfused in the ICS group compared to the control group. Introduction of the ICS reduced transfusion of allogeneic RBCs by eighteen units (total cost of 3348.- €), but required an investment of 4725.- € (75.- € per patient to collect shed blood). If the primary bias was removed from the study the reduction of allogeneic transfusion was only three units (total cost 560.-€) but required an investment of 2665.-€. Therefore, the cost made to collect shed blood was higher than the financial savings associated with the reduction of allogeneic blood transfusion.

CONCLUSIONS

Autologous transfusion is considered to be worthy as a prevention of transfusion-transmitted diseases, transfusion reactions and immune-related problems; although a unit of CS product costs slightly more than a unit of allogeneic blood.

The ICS used, as an adjuvant technique to the cell salvage from the CPB residual volume, in infants undergoing first time cardiac surgery proved to be save and effective to produce more CS product available for transfusion. The ICS was also effective in reducing postoperative allogeneic blood transfusion in terms of frequency as well as volume. Therefore, ICS was validated to be a useful blood conservation measure in infant cardiac surgery.

Prolongation of the acceptable transfusion time for the CS product, strict realisation of the postoperative transfusion protocol (CS product as the first line transfusion therapy) and adjustment of the transfusion trigger would be beneficial for the effectiveness of ICS. Under those conditions, ICS potentially could be an economic benefit.

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Chapter 5

Small, smaller, smallest. Steps towards bloodless neonatal and infant cardiopulmonary bypass

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ABSTRACT

In open heart surgery in neonates and small children, the cardiopulmonary bypass circuit surface and the priming volume are relatively large in relation to the patient's size and blood volume. Therefore, the use of allogeneic blood is inevitable to maintain the optimal hematocrit level during the bypass. To avoid the deleterious effects of blood transfusion, as well as to reduce the contact surface of blood with artificial materials, we stepwise reduced the bypass circuit size. Use of the commercially available minimized elements and an adjusted set-up of the system allowed us to reduce usage of allogeneic blood in the prime and during the bypass. However, other supplemental measures are needed to obtain asnguineous cardiopulmonary bypass for neonatal and infant patients.

INTRODUCTION

Well-known adverse effects of neonatal and infant cardiopulmonary bypass (CPB) are related to a systemic inflammatory response. This complex process is induced by many factors such as the exposure of blood to foreign surfaces, temperature fluctuations, ischemia-reperfusion injury and is enhanced by patient organ immaturity and congenital defects [1].

In neonates and small children, the CPB circuit surface and the priming volume are relatively large in relation to the patient's size and blood volume. Therefore, the use of allogeneic blood is inevitable to maintain the optimal hematocrit level during the bypass. The deleterious effects of allogeneic blood transfusion are well documented in adult patients and in animal models. Silliman et al have shown that blood transfusion is a major factor for postinjury multiorgan failure and that the transfusion related morbidity highly correlated with the duration of blood storage [2].

Recent miniaturizations of a CPB circuit enable bloodless open heart surgery to be performed in selected pediatric patients [3]. However, the asanguineous prime composition for neonates and infants is not yet a routine clinical practice. In keeping with safety standards and institutional protocols, we achieved the CPB circuit reduction from 700 ml to 300 ml during the past years. In this brief report, we present a retrospective analysis of the effect of stepwise miniaturization of CPB circuit on homologous blood requirement during the neonatal and infant CPB.

MATERIAL AND METHODS

This retrospective audit was performed in compliance with the Hospital Data Protection Policy. All patients, between 1-to12 months of age and weighing less than 10 kg, who underwent an elective, first time open heart operation at the Erasmus University Medical Center, Rotterdam, from January 1997 to July 2008, were included in the study. Procedures that required deep hypothermic circulatory arrest and postoperative reexplorations were excluded from the audit. We divided the entire cohort into four groups based on the CPB system:

Group 1 - (52 patients, operated from 1997 till 1999) the CPB system total priming volume was 700 ml and a Cobe VPCML flat-sheet membrane oxygenator with hard-shell reservoir (Cobe, Denver, Colorado, USA) was used, with a priming volume 450 ml.

Group 2 - (54 patients, from 2000 to 2003) the total priming volume of 450 ml, a Polystan Safe Mini hollow-fiber membrane oxygenator with hard-shell reservoir (Maquet Cardiopulmonary, Hirrlingen, Germany), with a priming volume 160 ml.

Group 3 - (42 patients, from 2004 till March 2005) the total priming volume of 330 ml, a Capiox Baby Rx hollow-fiber oxygenator with hard-shell reservoir (Terumo, Tokyo, Japan), with priming volume 60 ml.

Group 4 - (38 patients, from March 2005 till July 2008) the total priming volume of 300 ml, a Capiox Baby Rx oxygenator.

All the CPB systems utilized a roller pump with ¼" silicone tubing (Raumedic REHAU, Muri, Switzerland), an arterial filter and PVC ¼" arterial and venous tubing. The components of the CPB systems used in Groups 1, 2 and 3 were not coated. The CPB system used in the Group 4 had a phosphorylcholine coating.

All patients received standard anesthesia (as described before [4]). The CPB prime contained red blood cells (RBC); the amount was calculated to achieve a hematocrit of 0.28 L/L during CPB for acyanotic as well as cyanotic patients. Other, main prime components were: fresh-frozen plasma (FFP) and Ringer's Solution (Baxter, Utrecht, The Netherlands) or Gelofusine (B. Braun, Melsungen, Germany). Administrations of RBC products during CPB were at the discretion of the perfusionist, based upon the working volumes and hematocrit levels. Nonpulsatile CPB, with mild hypothermia of 28 °C to 32° C, was performed with blood flow rates between 1.8 L/min/m^2 to 3.2 L/min/m^2 to maintain venous oxygen saturation above 70% and mean arterial pressure between 40 to 60 mmHg. Details of CPB technique and postoperative transfusion criteria were described previously [4].

The total amount of the priming volume and the RBC used in the prime and during CPB were compared between the groups. Hematocrit (Ht), platelet count and fibrinogen concentration were measured one day before the operation, after the induction of anesthesia and during the CPB at the 5 min on bypass and at the end. Blood loss and urine production were noted at the end of the operation and postoperatively (the total chest tube output and urine output during the first 24 hours post operation). The volumes of blood products transfused peri- and postoperatively were recorded.

Data analysis

Continuous data are presented as mean ± standard deviation; categorical data - as proportions. Statistical significance of differences between the groups was determined by one-way analysis of variance and Bonferroni (in case of equal variances) or Tamhane T2 (in case of unequal variances) post-hoc corrections were applied to the p values for multiple comparisions. Categorical data were compared with the chi-square test. A p value less than 0.05 was considered statistically significant.

RESULTS

The baseline results are presented in Table1. Group 3 was significantly younger and lighter than Group 1, 2 and 4. The CPB and cross-clamp time were significantly shorter

Table 1. Population and CPB data.

Variabele	Group 1	Group2	Group 3	Group 4	p
	n = 52	n = 54	n = 42	n = 38	value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (mo)	6.2 ± 4.2	5.5 ± 3.0	4.9 ± 3.9*	5.8 ± 4.0	0.07
Weight (kg)	6.2 ± 1.9	5.7 ± 1.8	5.5 ± 2.0*	6.5 ± 2.1	0.09
CPB time (min)	76 ± 16#	91 ± 28	91 ± 28	81 ± 30	0.06
Cross-clamp time (min)	43 ± 29#	51 ± 19	58 ± 27	53 ± 25	0.04
Anomaly - correction					
ASD - closure	4	2	0	0	
VSD - closure	9	11	16	3	
AVSD - correction	19	19	14	15	
F4 - correction	11	11	4	6	
Other	9	11	8	14	

* p<0.05 group 3 vs. group 1, 2 and 4 (Bonferroni correction); # p<0.05 group 1 vs. group 2, 3 and 4 (Bonferroni correction); ASD - atrial septal defec; AVSD – atrioventricular septal defect; CPB-cardiopulmonary bypass; F4 – tetralogy of Fallot; IC – intensive care; SD - standard deviation; VSD – ventricular septal defect

Table 2. Homologous RBC transfusion (volume and incidence) and changes in hematocrit.

Variabele	Group 1	Group 2	Group 3	Group 4	p
	n = 52	n = 54	n = 42	n = 38	value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Total prime volume (ml)	718 ± 15	458 ± 15	334 ± 8	305 ± 10	<0.001
RBC prime (ml)	313 ± 5	205 ± 5	167 ± 8	116 ± 7	<0.001
RBC CPB (ml)	117 ± 8	88 ± 7	60 ± 8	51 ± 6	<0.001
RBC Prime (%)	100	100	100	94	<0.01
RBC CPB (%)	100	89	79	80	0.03
Ht pre OP (l/l)	0.38 ± 0.03	0.37 ± 0.01	0.38 ± 0.02	0.39 ± 0.05	NS
Ht pre CPB (l/l)	0.31 ± 0.02	0.31 ± 0.02	0.31 ± 0.03	0.35 ± 0.04	NS
Ht 5' CPB(l/l)	0.25 ± 0.02	0.26 ± 0.01	0.28 ± 0.01	0.27 ± 0.02	NS
Ht end CPB (l/l)	0.27 ± 0.02	0.27 ± 0.03	0.27 ± 0.02	0.26 ± 0.02	NS
Ht end IC (l/l)	0.37 ± 0.04	0.38 ± 0.03	0.36 ± 0.04	0.36 ± 0.02	NS

CPB – cardiopulmonary bypass; Ht - hematocrit; IC – intensive care; NS – not significant; OP – operation; RBC-red blood cells; SD – standard deviation

in Group 1 compared to the other groups. The hematocrit values during the study period did not differ among the groups; however, there was significant difference for RBC amount used in the priming, as well as during the CPB (Table 2).

The outcome variables are listed in the Table 3. Group 4 (the smallest priming volume) stayed significantly shorter at the Intensive Care unit and had the shortest time until the extubation. On the other hand, group 1 (the biggest priming volume) had significantly lower count of platelets after the CPB and received significantly more transfusion of FFP and platelets concentrate during the peri- and postoperative periods.

Table 3. Outcome variables

Variabele	Group 1	Group 2	Group 3	Group 4	p
	n = 52	n = 54	n = 42	n = 38	value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
IC stay (h)	33 ± 22	31 ± 18	23 ± 5*	20 ± 8†	0.03
Till extubation (h)	21 ± 15	20 ± 15	18 ± 15	10 ± 6††	<0.001
Blood loss (mL/kg)					
Perioperative	13 ± 7	14 ± 14	16 ± 7	15 ± 12	0.07
Postoperative	14 ± 7	17 ± 14	21 ± 19	18 ± 11	0.08
Urine output (ml/kg/h)					
Perioperative	8 ± 1	6 ± 1	7 ± 1	5 ± 1	0.15
Postoperative	6 ± 1#	3 ± 1	4 ± 1	3 ± 1	0.001
Platelet count (10^9/l)					
Pre-perfusion	357 ± 137	345 ± 125	321 ± 84	303 ± 77	0.35
End perfusion	132 ± 65#	147 ± 59	139 ± 39	157 ± 60	0.02
Fibrinogen (g/l)					
Pre-perfusion	2.2 ± 0.7	2.1 ± 0.5	2.3 ± 0.5	2.2 ± 0.5	0.87
End perfusion	1.4 ± 0.4	1.6 ± 0.3	1.3 ± 0.4	1.5 ± 0.4	0.76
RBC (ml)					
Perioperative	38 ± 14	28 ± 51§	48 ± 75	50 ± 51	<0.01
Postoperative	65 ± 50	79 ± 37	76 ± 52	71 ± 42	0.06
FFP (ml)					
Perioperative	53 ± 29#	42 ± 51	36 ± 45	38 ± 50	<0.01
Postoperative	88 ± 57#	69 ± 66	77 ± 58	72 ± 73	<0.01
Platelets (ml)					
Perioperative	77 ± 86#	57 ± 73	13 ± 32	12 ± 29	<0.001
Postoperative	36 ± 43#	20 ± 29	22 ± 39	12 ± 33†	<0.001

* p<0.05 group 3 vs. group 1, 2 and 4 (Bonferroni correction); †p< 0.05 group 4 vs. group 1, 2 and 3 (Bonferroni correction); ††p< 0.05 group 4 vs. group 1, 2 and 3 (Tamhane T2 correction); # p<0.05 group 1 vs. group 2, 3 and 4 (Bonferroni correction); §p<0.05 group 2 vs. group 1, 3, and 4(Bonferroni correction); CPB – cardiopulmonary bypass; FFP – fresh frozen plasma; Ht - hematocrit; IC – intensive care; RBC-red blood cells; SD – standard deviation

DISCUSSION

The current data demonstrate that consequent reduction of the CPB circuit size is a right step towards the transfusion – free cardiac surgery. By downsizing the oxygenator and reducing the circuit tubing length, we significantly reduced the priming volume and subsequently the total use of blood. The incidence of RBC transfusion in the priming and during the CPB was decreased from 100% to 94% and from 100% to 80% respectively. The hematocrit values during the CPB were within the expected range. Still, our CPB circuit volume of approximately 300 ml was higher than reported by others [5, 6].

The use of newly developed oxygenator and repositioning of the circuit elements to eliminate even more the tube length allow us priming reduction to 250 ml for the smallest children. Further reduction would be possible if we consider a closer position of the circuit to the patient, diminishing tube diameter and applying of vacuum–assisted venous drainage [7]. Other measures leading towards the asanguineous neonatal CPB could be the preoperative strategies to maximize the patient's RBC mass [8] and acceptance of lower hematocrit levels during the CPB [9, 10]. This multifactorial approach might contribute to essential reduction (40% to 60% reduction) in the total number of homologous blood exposures and finally asanguineous neonatal and infant CBP [3, 7].

Recent, stepwise miniaturization of the CPB circuit and reduction of RBC amount used during the bypass did not result in decrease of the total blood loss and peri- and postoperative RBC transfusion requirement. Otherwise, volume of peri- and postoperative transfusion of FFP and platelets concentrate was significantly higher in the group with the biggest CPB circuit. This group had also the lowest count of platelets after the bypass compared to the other groups.

Neonates operated with the smallest CPB circuits stayed significantly shorter at the ICU and were extubated after the shortest duration of ventilatory support. Those improved clinical outcomes indicate superior postoperative cardiopulmonary function of neonates operated with use of minimized CPB circuit [1, 5].

Major limitations of this study include its retrospective nature and absence of inflammatory endpoints. However, our results permit the investigation of the clinical benefits of a CPB circuit reduction in the prospective randomized study in the near future.

CONCLUSION

In summary, miniaturization of the CPB circuit size reduces the overall use of blood transfusion, and possibly, decreases patient inflammatory response. Together with the determination of the safe hematocrit strategy, this may render asanguinouse neonatal CPB.

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Chapter 6

Specific requirements for bloodless cardiopulmonary bypass in neonates and infants; a review

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ABSTRACT

A miniaturized cardiopulmonary bypass circuit enables the safe performance, in selected pediatric patients, bloodless open-heart surgery. As the latest survival rates in neonatal and infant cardiac surgery have become satisfactory, investigators concentrate upon the improvement of existing procedures. Institutional guidelines and multidisciplinary efforts undertaken in the pre- and postoperative period are of a great importance concerning the bloodless cardiopulmonary bypass and should be seriously pursued by all involved caregivers.

This review reflects upon the selective, most relevant requirements for success of asanguineous neonatal and infant CPB: acceptable level of hemodilution during the CPB, patient preoperative hematocrit value and volume of CPB circuit. We present an assessment of practical measures that were also adapted in our institution to achieve an asanguineous CPB for neonatal and infant patients.

INTRODUCTION

In open-heart surgery for neonates and small children, the cardiopulmonary bypass (CPB) circuit surface and the priming volume are relatively large in relation to patient size and blood volume, which exacerbate the systemic inflammatory response syndrome (SIRS) [1]. In addition, patient related factors including organ immaturity, complex congenital defects and the specific CPB techniques required during the surgical correction (deep hypothermic circulatory arrest, hypothermic low- flow perfusion) contribute to that response [2, 3]. Consequently, postoperative capillary leak syndrome, acute lung injury and multiorgan failure may occur [4, 5]. There is also evidence that SIRS aggravates post-ischemic cerebral injury [6, 7]. In the past years, multiple efforts were attempted to diminish those deleterious effects of CPB through circuit miniaturization. Reduction of the contact surface area and use of diverse coating materials proved to be efficient to attenuate negative effects of systemic inflammatory response [8, 9, 10].

Yet another goal has to be achieved by circuit miniaturization that is the reduction of the allogeneic blood in the bypass prime. In the conventional neonatal and infant circuit, use of allogeneic blood is inevitable to maintain an optimal hematocrit level during bypass. The deleterious effects of allogeneic blood transfusion are well documented in adult patients. Studies in adults demonstrated that low hematocrit was associated with postoperative renal dysfunction, but transfusion of red blood cells concentrate (RBCs) to compensate for hemodilution significantly increased the risk of renal impairment and failure [11,12, 13]. This suggests that severe hemodilution during CPB may diminish systemic oxygen delivery and that allogeneic blood transfusion may worsen ischemic organ injury. Silliman et al. have shown that blood transfusion is a major factor for postinjury multiorgan failure and that the transfusion related morbidity positively correlated with the duration of blood storage [14]. Potassium level and free hemoglobin level from erythrocyte lysis increase with duration of blood storage as well as activated complement fragments and inflammatory cytokine levels (IL-8 and TNF-α) [15]. The importance of the elevated lactate levels in the stored blood in relation to the clinical outcome has not been established [16], although high levels of lactate during CPB are associated with increased morbidity and mortality [17]. Therefore, total avoidance of allogeneic blood during pediatric open heart surgery became strongly advocated. This is supported by recent investigation in an animal model, which suggested that exclusion of allogeneic blood from the circuit prime might significantly reduce CPB – induced inflammation [18].

Miniaturized CPB circuit enables to perform safely, in selected pediatric patients, bloodless open heart surgery [19 - 25]. Still, the consequent effort toward the circuit reduction and diminishing of blood transfusion are of a great importance. This review reflects upon the most important requirements for success of asanguineous neonatal

and infant CPB: (1) acceptable level of hemodilution during the CPB, (2) patient preoperative hematocrit value, and (3) volume of CPB circuit. We also present a practical assessment of measures that should be adapted to achieve an asanguineous CPB.

HEMODILUTION DURING THE CPB

The prime composition in neonates and infants is primarily calculated to achieve a required hematocrit during CPB and this parameter determines the amount of allogeneic blood, which is added to the priming solution. Practically, the hematocrit level during the CPB is commonly calculated with empirical formula:
$Ht_{cpb} = (Ht_{pat} \times BV_{pat}) / (BV_{pat} + V_{prime})$, that can be rewritten in the equivalent form:

$$Ht_{cpb} = \frac{Ht_{patient}}{1 + \frac{V_{prime}}{BV_{patient}}}$$

Ht_{cpb} – expected hematocrit during the bypass, $Ht_{patient}$ – preoperative patient hematocrit, $BV_{patient}$ – patient total blood volume, V_{prime} – priming volume
The relationships between the hematocrit during the bypass and the prime volume for 3 kg neonate are presented in the Figure 1.

Hematocrit value during the bypass is directly proportional to the value of preoperative hematocrit of the patient and inversely proportional to the prime volume, therefore these factors must be re-evaluated in a context of asanguinous prime concept. Still, the most important issue is a definition of acceptable hemodilution level during CPB.

Hemodilutional anemia is an inevitable consequence of asanguineous CPB in neonates and small children and adequacy of hemodilution level during CPB is still a matter of controversy. Lowering the hematocrit during the bypass decreases blood viscosity and perfusion pressure, this consequently increases microcirculation and improves tissue perfusion. On the other hand, excessive hemodilution may compromise systemic oxygen delivery at the tissue level and cause hypotension during the bypass. There are no data available to define a safe threshold at which the benefits of RBCs transfusion outweight the risk of hemodilution. Therefore, hemodilution during CPB should be employed cautiously.

Jonas and associates investigated in randomized clinical trails the effect of a hematocrit level at the onset of low-flow hypothermic cardiopulmonary bypass on Psychomotor Development Index (PDI) and Mental Development Index (MDI) scores [26, 27]. The conclusion based upon data of 271 infants, was that a hematocrit level of approximately 24% or higher was associated with higher PDI at 1 year and with reduced lactate levels

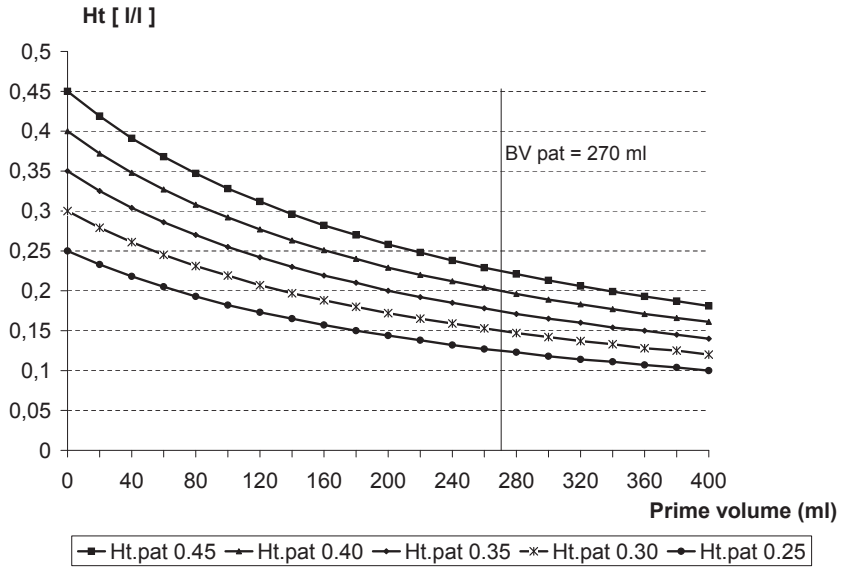

Figure 1. Hemodilution with asanguineous prime for 3 kg neonate.
BV pat – patient blood volume; Ht. – hematocrit; Ht. pat – patient preoperative hematocrit

after the bypass. The effect of hemodilution level on PDI scores was not linear; PDI scores were improving with increase of hematocrit up to 24%, followed by a plateau. There was no association between increasing hematocrit level and MDI scores. Although results of Jonas and associates were related to low-flow deep hypothermia CPB, they are still frequently cited and deterred to a significant hemodilution. Respondents to "Survey 2005 on pediatric perfusion practice in North America" offered as minimal acceptable hemodilution level during mild hypothermia a hematocrit of 27,3%, hematocrit of 34% at the end of CPB for cyanotic defects and hematocrit of 28,8% for noncyanotic patients [29].

Observational studies on asanguinous minimal CPB for pediatric Jehovah's Witness patients demonstrated that low hematocrit during the bypass (between 18% to 20%) was safe and did not result in relevant complications [23, 30]. The availability of the latest miniaturized CPB circuit and recent refinement of perfusion strategy (use of continuous in-line monitoring systems and near infrared spectroscopy) allowed large data clinical studies on the asanguinous CPB. Ando and associates reported in retrospective cohort of 158 patients weighing 5 kg or less, no neurological squealae, no renal and liver function impairment and no diminishing of Japanese psychomotor development scale scores related to the low hematocrit during CPB (nadir hematocrit approx. 16, 7%, target hematocrit 15%). However, the studied group included only acyanotic patients with simple heart lesion; mostly ventricular septal defect [20].

Study results of Miyaji and co-workers showed that they were able to safely perform transfusion free complex heart surgery in 45 out of 70 patients (64%) weighing between 4 and 7 kg. The use of a minimal CPB system of 140 ml priming volume produced the lowest hematocrit level during bypass of 22,2% .The limiting factor for bloodless heart surgery with minimal CPB circuit was bypass time and patient body weight, not preoperative hematocrit or complexity of procedure [24]. Other investigators concluded that open heart surgery without blood transfusion could be achieved in half of the patients weighing 5-20 kg without any major complications. For patients with a bodyweight less than 10 kg bloodless cardiac surgery was successfully perform in 29% of cases. The nadir hematocrit during bypass was for the nontransfusion group 20, 9% [25].

Owing to general availability of continuous monitoring of mixed venous oxygen saturation (Svo2), regional cerebral and systemic oxygenation (rSo2) and frequent measurement of plasma lactate level during bypass, investigators were able to accept a hemodilution levels as low as 20% during CPB for biventricular corrections and 25% for univentricular corrections.

If there were difficulties to maintain the Svo2 above 70% and rSo2 above 50%, despite of increased pump flow and oxygen concentration during the bypass, allogeneic blood transfusion was administrated. Similarly, when plasma lactate level was increased above 4.0 mmol/l blood transfusion was performed [23, 25].

Depending on those new technical possibilities and the positive results from clinical studies a lower level of hemodilution during CPB was easily accepted and this allowed to perform a bloodless CPB and even bloodless open heart surgery in pediatric patients.

PREOPERATIVE PATIENT HEMATOCRIT

Preoperative patient hematocrit is an important factor that strongly influences level of hemodilution during asanguinous CPB. Higher level of preoperative hematocrit is associated with higher hematocrit during the bypass (Fig.1). Since recombinant human erythropoietin (EPO) has become available for clinical use, it is successfully administrated in adult patients undergoing open-heart surgery to avoid transfusion of allogeneic blood [31].

In preparation for bloodless heart surgery, especially in Jehovah's Witness pediatric patients, the strategy to maximize patient red cell mass by administrating erythropoietin (EPO) and iron supplement is recorded [23]. Shimpo and collaborators proved that EPO is an effective adjuvant therapy for open heart surgery without blood transfusion in children [32]. They assessed efficacy and determined the effective dose of EPO in 48 children between 3 and 13 years of age. EPO was administrated on the day of hospital

admission (6 to 7 days prior to surgery), on the following day, immediately after surgery and on the following day.

A relatively high dose of EPO (300 U/kg) was effective for pediatric patients. Open-heart surgery in the high dose EPO group was completed without blood transfusion in all patients (100%) and there were no adverse reactions to the drug administration. Other authors applied an autologous predonation protocol using EPO in pediatric cardiac surgery [33]. In the group that included 69 children weighing 8 kg or more, twice 8 ml/kg of blood was taken before operation. At each donation, EPO was given subcutaneously. Although between donations the hematocrit decreased, one day after the operation it normalized. No harmful events occurred during the donation period. From the study group 93,5% patients completed heart surgery without homologous blood transfusion. Perioperative administration of EPO, with or without predonation protocol, was concluded to be an effective strategy for bloodless heart surgery. On the downside, there are costs involved with EPO administration and predonation strategy (need for prolonged hospitalization) as well as physical and psychological stress for the patient. In addition, some patients, due to their cardiac conditions, cannot wait for this strategy to result in the desired, higher level of hematocrit.

CIRCUIT MINIMALIZATION AND VOLUME REDUCTION

In recent years, commercially available oxygenators, arterial line filters and hemofilters, designed to serve pediatric patient underwent consequent miniaturization (Table 1). This process of technical refinement is still going on and the latest products are very promising. The newest oxygenators incorporate an arterial line filter thus further limiting priming volume (Terumo Capiox Fx 0.5, Maqet Quadrox –i Neonate and Pediatric).

Despite of the availability of minimized system elements also the rest of CPB circuit should be drastically reduced in volume. For the circuit lines this means reduction of length and diameter. Length reduction of arterial, venous, suction and venting lines is possible by positioning the circuit into close proximity to the operating table and shortening the distances between the circuit elements. A dedicated neonatal pump console is of great help to achieve this goal. Conventional mast mounted, remote pump heads consoles are reported to reduce the priming volume with 29% [35]. To position the CPB circuit close to the operating table, a protective sterilized sheet is often utilized to create a barrier between the operators and the heart-lung machine [20, 24]. Diameter of most commonly used tubes in neonatal and infant CPB systems varies from ¼" throughout 3/16" to 1/8". Although the smallest size of tubing considerably reduces the priming volume of the system (10 cm of 1/8" tubing have a volume of 0.75 ml, for 3/16" tubing it is 1.73 ml and for ¼" tubing it is 3.11 ml) there are practical limits for its utilization. In the

Table I. Commercially available pediatric products.

Type	Blood Flow (l/min)	Surface Area (m^2)	Volume (ml)
Terumo			
Capiox Fx 05	1.1 - 1.5	0.53 + 0.013	43
Capiox Rx 05	0.1 – 1.5	0.53	43
Arterial filter Pall AL3	< 3	0.0175	28
Sorin			
Kids 100	< 0.7	0.22	31
Arterial filter D130			16
Kids 101	< 2.5	0.61	87
Arterial filter D 131			28
Sorin			
Lilliput 1	< 0.8	0.36	60
Lilliput 2	< 2.3	0.66	105
Arterial filter Micro	< 2.5	0.014	40
Maquet			
Safe Micro	0.8	0.42	46
Safe Mini	0.3 – 2.3	0.83	90
Quadrox –i Neonate	0.2 – 1.5	0.38	38 +2
Quadrox- i Pediatric	0.2 – 2.8	0.8	81 + 18

3/16"arterial line the unwanted effect of flow change from laminar into turbulent can occur when the flow reaches a velocity of 1.8 l/min (at this flow it is established that the Reynolds number reaches a value of 1000) [21]. Therefore, it is very important to estimate the expected arterial pump flow under every condition, for example, the reduction of oxygen carrying capacity and the decline of arterial pressure due to hemodilutional effect of bloodless priming.

The 3/16"diameter venous tube can accommodate gravity drainage up to approximately 550 ml/min. A higher arterial pump flow requires a supported rate of venous drainage by vacuum assisted venous drainage technique (VAVD). As the result of VAVD, downsizing of the tubing reduces priming volume as well as the need for allogeneic blood transfusion in pediatric patients [19, 36]. Advantages of VAVD must be always balanced against potential risks of embolization in the arterial line or overestimation of arterial pump flow [37, 38]. The safe use of VAVD necessitates refinement of perfusion techniques, adequate choice of application and further development of the CPB circuit. Latest in vitro studies proved that VAVD in combination with unprimed venous line could also be safely performed [39]. The results of Hudecko and co-workers suggest that, if an oxygenator and arterial filter with sufficient air handling capabilities are used, this method to reduce prime volume does not increase gaseous microemboli in the arterial line distal to the arterial filter [39].

All technical measures to reduce priming volume result in such small neonatal and infant CPB circuits that their hemodilutional effects are markedly diminished. For ex-

ample, Durandy and co-operators created a system of 120 ml volume for patients up to 10 kg [22], Merkle and associates used a circuit of 190 ml volume for children with a body weight under 6 kg [21], and Charette with associates reduced their CPB system to 172 ml [40].

INSTITUTIONAL GUIDELINES FOR ASANGUINEOUS NEONATAL AND INFANT CPB

As there is a general agreement that bloodless CPB for small children could be safely and successfully performed, a specific centre - related program is required to achieve this objective. In that regard, the institutional guidelines must include aspects of:

- CPB circuit reduction
- increasing of preoperative patient hematocrit
- agreement on acceptable safe hematocrit during CPB
- assessment of expected reduction of blood transfusion during CPB

In the Erasmus University Medical Center of Rotterdam, from January 1997 until present, volume of pediatric CPB system was significantly reduced from 700 ml to 300 ml in 2008, and recently even further to 280 ml. All that volume reduction was mainly achieved by implementation of the latest smaller oxygenators and arterial filters, and from the year 2008 through utilisation of the Stöckert S5 heart-lung machine with mast mounted pump heads (Stöckert, Munich, Germany). During all those years there was no change in the tubing diameter of arterial-venous loop: ¼ x ¼ inch, and pump boot: ¼ inch. Only the suction lines were at some point in time converted from ¼ inch diameter in to 3/16 inch. There was also not much of change in the circuit design as to the elements position and distances. Therefore, total priming volume with regard to the lines did not change significantly (Figure 2 and Figure 3).

Additionally, our hematocrit target during CPB was invariably established at the same, relatively high level of 28%. This approach, based solely upon the CPB circuit reduction, resulted in significant reduction of RBCs volume used in the priming and during the CPB, but only in minimal decrease of transfusion incidence. In the year 1997 100% patients with the body weight up to 10 kg received blood in the priming and 100% required additional blood transfusion during the CPB, this percentage was in 2008 reduced to 94% and 80% respectively [34].

At present, pediatric oxygenators with integrated arterial line filters offer a new opportunity to create a smaller CPB circuit. Newly developed, customized CPB circuit based upon the Terumo Capiox Fx 0.5 oxygenator, with redesigned tubing set of existing diameter, will reduce our prime volume to 230 ml without any concession to safety of CPB performance.

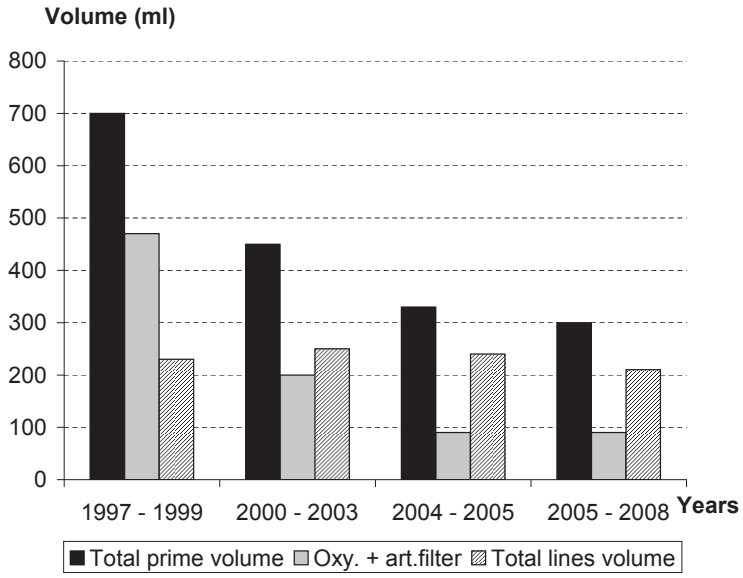

Figure 2. Volume changes of CPB circuit.
CPB – cardiopulmonary bypass; Oxy. + art. filter – oxygenator + arterial filter

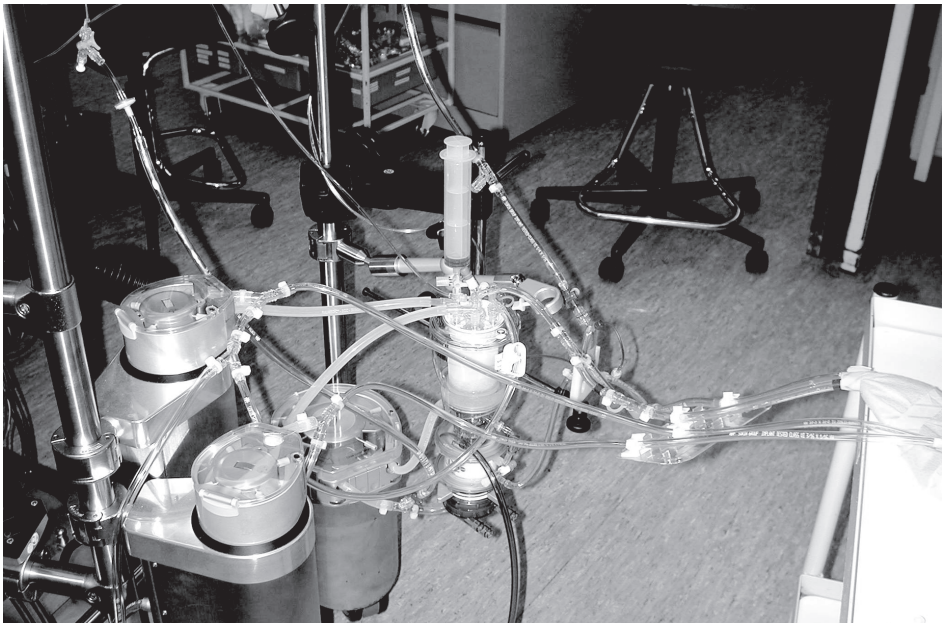

Figure 3. Miniaturized circuit with Sorin Kids 100 oxygenator.

In absence of an active pediatric predonation and EPO administration program in Erasmus University Medical Center, our institutional guideline concerning preoperative patient hematocrit emphasises the importance of limitation of all undesired hemodilution during direct preoperative period. Multidisciplinary efforts undertaken in our clinic to reduce homologous blood transfusion in patients with bodyweight less than 10 kg, already resulted in limitation of induction related hemodilution. Between year 1997 and 2005 the mean preoperative hematocrit of 38% (measured day before operation) was decreased during the induction of anesthesia to the value of 31%, yet between 2006 and 2008 induction only diminished hematocrit value from 39% to 35%. That consequently allowed less homologous blood transfusion during CPB [34].

New agreement on acceptable safe hematocrit during CPB, due to present availability of near infrared spectroscopy for measurements of regional tissue oxygenation (cerebral and systemic monitoring) together with on-line continuous measurement of mixed venous blood oxygen saturation, allows to establish target hematocrit value during CPB down to 24% .

To evaluate the prospective positive results of institutional guidelines on RBCs requirement in the CPB priming, we recalculated the new bypass conditions within the existing pediatric database from year 2008 and 2009. Our presumption was that bloodless prime would be more frequently achieved than the present 6% cases. Reduction of CPB circuit volume to 230 ml with an unchanged hematocrit target at 28% during CPB would only increase the frequency of bloodless prime to 10%. However, reduction of the CPB circuit volume together with a decreased hematocrit target at 24% would result in 31% of bloodless prime cases.

Certainly, bloodless prime is no guarantee for bloodless CPB or for bloodless open heart surgery. Still, it establishes a satisfactory onset for asanguineous pediatric cardiac surgery.

CONCLUSIONS

The reduction of CPB prime volume together with an adequate level of hemodilution during the bypass are simple and safe techniques to reduce allogeneic blood transfusion in neonatal and infant open heart surgery. Adherence to institutional guidelines and multidisciplinary efforts undertaken in the pre- and postoperative period are of a great importance concerning the bloodless CPB and should be seriously pursued by all involved caregivers.

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Chapter 7

Risk factors for low colloid osmotic pressure during infant cardiopulmonary bypass with colloidal prime

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Interact Cardiovasc Thorac Surg. 2009; 8: 512-6

ABSTRACT

Background: Extensive variations of colloid osmotic pressure (COP) measured in the priming as well as during infant cardiopulmonary bypass motivated us to audit a clinical and laboratory data to identify the risk factors for low COP at the end of bypass.

Methods: Data of 73 consecutive infant patients with body weight less than 10 kg, who underwent elective, first time open-heart surgery between March 2005 and December 2006 were examined. The following variables were analyzed: COP, blood loss, transfusion requirements and haematological data. Univariate and multivariate analysis of risk factors for low COP (< 15 mmHg) was performed.

Results: Forty-eight percent of patients had COP <15 mmHg at the end of bypass. Those patients had significantly lower COP before start of bypass, during and at the end of the operation. Significant univariate predictors of low COP at the end of bypass were; lower patient weight; lower COP before start of bypass, lower priming COP and larger volume of cardioplegia received into the circulation. After multivariable analysis lower patient COP before bypass remained the only significant predictor for low COP at the end of bypass.

Conclusions: Pre-bypass crystalloid dilution during induction should be avoided, as this is the most important cause of low COP during the bypass. Priming COP and COP management strategy should be adapted to the individual patient demand.

INTRODUCTION

Despite the latest minimization of extracorporeal circuit for infant cardiopulmonary bypass (CPB) and reduction of its priming volume, severe hemodilution with dilution of plasma proteins may occur. Decrease of plasma colloid osmotic pressure (COP) favours a fluid shift from the intravascular space into the interstitial space that consequently augments total body water and enhances the risk of multiple organ failure [1]. During the perioperative period, any estimation of the COP from the total plasma protein or albumin level would be altered by infusion therapy [2, 3, 4]. Therefore, the importance of direct measurement of COP during open heart surgery in children is widely acknowledged [5]. Still, the effects of colloidal or crystalloid priming solutions are predominantly studied in adult patients [6, 7] and remarkably few data address this issue in pediatric patients [8, 9]. In our institution, priming of infant CPB circuit constituted of different colloidal solutions and the COP values were routinely measured. Accordingly to the pediatric protocol, human albumin solution was administrated during the bypass to manage COP at appropriate level.

Extensive variations of COP values measured in the priming as well as during the infant CPB motivated us to audit all clinical and laboratory data. The primary objective was to recognize patients prone to low COP at the end of bypass. Secondarily, we validated the existing protocol to propose the future adjustments of infant priming composition and COP regulation during the bypass.

MATERIAL AND METHODS

An audit of clinical and laboratory data of consecutive infant patients with body weight (BW) less than 10 kg was conducted. All patients underwent elective, first time cardiac operation with CPB between March 2005 and December 2006. Patients with known clotting disorders (n = 0) and procedures that required deep hypothermic circulatory arrest (n = 6) were excluded from the study. Patients with COP measured at the end of CPB lower than 15 mmHg were appointed to Group Low COP, whereas all other patients were assigned to Group High COP. The same surgical, anaesthesia and perfusion team performed all the operations. Collection and audit of the data was performed in compliance with the Hospital Data Protection Policy.

Infant CPB, Anesthesia and Anticoagulatin

Infant CPB circuits consisted of a Capiox Baby Rx hollow-fiber oxygenator with hard-shell reservoir (Terumo, Tokyo, Japan), a roller pump and arterial filter. Tubing internal diameter was ¼ inch. The circuits were not coated. Circuit prime volume was 330 ml and

contained homologous red blood cells (RBCs), fresh-frozen plasma (FFP) and Gelofusine (B.Braun, Melsungen, Germany). The amount of RBCs in the priming was calculated to achieve a hematocrit of 0.28 L/L during CPB. The prime was always completed with 0.5 g/kg BW mannitol, 0.5 g/kg BW human albumin 20% solution (Sanquin, Amsterdam, The Netherlands), 4.2 IU heparine / mL priming volume and 2-5 ml $NaHCO_3$ 8.4%.

Administration of RBCs, FFP, crystalloids or colloids during CPB was based upon the system working volumes and target values for hematocrit (not lower than 0.28 L/L for acyanotic as well as cyanotic patients). Human albumin was added to maintain the COP ≥15 mmHg. In accordance with protocol no modified ultrafiltration and no antifibrinolitic medication was used.

All patients received standard general anesthesia. Activated clotting time was monitored during the bypass and maintained above 480 sec. Nonpulsatile CPB, with mild hypothermia of 28 °C to 32° C, was performed with blood flow rates between 1.8 L/min/m^2 to 3.2 L/min/m^2 to maintain venous oxygen saturation above 70% and mean arterial pressure between 40 to 60 mmHg. During CPB α – stat regulation was used. Myocardial protection was achieved with crystalloid cardioplegia. Cardioplegic solution was preferably sucked into the cell-saving device (CS). Perioperative blood loss was collected and processed by CS device, together with residual volume of the CPB circuit. After the CPB, acyanotic as well as cyanotic patients received RBCs transfusion to maintain hematocrit above 0.30 L/L and the CS product was always considered first line blood replacement therapy. Transfusion of FFP was administrated in case of enhanced blood loss and prothrombin time ratio >1.5). Platelet concentrate was administrated if the platelet count at the end of CPB was less than 100 x 10^9/L.

Data collection

Hematocrit (Hct), platelet count (Plt) and fibrinogen concentration (Fib) were measured one day before the operation, at the start and end of the operation, during the CPB after 5 min on bypass and at the end, postoperatively at the 6 and at 24 hours.

COP measurements were taken from the CPB circuit before start of bypass, after the 5 min on bypass and at the end of the CPB. Additionally, patient's COP was measured at the start and at the end of the operation. Plasma COP was determined by the commercially available membrane osmometer Osmomat 050 (Gonotec, Berlin, Germany) using a membrane with molecular mass cut-off at 20 kDa.

Blood loss, urine production and volume of perioperatively transfused blood products were recorded.

Data analysis

Continuous data are presented as a mean ± standard deviation (SD); categorical data - as proportions. Continuous independent data were compared with unpaired t test and one-

way analysis of variance ANOVA (in case of normally distributed data) or Mann – Whitney test (in case of non-normally distributed data). Repeated measures of continuous variables were compared using repeated measures ANOVA. Categorical data were compared with the chi-square test. The Cox proportional hazards regression analysis (uni- and multivariate) was used to evaluate variables as predictors for low COP at the end of bypass. All tests were two-sided and a p value less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 13.0 statistical software (SPSS, Chicago, IL).

RESULTS

Data from a 73 infants were evaluated in the study. Patient characteristics and CPB data are presented in Table 1. There were no postoperative re-explorations and all patients survived.

Table 1. Population and CPB data.

Variable	All patients (n = 73)	Group Low COP (n = 35)	Group High COP (n = 38)	
	Mean ± SD Range	Mean ± SD Range	Mean ± SD Range	p
Male (%)	57	57	58	0.25
Age (months)	4.9 ± 4.6 (0.03 – 23.0)	4.1 ± 4.4 (0.03 –20.6)	5.6 ± 4.8 (0.2 – 23.0)	0.90
Weight (kg)	5.5 ±1.8 (2.5 – 9.5)	4.9 ± 1.7 (2.5 – 9)	6.0 ± 1.8 (3 – 9.5)	0.10
CPB time (min)	96 ± 42 (34 – 224)	99 ± 42 (34 – 176)	94 ± 43 (39 – 224)	0.42
Cross-clamp time (min)	52 ± 33 (0 – 156)	58 ± 30 (0 – 126)	47 ± 34 (0 – 156)	0.14
Lowest temperature (°C)				
Nasopharyngeal	28,2	28,2	28,4	
Rectal	28,7	28,7	28,8	
ICU time (hours)	25 ± 11 (6 – 92)	25 ± 13 (6 – 92)	25 ± 9 (18 – 64)	0.67
Cyanotic anomaly (%)	52	46	58	0.31
ASD – closure (n)	2	0	2	
VSD – closure (n)	6	1	5	
AVSD – correction (n)	21	14	7	
F4 – correction (n)	12	6	6	
TGA – switch (n)	7	6	1	
Other (n)	25	8	17	

ASD - atrial septal defect; AVSD - atrioventriculair septal defect; CPB - cardiopulmonary bypass; F4 - tetralogy of Fallot; ICU - Intensive Care Unit; SD - standard deviation; TGA - transposition great arteries; VSD- ventricular septal defect

Thirty-five patients had COP lower than 15 mmHg at the end of CPB and were therefore assigned to Group Low COP. Group Low COP had significantly lower value of COP before the bypass, during the CPB and at the end of the operation. Additionally, value of the priming COP in this group was also significantly lower than in Group High COP (Table 2).

Absolute amount of priming used in both groups was not significantly different, Group Low COP: 349 ± 15 ml versus Group High COP: 342 ± 16 ml, p=0,09.The relative amount

Table 2. COP changes during operation.

COP (mmHg)	All patients (n = 73)	Group Low COP (n = 35)	Group High COP (n = 38)	P value
	Mean ± SD Range	Mean ± SD Range	Mean ± SD Range	
Priming	23 ± 5 (15 – 36)	22 ± 4 (15 – 29)	24 ± 6 (15 – 36)	0.027
Before CPB	16 ± 3 (10 – 22)	15 ± 2 (10 – 19)	18 ± 3 (13 – 22)	<0.001
CPB start	17 ± 3 (11 – 23)	15 ± 2 (11 – 19)	18 ± 3 (12 – 23)	<0.001
CPB end	16 ± 3 (12 – 23)	14 ± 1 (12 –15)	18 ± 2 (16 – 23)	<0.001
End operation	16 ± 2 (12 – 23)	15 ± 2 (12 – 19)	17 ± 2 (14 – 23)	<0.001

COP - colloid osmotic pressure; CPB - cardiopulmonary bypass; SD - standard deviation

Table 3. Priming components and fluids addition during cardiopulmonary bypass.

	All patients n =73	Group Low COP n = 35	Group High COP n = 38	
(ml/kg BW)	Mean ± SD Range	Mean ± SD Range	Mean ± SD Range	P value
Priming volume	69 ± 21 (36 – 139)	79 ± 25 (39 – 139)	63 ± 21 (36 – 110)	0.006
RBCs	29 ± 16 (0 – 69)	34 ± 15 (0 – 63)	25 ± 15 (6 – 69)	0.013
FFP	19 ± 11 (7 – 80)	21 ± 13 (7 – 80)	17 ± 8 (7 – 36)	0.13
Gelofusine	16 ± 6 (5 – 33)	17± 6 (6 – 32)	16 ± 6 (5 – 33)	0.33
Albumin 20%	2.7 ± 0.4 (2 – 4)	2.8 ± 0.5 (2 – 4)	2.6 ± 0.3 (2 – 3)	0.13
Mannitol 20%	2.8 ± 0.3 (2 – 4)	2.7 ± 0.4 (2 – 3)	2.8 ± 0.5 (2 – 4)	0.21
CPB				
RBCs	13 ± 10 (0 – 52)	14 ± 10 (0 – 52)	13 ± 10 (0 – 43)	0.58
FFP	8 ± 7 (0 – 29)	8 ± 8 (0 – 29)	8 ± 6 (0 – 19)	0.95
Gelofusine	6 ± 8 (0 – 37)	5 ± 5 (0 – 37)	8 ± 9 (0 – 18)	0.09
Albumin 20%	1.0 ± 2 (0 – 8)	1.5 ± 1.8 (0 – 8)	0.6 ± 1.3 (0 – 6)	0.03
CP in circulation	12 ± 10 (0 – 39)	14 ± 10 (0 –32)	9 ± 10 (0 – 39)	0.06

CP - cardioplegia; CPB - cardiopulmonary bypass; FFP - fresh frozen plasma; RBCs - red blood cells concentrate

(ml/kg BW) of priming components and fluids added into the circulation during CPB are presented in Table 3. Group Low COP received significantly more priming volume per kg BW than Group High COP. Volume of human albumin used during the bypass in Group Low COP was also significantly bigger than in Group High COP.

Figure 1 presents total blood loss and transfusion requirements after termination of CPB. Group Low COP received after the cessation of bypass significantly more FFP transfusion then Group High COP (33 ±18 ml/kg BW versus 24 ± 15 ml/kg BW, p= 0.03).

Urine output after CPB till 24 hours postoperatively was not significantly different between the groups (Group Low COP: 7 ml/kg BW/h versus Group High COP: 6 ml/kg BW/h, p=0.08).

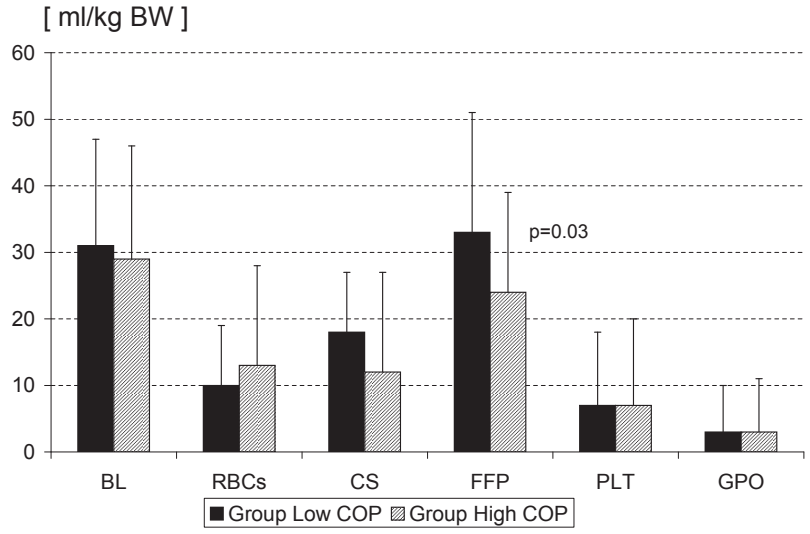

Figure 1. Blood loss and transfusion after cardiopulmonary bypass.
BL - blood loss; COP – colloid osmotic pressure; CS - cell saving product; FFP – fresh frozen plasma; GPO – pasteurised plasma protein solution; PLT – platelet concentrate; RBCs – red blood cells

Figures 2, 3 and 4 display the time course of hematocrit, platelet count and fibrinogen concentration.

Significant univariate predictors of the COP value lower than 15 mmHg at the end of bypass were patient weight and COP before start of CPB, priming COP, volume of human albumin added into the circulation during CPB and volume of cardioplegia received into the circulation during CPB. After multivariate analysis patient COP before CPB remained the only significant predictor of lower COP at the end of CPB (Table 4).

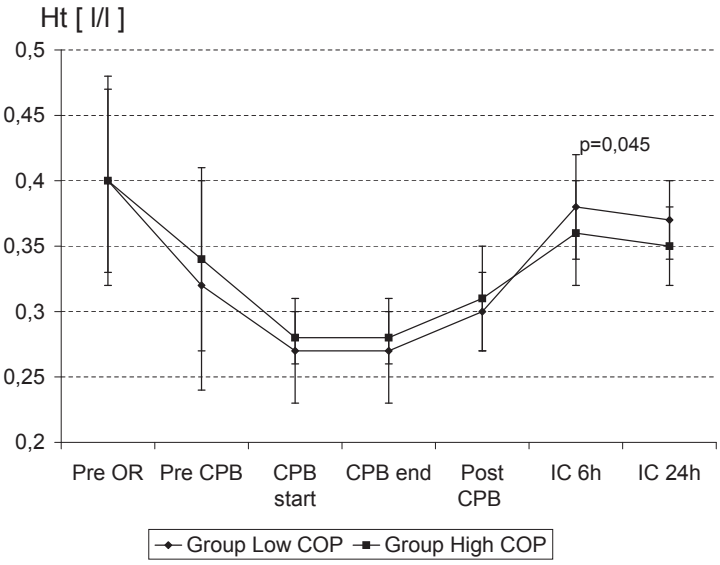

Figure 2. Perioperative values of hematocrit.
CPB – cardiopulmonary bypass; COP – colloid osmotic pressure; IC 4h and IC 6h – Intensive Care unit at 4 and 6 hours; Post CBP – at the end of the operation; Pre CBP – start of the operation; Pre OR – 1day before operation.

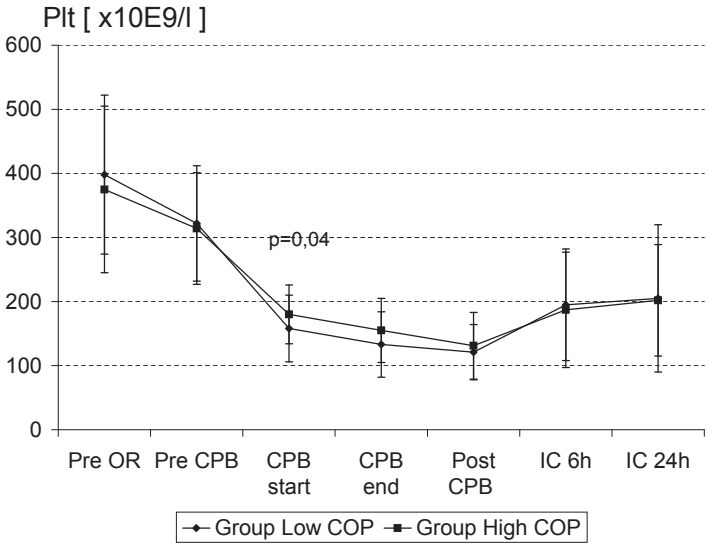

Figure 3. Perioperative values of platelet concentration.
CPB – cardiopulmonary bypass; COP – colloid osmotic pressure; IC 4h and IC 6h – Intensive Care unit at 4 and 6 hours; Post CBP – at the end of the operation; Pre CBP – start of the operation; Pre OR – 1day before operation.

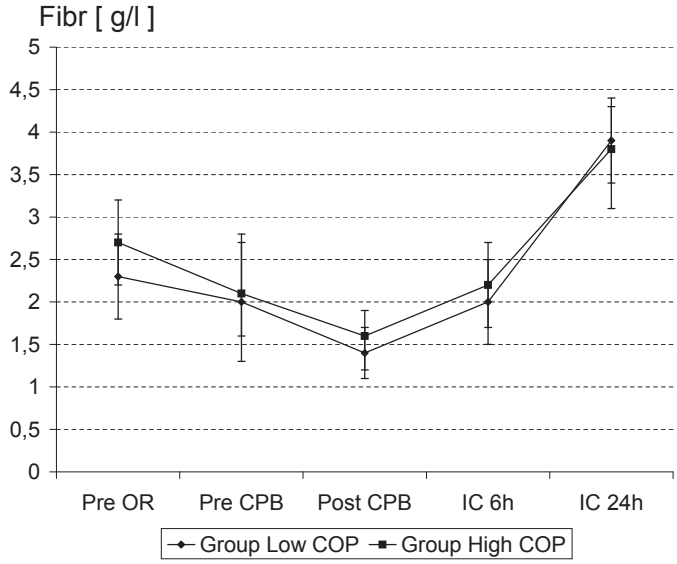

Figure 4. Perioperative values of fibrinogen concentration.
CPB – cardiopulmonary bypass; COP – colloid osmotic pressure; IC 4h and IC 6h – Intensive Care unit at 4 and 6 hours; Post CBP – at the end of the operation; Pre CBP – start of the operation; Pre OR – 1day before operation.

Table 4. Risk factors for COP lower than 15 mmHg at the end of CPB.

Risk factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (months)	0.92 (0.84-1.04)	0.19	1.16 (0.93-1.44)	0.19
Weight (kg)	0.70 (0.53-0.93)	0.014	0.77 (0.42-1.42)	0.41
Gender (male)	0.66 (0.26-1.67)	0.36		
Cyanotic disease	0.61 (0.24-1.55)	0.30		
CPB time	1.00 (0.99-1.01)	0.58		
COP patient before CPB (mmHg)	0.68 (0.54-0.84)	0.001	0.71 (0.53-0.95)	0.02
COP priming (mmHg)	0.89 (0.79-0.99)	0.04	0.90 (0.76-1.05)	0.18
Albumin 20% (ml/kg)	1.48 (1.03-2.12)	0.04	0.96 (0.61-1.59)	0.95
FFP (ml/kg)	1.00 (0.94-1.07)	0.95		
Gelofusine (ml/kg)	0.95 (0.88-1.01)	0.11	0.94 (0.86-1.02)	0.12
Cardioplegia (ml/kg)	1.05 (1.00-1.11)	0.05	1.06 (0.99-1.13)	0.12

CI – confidence interval; COP- colloid osmotic pressure; CPB – cardiopulmonary bypass; FFP – fresh frozen plasma; OR – odds ratio

DISCUSSION

Our results show that despite colloidal prime and volume replacement therapy, guided by COP measurements, the desired level of COP was not always achieved at the end of bypass. The significant risk factor for low COP at the end of bypass was low level of patient's COP measured before the start of CPB.

Although the impact of the priming components and priming volume can have significant effect on neonates and infants, there is no consensus about the choice of the priming solution and intravascular volume replacement regime as well as the optimal level of COP.

Meta-analysis of control adult trials by Russell at al [7] concluded that albumin prime favourably influenced COP, on-bypass positive fluid balance, postoperative weight gain, and colloid usage, than crystalloid priming. Eising et al. established that hyperoncotic CPB prime (COP = 48 mmHg) prevented long water accumulation in the early post-pump period, while pulmonary function was unchanged [6]. Haneda et al. advocated addition of colloids to the prime in the pediatric patients [5]. Their retrospective study suggested that maintaining COP during CPB around 19 mmHg by using colloid hemodilution prime reduced significantly fluid balance at the end of CPB compared to crystalloid hemodilution. More recent study of Aukerman et al [11] provided information that albumin in the prime resulted in less weight gain in children after bypass. Riegger et al [8] presented the same conclusions concerning weight gain after pediatric CPB, but they associated albumin prime with an increase transfusion rate (RBCs). The optimal COP level during bypass remains equivocal. An animal model suggested that COP of 16 mmHg is optimal [10]. Ekblad et al [12] also concluded in their study that infants with a COP of umbilical cord plasma greater than 16 mmHg are unlikely to develop respiratory distress syndrome.

In our institution, COP target value during bypass was agreed at 15 mmHg based upon the results from the literature studies [13]. Still, forty-eight percent of patients from the study population had at the end of bypass COP of 14 ± 1 mmHg. Those patients had already before the start of bypass significantly lower COP than the others (15 ± 2 mmHg versus 18 ± 3 mmHg, $p<0.001$), presumptively due to the crystalloid infusion during induction. Since that was the only significant risk factor for low COP at the end of bypass (multivariate analysis OR=0.71, $p= 0.02$) it is advisable to replace the crystalloids by colloidal solutions to avoid this unwanted dilution effect. All patients received colloidal prime, but prime COP in Group Low COP was significantly lower than in Group High COP (22 ± 4 mmHg versus 24 ± 6 mmHg, $p=0.027$). Prime components were routinely calculated to target required hematocrit, with no specific regard to the achieved level of COP. In consequence, our colloidal priming was not able to counterbalance for patient's low COP before the bypass. During the CPB Group Low COP received significantly more

human albumin than the other group (Table 3). Even so, the COP level in this group significantly dropped at the end of bypass (from 15 ± 2 mmHg to 14 ± 1 mmHg, p=0.04). Transfusion of albumin solution during CPB to increase COP level was not effective (multivariate analysis OR=0.96, p=0.95) and therefore the COP management strategy during the bypass should be reconsidered. On the other hand, the amount of cardioplegic solution returned to the circulation during the bypass showed tendency for association with low COP level (OR=1.06, p=0.12) and should be avoided.

Clinical relevance of low COP during the bypass was less evident, as both groups showed no significant differences in postoperative blood loss, urine production and length of stay in the ICU. Postoperative transfusion requirements with exception of FFP were also not significantly different. Group Low COP received in postoperative period significantly more FFP than Group High COP (33 ± 18 ml/kg BW versus 24 ± 15 ml/kg BW, p=0.03), which could be related to the extravasation of fluids caused by low levels of COP.

Study limitations

The main limitation of this single center study was the retrospective character and the lack of definite study endpoints related to changes of COP. A prospective randomized study with clinical endpoints as; body weight gain, perioperative plasma albumin concentration and fluid balance, is scheduled to evaluate new composition of colloid prime and volume replacement therapy during CPB to achieve COP not lower than 18 mmHg at the end of bypass.

CONCLUSIONS AND RECOMMENDATIONS

Results of our study demonstrated that it is advisable to evaluate the customary protocol and identified existing risk factors in regard to protocol adjustments. Pre-bypass crystalloid dilution during induction should be avoided as well as return of the crystalloid cardioplegic solution into the circulation. Priming COP and COP management strategy during bypass should be tailored to individual patient demand.

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Chapter 8

Relevance of colloid oncotic pressure regulation during neonatal and infant cardiopulmonary bypass: a prospective randomised study

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ABSTRACT

Background: In neonatal and infant cardiac surgery with cardiopulmonary bypass (CPB) hemodilution with reduction of plasma albumin concentration and low colloid oncotic pressure (COP) are the main factors associated with tissue edema and postoperative weight gain. The aim of our study was to evaluate the influence of two different COP regulatory strategies on post bypass body weight gain, fluid balance and clinical outcomes.

Methods: Seventy elective patients with body weight < 10 kg underwent first time cardiac surgery with CPB and were randomized into two groups. The standard COP group received a 0.5 g/kg of human albumin in the priming and during CPB albumin was added to maintain the COP >15 mmHg. In the high COP group albumin concentration in the priming was 5% and during CPB the COP was maintained above 18 mmHg. All patients were monitored before, during and until 24 hours postoperatively. Data were collected on: body weight gain, colloid oncotic pressure, albumin concentration, fluids transfusion, blood loss, urine production and laboratory results.

Results: Patient's demographics and operative data were comparable. Although the high COP group had perioperatively significantly higher COP and albumin concentration than the standard COP group, no significant difference was found in the body weight gain. There were also no significant differences between the groups in fluid balance, urine output and blood loss. However, the high COP group had significantly shorter postoperative duration of mechanical ventilation (10 h versus 14 h, $p = 0.02$) and lower plasma lactate concentration post operation (1.1 mmol/l versus 1.4 mmol/l, $p = 0.046$).

Conclusions: The COP regulatory strategy for neonatal and infant CPB, based upon the 5% concentration of albumin in the priming and a COP target at 18 mmHg during the bypass, better preserves the plasma albumin concentration within the physiological range and stabilizes the colloid pressure than the standard strategy (0.5 g/kg albumin in the priming, bypass COP target at 15 mmHg). Nevertheless, only the lower postoperative plasma lactate concentration and the shorter duration of mechanical ventilation in the high COP group pointed at the potential clinical benefit of this new strategy.

INTRODUCTION

Colloid oncotic pressure (COP) and hydrostatic pressure are the primary forces that control the exchange between the aqueous plasma solutions and the interstitial fluids. Proteins concentration in plasma generates a pressure that draws water out of the interstitium into the plasma, and is known as the COP. The capillary wall acts in this process as a filtration barrier.

Under physiological conditions, fluid gain and loss from the plasma are closely balanced and there is little or no change in plasma and interstitial fluid volumes [1].

Although albumin in plasma comprises only 50-60% of the total protein content it generates about 80% of intravascular COP. The albumin concentration in plasma in healthy humans ranges between 33 and 52 g/l and there is a steady state between its synthesis and metabolism. The COP in healthy adult subjects is about 25 mmHg [1,2]. There have been controversies about the normal COP range in newborns and infants [3], but the study results from Sussmane and co-workers [4] showed that in healthy male and female infants (n=37) the 95% confidence interval for COP was between 24.3 to 26.0 mmHg.

Open heart surgery with cardiopulmonary bypass (CPB) disturbs the balance between the regulatory forces of plasma – interstitial fluid exchange. Especially in neonatal and infant patients this results in tissue edema and weight gain [5] directly after the CPB. Inflammatory response to CPB [6], hypothermia [7] and hemodilution with reduction of plasma albumin concentration [8] are the main contributing factors in this regard.

In our institution, priming of neonatal and infant CPB circuit constitutes of different colloidal solutions with addition of hyperoncotic 20% human albumin (HA) to regulate COP at an appropriate level. Extensive variations of COP values measured in the priming as well as during the CPB motivated us to audit all clinical and laboratory data. Results of our previous study [9] demonstrated that pre-bypass crystalloid dilution during induction as well as return of the crystalloid cardioplegic solution into the circulation were associated with lower level of COP at the end of CPB. On the other hand, the existing COP regulatory strategy was not adequate to compensate for this unwanted hemodilution. In present study, we examined in a randomized fashion the impact of "up regulation" of COP in the priming and during the CPB on postoperative weight gain, fluid balance and clinical outcomes.

MATERIAL AND METHODS

Study design

Between April 2008 and December 2009, with approval from the institutional Medical Ethics Committee (MEC-2008-037) and written parental consent, 70 elective patients with body weight less than 10 kg who underwent first time cardiac surgery with CPB entered the study. Exclusion criteria were: prematurity, preoperatively recognized metabolic disorders leading to hypo- or hyperalbuminemia and procedures with deep hypothermic circulatory arrest. Patients were randomly allocated (block randomization per 10) into two groups: standard COP and high COP group. Each patient in the standard COP group received a 0.5 g/kg body weight of HA in the priming and during the CPB supplementary albumin was added to maintain the COP >15 mmHg. In the high COP group volume of HA was calculated to achieve 5% albumin concentration in the priming solution and during the CPB additional albumin was used to preserve the COP > 18 mmHg. The same surgical team performed all the operations. Surgeons, anaesthesiologists and all personnel at the Intensive Care Unit (ICU) except the perfusionist were blinded to the study group. Study abortion criteria were allergic reaction to HA or postoperative hemodynamic instability. The following variables were primarily investigated: (1) relative and absolute body weight gain directly after CPB, (2) COP value at the end of CPB and (3) plasma albumin concentration at the end of operation. Patients were weighted immediately before CPB and at the end of surgery using Sartorius QS 16 digital scale (DWS, Elk Grove, IL). COP measurements were taken from the CPB priming, before the start of CPB, at 5 min on bypass, at the end of CPB and at the end of operation. All measurements were performed by Osmomat 050 (Gonotec, Berlin, Germany) with a 20 kDa membrane. Additionally we studied (1) postoperative plasma albumin (Alb) level, (2) postoperative fluid balance and (3) mechanical ventilation support duration. Blood analysis included hematocrit (Hct), platelet count (Plt) and lactate concentration (Lac). Laboratory data were obtained starting one day before operation until 24 hours after surgery. Blood loss and urine production were recorded as well as the volume of crystalloids, colloids and blood products transfused in the OR and at the ICU.

CPB, Anesthesia and Anticoagulation

Infant CPB circuits consisted of a Capiox Baby Rx hollow-fiber oxygenator with hard-shell reservoir (Terumo, Tokyo, Japan), a roller pump and arterial filter. Tubing internal diameter was ¼ inch. The circuits were phosphorylcholine (Phisio) coated (Sorin Group, Mirandola, Italy). Priming volume was 300 ml and contained homologous red blood cells (RBCs), fresh-frozen plasma (FFP) and Gelofusine (B.Braun, Melsungen, Germany). The amount of RBCs in the priming was calculated to achieve a hematocrit of 28% during CPB. The prime was always completed with an amount of HA determined by the group

assignment, 0.5 g/kg BW mannitol, 4.2 IU heparine / mL priming volume and 2-5 ml $NaHCO_3$ 8.4%. All patients received standard general anesthesia as previously reported [10]. Activated clotting time was monitored during the bypass and preserved above 480 sec. Nonpulsatile CPB, with mild hypothermia of 28 °C to 32 °C, was performed with blood flow rates between 1.8 L/min/m^2 to 3.2 L/min/m^2 to maintain venous oxygen saturation above 70% and mean arterial pressure between 40 to 60 mmHg. During CPB α – stat regulation was used. Myocardial protection was achieved with crystalloid cardioplegia. Cardioplegic solution was preferably aspired into the cell-saving device (CS). Perioperative blood loss was collected and processed by CS device, together with residual volume of the CPB circuit. Administration of RBCs, FFP, crystalloids or colloids during CPB was based upon the system working volumes, target values for hematocrit and COP. For patients with acyanotic as well as cyanotic diseases required hematocrit on bypass was not lower than 28%. In accordance with our institutional protocol no modified ultrafiltration and no antifibrinolitic medication was used. After the CPB, all fluids transfusion inclusive RBCs, CS product, FFP and platelet concentrate was based upon patient's clinical status and laboratory results.

Data analysis

One of the primary interests of this study was a comparison of patient weight gain after the CPB with standard COP or with high COP during the bypass. A total sample size of 64 patients was capable of detecting a difference in body weight gain of 100 g, with 80% power using a cut-off for statistical significance of 0.05, assuming a standard deviation of 140 g (data from the pilot). Continuous data are presented as a mean ± standard deviation (SD); categorical data are presented as proportions. Continuous independent data were compared with unpaired t test (in case of normally distributed data) or Mann – Whitney test (in case of non-normally distributed data). Categorical data were compared with the chi-square test. Repeated measures of continuous variables were compared using paired t-test. All tests were two-sided and a p value less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 15.0 statistical software (SPSS, Chicago, IL).

RESULTS

Population and CPB data

A total number of 69 patients completed the study. All patients survived. One patient with delayed sternum closure (1 day after operation) survived but was excluded from postoperative follow-up with regard to our study. There were no patients excluded due to preoperative metabolic disorders and allergic reactions to HA. Demographics and

intraoperative data were comparable between the groups. Preoperative patient characteristics, CPB time, aorta cross-clamp time and lowest temperature on CPB are presented in Table 1.

Table 1. Population and CPB data.

	Standard COP	High COP	
Variable	N = 35	N = 34	P value
	Mean ± SD	Mean ± SD	
Gender (female/male)	10/25	13/21	0.29
Age (months)	5.3 ± 3.8	5.0 ± 4.1	0.75
Weight (kg)	6.3 ± 1.7	5.9 ± 2.1	0.44
BSA (m2)	0.35 ± 0.06	0.33 ± 0.08	0.37
CPB time (min)	88 ± 42	89 ± 36	0.88
Cross-clamp (min)	58 ± 37	59 ± 30	0.93
Lowest temp. on CPB (C°)	29.1 ± 2.5	28.6 ± 3.7	0.65
Anomaly - correction			
ASD - closure	1	2	
VSD - closure	5	4	
ASD + VSD - closure	8	6	
AVSD - correction	6	3	
F4 - correction	8	9	
TGA – Arterial Switch	1	4	
TAPVR - correction	2	3	
UVH - PCPC	1	1	
Other	3	2	

ASD - atrial septal defec; AVSD – atrioventriculair septal defect; BSA - body surface area; CPB- cardiopulmonary bypass; F4 – tetralogy of Fallot; PCPC – partial cavopulmonary connection; SD - standard deviation; TAPVR – total anomalous pulmonary venous return; TGA – transposition great arteries; UVH – univentricular heart; VSD – ventricular septal defect

Study variables and additional clinical data

Table 2 shows for both groups the total priming volume together with specification of all components and additional fluids transfusion during and post - CPB. The total priming volume was not significantly different between the groups. In compliance with the study design in the high COP group significantly larger volume of HA was used and that resulted in the significantly smaller volume of FFP and Gelofusine. In each group the ratio between FFP and Gelofusine was not significantly different (p= 0.89). The achieved albumin concentration in the priming in the high COP group was significantly higher than in the standard COP group (4.7 ± 0.4% versus 3.1 ± 0.3% respectively, $p < 0.001$). To maintain the COP during CPB significantly more HA was added to the circulating volume during the bypass in the high COP group. After the CPB there was a significantly smaller

Table 2. Priming composition, fluid transfusion on CPB and until 24 hours post CPB.

	Standard COP	High COP	
Variable (ml)	N = 35	N = 34	P value
	Mean ± SD	Mean ± SD	
Total priming volume	299 ± 14	301 ± 15	0.62
RBCs	111 ± 47	120 ± 45	0.45
FFP	77 ± 26	64 ± 27	0.04
Gelofusine	75 ± 19	61 ± 20	0.005
HA	17 ± 4	37 ± 4	<0.001
Mannitol	17 ± 5	15 ± 5	0.28
Total volume during CPB	172 ± 41	154 ± 42	0.04
RBCs	59 ± 42	61 ± 44	0.64
FFP	30 ± 31	25 ± 26	0.51
Gelofusine	37 ± 40	22 ± 26	0.05
HA	1 ± 4	5 ± 8	0.01
Cardioplegia	42 ± 44	40 ± 36	0.88
Total volume during 24 h post CPB	347 ± 66	365 ± 75	0.47
RBCs + CS	115 ± 48	123 ± 65	0.57
FFP	152 ± 66	181 ± 96	0.18
GPO	65 ± 77	32 ± 41	0.05
Platelets concentrate	16 ± 39	33 ± 51	0.17

CPB – cardiopulmonary bypass; CS – cell saving product; FFP – fresh frozen plasma; GPO – pasteurised plasma protein solution; HA – 20% human albumin solution; ICS – intraoperative cell-salvage; RBCs - red blood cells concentrate; SD – standard deviation

volume of pasteurised plasma protein solution (GPO) used in the high COP group, but no significant difference between the groups in total transfuse volume was noted.

Before CPB, patients in the both groups had not significantly different plasma albumin concentration and COP (Fig.1 and Fig.2). Mean priming COP in high COP group was significantly higher (31.7 mmHg) than in the standard COP group (25.2 mmHg, $p = 0.0001$) and during the CPB this significant difference in the COP level was sustained. The high COP group maintained albumin concentration within the physiological range during the whole study period.

Table 3 presents the study variables. At the end of the operation, patient body weight increased significantly ($p<0.001$) within the both groups compared to the preoperative measurement. On the other hand, relative and absolute body weight gain was not significantly different between the groups. However, the high COP group had a significantly higher COP at the end of bypass as well as a higher albumin concentration at the end of operation comparing to the standard COP group. In addition, duration of mechanical ventilation was significantly shorter in the high COP group than in the standard COP group.

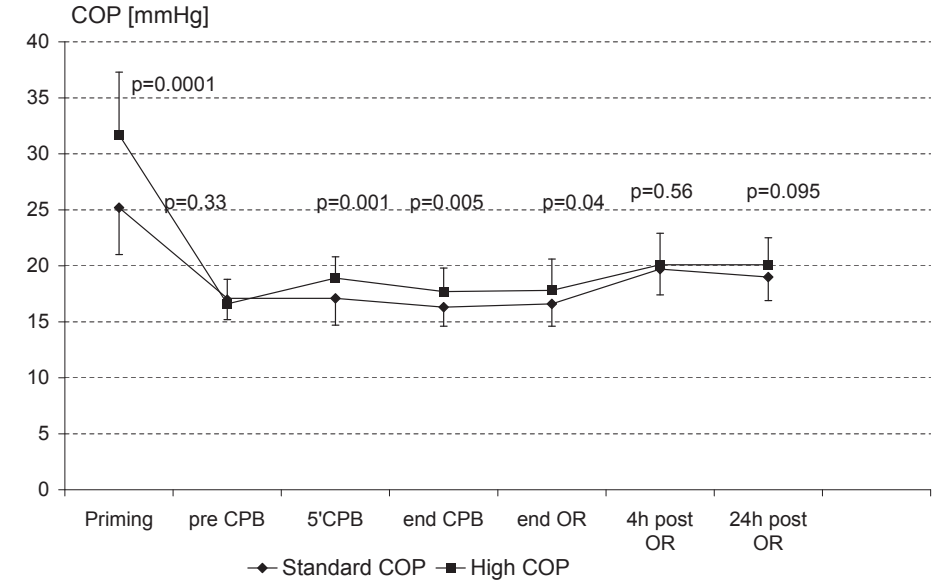

Figure 1. Colloid osmotic pressure during the study period.
CPB – cardiopulmonary bypass; OR – operation

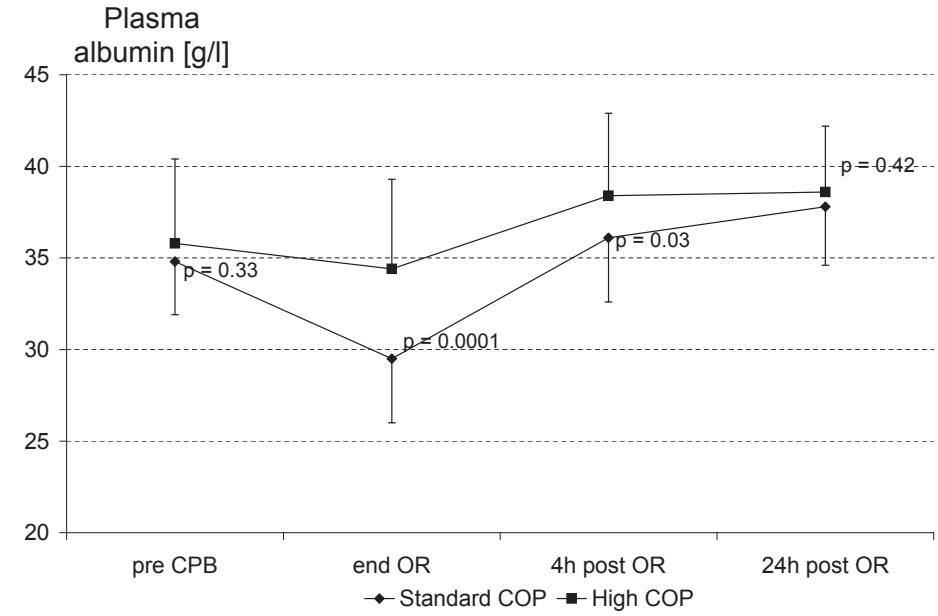

Figure 2. Plasma albumin concentration during the study period.
CPB – cardiopulmonary bypass; OR – operation

Table 4 shows a supplementary clinical data. From all collected data the platelets count at 24 hours post operation and plasma lactate concentration at the end of operation showed significant differences between the groups, with clinically better results in the high COP group.

Table 3. Primary and secondary study variables.

	Standard COP	High COP	
Variable	N = 35	N = 34	P value
	Mean ± SD	Mean ± SD	
Relative weight gain (%)	5.2 ± 4	5.3 ± 4	0.67
Absolute weight gain (g)	310 ± 243	285 ± 179	0.66
COP end CPB (mmHg)	16 ± 2	18 ± 2	0.005
Albumin end OR (g/l)	29 ± 5	34 ± 3	0.0001
Albumin 4 h post OR (g/l)	36 ± 5	38 ± 4	0.026
Albumin 24 h. post OR (g/l)	38 ± 4	39 ± 3	0.42
Fluid balance end OR (ml)	424 ± 68	449 ± 79	0.79
Fluid balance 24 h (ml)	- |110 ± 115|	- |98 ± 95|	0.83
Mechanical ventilation (h)	14 ± 7	10 ± 5	0.02

COP – colloid osmotic pressure; CPB – cardiopulmonary bypass; OR – operation;
SD- standard deviation

Table 4. Supplementary clinical results.

	Standard COP	High COP	
Variable	N = 35	N = 34	P value
	Mean ± SD	Mean ± SD	
Blood loss end OR (ml)	113 ± 110	122 ± 128	0.45
Blood loss 24 h (ml)	72 ± 38	87 ± 72	0.77
Urine output end OR (ml)	120 ± 101	79 ± 77	0.07
Urine output 24 h (ml)	366 ±190	355 ± 201	0.57
Hct pre CPB (%)	33 ± 4	33 ± 6	0.75
Hct end OR	29 ± 3	29 ± 3	0.78
Hct 24 h	34 ± 3	35 ± 5	0.32
Plt pre CPB (x 10E9/l)	298 ± 73	322 ± 83	0.21
Plt end OR	121 ± 35	139 ± 57	0.11
Plt 24 h post CPB	182 ± 55	220 ± 63	0.01
Lac pre CPB (mmol/l)	0.8 ±0.07	0.9 ± 0.05	0.86
Lac end OR	1.4 ± 0.1	1.1 ± 0.1	0.046
Lac 24 h	1.9 ± 0.3	1.7 ± 0.5	0.38

CPB – cardiopulmonary bypass; Hct – hematocrit; Lac – plasma lactate concentration; OR – operation; Plt – platelets count; SD- standard deviation

DISCUSSION

The relevance of COP during hypothermic CPB is since long documented and studied [12, 13]. Furthermore, the influence of different priming solutions, with associated COP, on perioperative fluid balance was also previously examined [14, 15]. Our study results confirm that the increased oncotic pressure during the CPB, based upon the 5% human albumin concentration in the priming and the COP target value above 18 mmHg during the bypass, maintained the albumin concentration within the physiological limits in the direct postoperative period. On the contrary, the priming albumin concentration of 0.5 g/kg body weight and the COP target of 15 mmHg during the bypass resulted in a low postoperative albumin concentration, well under the lowest physiological limit, and the low postoperative COP level. Although there was no significant difference in patients body weight gain after the bypass between the both study groups, the high COP group had significantly lower level of plasma lactate concentration at the end of operation, shorter duration of mechanical ventilation and higher platelets count 24 h after CPB.

Clinical [15, 17] and animal [16] studies have previously shown that increased oncotic prime pressure (albumin or hydroxyethyl starch priming solutions) prevents water accumulation and body weight gain after CPB [17]. Latest miniaturization of neonatal and infant CPB circuit together with introduction of modified ultrafiltration subsequently ameliorated deleterious effects of extreme hemodilution and systemic inflammatory response [13]. Still there is no consensus about the optimal priming solution for neonatal and infant CPB. Riegger and collaborators studied the effects of crystalloid prime solution versus albumin prime in young children and concluded that albumin may attenuate the extravasation of fluid out of the vascular space, but it may be associated with an increased transfusion rate [14]. Additionally, the recent studies of Tassani and co-workers did not support the hypothesis of capillary leak and increased escape rate of albumin triggered by the inflammatory response after CPB in newborns [6] and adult patients [18], but they concluded that fluids shift might be a consequence of hypo-oncotic hemodilution by crystalloid priming and use of crystalloid cardioplegic solutions. This led us to study the clinical relevance of higher oncotic pressure and plasma albumin concentration during neonate and infant CPB (up regulation) comparing to the existing regulatory strategy.

In our previous studies, we recognized that general anesthesia lowers plasma colloid pressure in infant patients [9]. The animal studies of Dismukes and associates concluded that in healthy dogs general anesthesia may decrease COP by 5 mmHg on average and that this decrease may not be predicted by the volume of administrated fluids or by the measuring of total plasma protein concentration [19]. Additionally, Solo and Gregory reported in 60 pre-term, sick infants significantly lower COP of 12.5 ± 2.5 mmHg compared to the mean COP of healthy full-term 99 infants (19.4 ± 2.2 mmHg, $p < 0.001$)

[20]. Therefore, we hypothesised that higher COP in the priming could compensate for this initial COP drop at the start of CPB and the priming albumin concentration at 5% would maintain plasma albumin within the physiological range. Those circumstances should decrease extravasation of fluids during the CPB and reduce the body weight gain directly after CPB. With utilization of our new protocol, we achieved a stable, high level of COP during CPB (average 18 mmHg) and plasma albumin concentration at the end of operation of on average 34 g/l. Nevertheless, there was no significant difference in the body weight gain after the CPB between the study groups. On the other hand, within the groups we recorded significant relative body weight gain of 5% after the CPB. That compares to the study results of Loeffelbein and co-workers [21]. In their data, relative body weight gain in the HA group (albumin priming with mean COP value of 27.9 mmHg) was 2% and the FFP group (no- albumin priming with mean COP value of 5.8 mmHg) gained 8% of body mass after the CPB. Apparently, in our study the difference in the COP values between the groups during the whole CPB was too small (on average the COP difference between the groups during the CPB was 1.5 mmHg) to manifest itself in a difference in postoperative body weight gain. Results of the other authors [14, 21], that recorded a significant differences in the body weight gain post perfusion, were associated with the extreme differences between the groups COP value.

Although high oncotic pressure is considered to be nephrotoxic [22], we did not recognize any significant difference in urine production between the study groups. The urine output during CPB was decreased in the high COP group, but in the 24 hours after the CPB no significant difference in urine output was observed between the groups. Also, Rigger and co-workers recorded higher urine output in the crystalloid group through postoperative day 3 compared to the albumin group, but they did not elaborate on this finding [14]. On the other hand, Loeffelbein and associates found more physiological creatinine clearances in the HA group versus FFP group and no significant differences in renal protein loss per gram creatinine between the groups [21]. There were also no significant differences in per- and postoperative blood loss and total fluid balance between our study groups. The high COP group received less GPO transfusion in the postoperative period. This observation corresponds with result of Russell and associates [17] that described less colloidal transfusion in patients with high oncotic pressure during CPB. In addition, the significantly higher platelet count found in our high COP group at 24 hours post operation also agrees with their conclusion that albumin prime better preserves platelet counts than crystalloid [17]. In contrary, Loeffelbbein noted that in his study the absolute thrombocyte count in the HA group at 6 hours post CPB was lower than in the FFP group, but did not reach significance [21].

Significantly shorter duration of mechanical ventilation and significantly lower plasma lactate concentration at the end of the operation recorded in the high COP group could indicate positive effects of higher oncotic pressure on the water accumulation in the

lungs and whole tissue perfusion. Considering we did not measured the lung water and tissue micro-perfusion during our study this results required further investigation. Eising and associates found also an improvement of cardiopulmonary function in relation to the hyperoncotic CPB prime using hydroxyethyl starch 10% [15]. In contrast, there were no differences in duration of ventilation between the study groups from the Riegger trial [14] and Loeffelbein and co-workers did not find differences in the lactate level at 6 h post CPB in their study groups [21]. Those contradictory study results are characteristic for pediatric trials that are mostly single center, performed with small groups of patients and very often over a longer period of time. Therefore, due to the specific, institutional protocols and study conditions, the large variability of cardiac pathology and surgical techniques comparison of those study results is very difficult if not impossible.

Study limitations

This prospective, randomized study has some limitations. In the both groups, priming of the CPB circuit as well as the fluids transfused during the CPB (in compliance with the institutional protocol) were mainly colloidal solutions. That greatly diminished the differences in COP value between the study groups and in consequence attenuated the expected differences between the study variables. Due to the logistic and technical problems, the body weight was only measured directly before and after the operation, and there was no follow up for this variable. On the other hand, the redistribution of water largely takes place during CPB and is less prominent afterward.

CONCLUSIONS

Results of our study permit the conclusion that the priming for neonatal and infant CPB, based upon the 5% concentration of human albumin, better counteracts the preoperative decrease in patient colloid oncotic pressure than priming with albumin dose of 0.5 g/kg body weight. Additional supplementation of human albumin during the CPB to maintain colloid oncotic pressure at least at 18 mmHg preserves the plasma albumin concentration within the physiological range and stabilizes the colloid pressure during the bypass better than regulatory strategy with target at 15 mmHg. As there was no significant difference between the study groups in the postoperative body weight gain, only the lower plasma lactate concentration post-operation and the shorter duration of mechanical ventilation in the high COP group indicate the prospect of clinical benefit of this new strategy. To ameliorate the outcome of neonatal and infant CPB the clinical relevance of these results should be further investigated in relation to the inflammatory response mechanisms.

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Chapter 9

Intraoperative Glycemic Control during Pediatric Cardiac Surgery for Congenital Heart Disease

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Submitted

ABSTRACT

Background: Many studies are reporting that the occurrence of hyperglycemia in the postoperative period is associated with increased morbidity and mortality rates in children after cardiac surgery for congenital heart disease. This study sought to determine blood glucose levels in standard pediatric cardiac anesthesiological management without insulin infusions.

Methods: The study population consisted of 204 consecutive pediatric patients aged from 3 days to 15.4 years undergoing open cardiac surgery for congenital heart disease between June 2007 and January 2009. Glucose containing fluids were not administrated intraoperatively, all patients received high dose of opioids (sufentanil 10mcg/kg) and steroids (30mg/kg methylprednisolone) iv. Glucose levels were measured before CPB, 10 minutes after initiation of CPB, every hour on CPB, post CPB and on arrival at Intensive Care Unit (ICU).

Results: Intraoperatively only 1 patient had a glucose level < 50 mg/dl (=34.2 mg/dl), 57/204 patients (27.9%) had at least one intraoperative glucose > 180 mg/dl, but only 12 patients (5.8%) had a glucose level > 180 mg/dl at ICU arrival. 30 days mortality was 1.5% (3/204). Younger age, lower body weight and lower CPB temperature were associated with hyperglycemia at ICU arrival, as were higher pre CPB blood glucose and higher RACHS and Aristotle severity scores.

Conclusion: A conventional (no insulin, no glucose) anesthetic management seems sufficient in the vast majority of patients (95%). Special attention should be paid to small neonates with complex congenital heart surgery, in whom insulin treatment may be contemplated

INTRODUCTION

Several studies report that the occurrence of hyperglycemia in the postoperative period is associated with increased morbidity and mortality rates in children after cardiac surgery for congenital heart disease [1-4]. However, no association with intraoperative management or complexity of congenital heart disease has yet been assessed.

Lately there is concern that glycemic control in the peri-operative period, aiming at avoiding hyperglycemia while maintaining a strict euglycemic target, could place patients at risk for hypoglycemia and hereby enhance the risk for adverse outcome [1,2,5-7]. In addition, the NICE-sugar Study [6] found that postoperative intensive glucose control (81 to 108 mg/dl; 4.5 to 6.0 mmol/l) increased mortality and a moderate blood glucose target <180mg/dl (<10mmol/l) resulted in lower mortality in adults.

Infants often have reduced glycogen reserve, especially in the setting of physiological stress, and insulin therapy in this setting may place them at risk for developing hypoglycemia [8]. To our knowledge there is only one published report on adverse outcome and intraoperative glucose levels during complex congenital heart surgery in children [2].

In this light we report on our pediatric cardiac anesthesiological management and the blood glucose levels in 204 consecutive children during open cardiac surgery for congenital heart disease, exploring the association between blood glucose and complexity of congenital heart disease patient and preoperative characteristics.

METHODS

The study population consisted of 204 consecutive pediatric patients aged from 3 days to 15.4 years undergoing open cardiac surgery for congenital heart disease between June 2007 and January 2009. The Erasmus MC internal review board approved the retrospective study and the need for informed consent was waived.

Pre-operatively children were not allowed any food at least four hours before induction of anesthesia, but were allowed glucose containing clear liquids until two hours before anesthesia. None of the patients received premedication. Before induction of anesthesia, all patients were monitored with a five-lead, two-channel electrocardiogram, non-invasive blood pressure measurement, and pulse oximetry. All patients without a peripheral intravenous (iv) access had an inhalation induction with sevoflurane 8%. After insertion of iv catheter, midazolam 0.3 mg/kg, sufentanil 2 mcg/kg, pancuronium 0.15 mg/kg and 40mg/kg cefazoline were administrated and sevoflurane was stopped. Patients were nasotracheally intubated and pressure controlled ventilated after an alveolar recruitment strategy [9]. Anesthesia was maintained with midazolam 0.1 mg/kg/h. Invasive monitoring via 20G arterial line in the femoral artery, an internal jugular central

venous catheter, a Foley bladder catheter, a rectal temperature probe and the Oldelft MicroMultiplane TEE probe (Oldelft, Delft, The Netherlands) were routinely inserted [10].

Before incision we administered another 0.2mg/kg midazolam, 2mcg/kg sufentanil together with 30mg/kg magnesium sulfate, 30mg/kg methylprednisolone, 1 mg/kg ranitidine and 1mg/kg furosemide. All patients received a continuous infusion of NaCl 0.9% during the pre-incision period. Glucose containing fluids were not administrated intraoperatively. In case of normovolemic hypotension we administered 1 mcg/kg phenylephrine, in case of hypertension sevoflurane was used. Before initiation of CPB we administered 2mcg/kg sufentanil, 0.1 mg/kg midazolam, 300 IU heparine and 20mg/kg cefazoline,. Another bolus of 2mcg/kg sufentanil and 0.1 mg/kg midazolam was administrated during rewarming phase of CPB and dobutamine 4 mcg/kg/min was started. After declamping of the aorta enoximone 0.2mg/kg was administrated.

Pediatric CPB circuits consisted always of hollow-fiber oxygenator with hard-shell reservoir, a roller pump and arterial filter. The circuits were phosphorylcholine coated. Prime volumes varied depending on patient's body weight; for neonates and infants up to 10 kg - 300 ml, for patients up to 25 kg - 450 ml and for patients up to 45 kg – 850 ml. Prime was composed of homologous red blood cells (RBCs), fresh-frozen plasma (FFP) and Gelofusine (B.Braun, Melsungen, Germany) and was always completed with 0.5 g/kg BW mannitol, 0.5 g/kg BW human albumin 20% solution (Sanquin, Amsterdam, The Netherlands), 4.2 IU heparine / mL priming volume and 2-5 ml $NaHCO_3$ 8.4%.

Administration of RBCs, FFP, crystalloids or colloids during CPB was based upon the system working volumes and target values for hematocrit during the CPB (not lower than 0.28 L/L for acyanotic as well as cyanotic patients). Human albumin was added to maintain the COP ≥15 mmHg. In accordance with protocol no modified ultrafiltration and no antifibrinolitic medication was used.

Activated clotting time was monitored during the bypass and maintained above 480 sec. Nonpulsatile CPB, with mild hypothermia of 28 °C to 32 °C, was performed with blood flow rates between 1.8 L/min/m^2 to 3.2 L/min/m^2 to maintain venous oxygen saturation above 70% and mean arterial pressure between 40 to 60 mmHg. In case of a deep hypothermic circulatory arrest (DHCA) patients were cooled till 18 °C nasopharyngeal and 21 °C rectal temperature. Anterograde cerebral perfusion was utilized when appropriate. During CPB α – stat regulation was employed together with target value for arterial oxygen tension of 20 kPa. Myocardial protection was achieved with non-glucose containing crystalloid cardioplegia. Cardioplegic solution was preferably sucked into the cell-saving device (CS). Perioperative blood loss was collected and processed by CS device, together with residual volume of the CPB circuit. The CS product was always considered first line blood replacement therapy.

After weaning from CPB another 2 mcg/kg sufentanil and 0.1 mg/kg midazolam was administered. All patients received a total of 10 mcg/kg of sufentanil throughout the whole surgical procedure.

Glucose levels were measured before CPB, 10 minutes after initiation of CPB, every hour on CPB, 10 minutes after administrating 4 mg/kg Protamine and on arrival at Intensive Care Unit (ICU).

In line with previous publications, we defined the following blood glucose categories: severe hypoglycemia (< 30mg/dl; 1.7 mmol/l), moderate hypoglycemia (30-60mg/dl; 1.7-3.3 mmol/l)), euglycemia (60-125 mg/dl; 3.3-6.9 mmol/l), mild hyperglycemia (126-139 mg/dl; 6.9-7.7 mmol/l), moderate hyperglycemia (140-179 mg/dl; 7.7-9.9 mmol/L), or severe hyperglycemia (>180 mg/dl, >9.9 mmol/l) [2-5,11].

For reasons of safety, 2 ml/kg glucose 10% solution was given when blood glucose level dropped under 50 mg/dl (2.8 mmol/l).

Statistical analyses

All statistical analyses were performed with SPSS 15.0 (SPSS Inc, Chicago, IL, USA).

Continuous variables are displayed as mean (SD), median and interquartile range, categorical variables are displayed as proportions. The One-Sample Kolmorogov-Smirnov Test was used to analyse distribution of continuous variables. In case of a normal distribution comparison of continuous variables was done using the independent samples T-test, otherwise the Mann-Whitney U-test was used. The Spearman Correlation test was applied to assess correlation between blood glucose level on arrival at ICU and age, weight, Aristotle complex score, RACHS score, CPB time, aortic cross clamp time (AoX), lowest intraoperative boby temperature, blood glucose level before CPB.

Univariable binary logistic regression analysis was used to study potential determinants of blood glucose level > 180 mg/dl on arrival at ICU. The following factors were considered as potential determinants: patient age, weight, Aristotle score, RACHS score, CPB time, AoX time, lowest intraoperative boby temperature, blood glucose level before CPB as covariates was used.

Graphs were constructed with Graphpad software package (version 4.0, Graphpad Software Inc., San Diego, USA).

RESULTS

204 consecutive pediatric patients from 2.4 kg to 45 kg (130 male/ 74 female) operated for congenital heart disease with use of CPB at the Thoraxcenter Rotterdam, The Netherlands, were included. Patients demographics, surgical procedure code by Aristotle Complexity Score [12], RACHS (risk adjustment for surgery for congenital heart disease)

Table 1. Patients demographics and operative details.

Age: n = 204	
Mean (days;SD)	726 (1060)
Median (IQR)	221 (81-965)
< 30 days (N)	22
>30 days < 1 year (N)	101
>1 year	81
Weight (kg): n = 204	
Mean (days;SD)	10.2 (7.9)
Median (IQR)	8 (4.5-13.3)
<5kg (N)	59
>5kg (N)	145
Aristotle score: n = 204	
Mean (SD)	7.9 (3.01)
Median (IQR)	8 (6-9)
|RACHS score: n = 204	
Mean (SD)	2.4 (1.03)
Median (IQR)	2 (2-3)
CPB (min): n = 204	
Mean (SD)	92.58 (61.47)
Median (IQR)	82 (52.5-107)
AOX (min): n = 204	
Mean (SD)	52.86 (37.06)
Median (IQR)	47 (26-67.5)
DHCA (min): n = 9	
Mean (SD)	47 (32.4)
Median (IQR)	53 (21.5-70.5)
CPB temp (Celsius): n = 204	
Mean (SD)	30.48 (3.66)
Median (IQR)	30.3 (28.7-33.5)
Extubation (hours): n = 142	
Mean (SD)	8.4 (4.9)
Median (IQR)	7.1 (4.9-10.18)
Blood glucose pre CPB (mg/dl): n = 204	
Mean (SD)	92 (25)
Median (IQR)	86 (75-103)
Blood glucose ICU (mg/dl): n = 204	
Mean (SD)	129 (35)
Median (IQR)	126 (106-151)

SD= standard deviation; IQR= Interquartile range; RACHS= risk adjustment for surgery for congenital heart disease; CPB= cardiopulmonary bypass; AoX= aortic cross clamp time; DHCA= deep hypothermic cardiac arrest; ICU= intensive care unit.

[13], CPB time, AoX time and lowest body temperature are listed in Table 1. According to the Kolmogorov-Smirnov Test all groups of Table 1 are not normally distributed except for blood glucose level on arrival at ICU. Operations by RACHS-1 category are shown in Table 2.

Box plots of per-operative and on arrival at ICU blood glucose levels are displayed in Figure 1. No patients received insulin during surgery.

Fifty-seven of the two-hunderd-four patients (27.9%) had at least one intraoperative glucose level > 180 mg/dl (10 mmol/l), 132/204 patients (64%) had at least one intraoperative glucose level > 140 mg/dl (7.7 mmol/l), but only 12 patients (5.8%) had a glucose level > 180 mg/dl (10 mmol/l) on arrival at ICU, 59 patients (28.9%) had a glucose level > 140 mg/dl (7.7 mmol/l) on arrival at ICU (Table 3). Intraoperatively only 1 patient (a 2 year old boy with ASD) had a blood glucose level < 50 mg/dl (2.8 mmol/l). We measured 34.2 mg/dl and after administration of 2ml/kg glucose 10% blood glucose level rose to 48.6 mg/dl where after another glucose bolus was administrated and blood glucose level rose to 120 mg/dl.

Nine out of 204 patients had Deep Hypothermic Cardiac Arrest (DHCA), of which 5/9 (56%) had blood glucose levels > 180 mg/dl (10 mmol/l) on arrival at ICU, while only 7 of 195 (3.5%) of the patients who did not undergo DHCA had blood glucose levels > 180 mg/dl on arrival at ICU.

Of the 204 patients 142 had representative extubation times (Table 1), the other 62 patients received supplemental sedation for early transportation to the children ICU (logistic problem), or needed supplemental sedation because of their actual clinical condition or both.

30 days mortality was 1.5% (3/204); one sudden death 23 days postoperative after good recovery from TOF repair, one death a week after Norwood procedure due to respiratory infections complicated with necrotic enterocolitis and 1 death due to a mediastinale hemorrhage after Norwood procedure which needed postoperative ECMO support.

Factors potentially associated with hyperglycemia (blood glucose level > 180 mg/dl) on arrival at ICU are shown in Table 4. Patients age < 30 days had higher glucose levels on ICU arrival compared to patients age > 30 days (156.1 $\pm$ 54.1 versus 126.2 $\pm$ 30.5; p=0.001). Patients weighing 5 kilos or less had higher glucose levels on ICU arrival compared to patients weighing more than 5 kilos (139.0 $\pm$ 44.1 versus 125.5 $\pm$ 29.8; p=0.008).

Table 5 displays the correlation results between intraoperative blood glucose levels and LOS, ICU days, extubation time and mortality. All correlations were either nonsignificant or at the most very weak (Spearman´s Rho (0.30).

Linear regression suggested that neither lower intraoperative blood glucose levels (<60 or <75 mg/dl) nor higher intraoperative blood glucose levels (>140 or >180mg/dl) had influence on LOS, ICU stay, mortality or extubation time (Table 6). Blood glucose levels at ICU arrival were associated with longer ICU stay (p=0.04) (Figure 2).

Table 2. Individual procedures by RACHS-1 category.

Risk Category 1
ASD closure (29)
Coarctation repair with left-left shunt at age > 30d (1)
Partially anomalous pulmonary venous return repair (2)
Sinus venosus atrial septal defect closue (2)
Risk Category 2
Aortic-pulmonary window repair and ASD closure (1)
Aortic valvuloplasty at age > 30d (1)
Partial cavo-pulmonary connection (16)
Pulmonary valvuloplasty (5)
Pulmonary valve replacement (1)
Total repair of TOF (21)
VSD closure (29)
VSD and ASD closure (9)
VSD closure and pulmonary valvuloplasty (2)
VSD closure and right vemtricle infundibulectomy (5)
VSD closure and subaortic stenosis (3)
Risk Category 3
Anomalous left coronary artery from pulmonary artery reimplantation (1)
Aortic- and mitral valvuloplasty (1)
Aortic-pulmonary window (2)
Arterial switch operation (3)
CAVSD repair (19)
Coarctation repair and VSD closure (2)
Heart transplantation (2)
Intracardiac tumor excision (1)
Left Ventricular Assist Device (1)
Mitral valvuloplasty (1)
Pulmonary artery banding and VSD closure (1)
Pulmonary valve replacement and VSD closure (1)
Ross procedure (1)
Tricuspid valvuloplasty (1)
TOF repair with pulmonary atresia (1)
Total cavo-pulmonary connection (16)
Tricuspid valve repositioning for Ebstein anomaly at age > 30d (1)
Risk Category 4
Atrial septectomy (1)
Arterial switch operation and VSD closure (6)
Hypoplastic aortic arch repair and VSD closure (2)
Interrupted aortic arch repair (1)
TAPVR repair at age < 30d (5)
TAPVR, CAVSD and TGA repair (1)
Risk Category 5
Damus-Kaye-Stansel procedure (1)
Norwood operation (5)

ASD=atrial septal defct, CAVSD=complete atrioventricular septal defect, TAPVR=Total anomalous pulmonary venous return, TGA=transposition of great arteries, TOF=tetralogy of Fallot, VSD=ventricular septal defect.

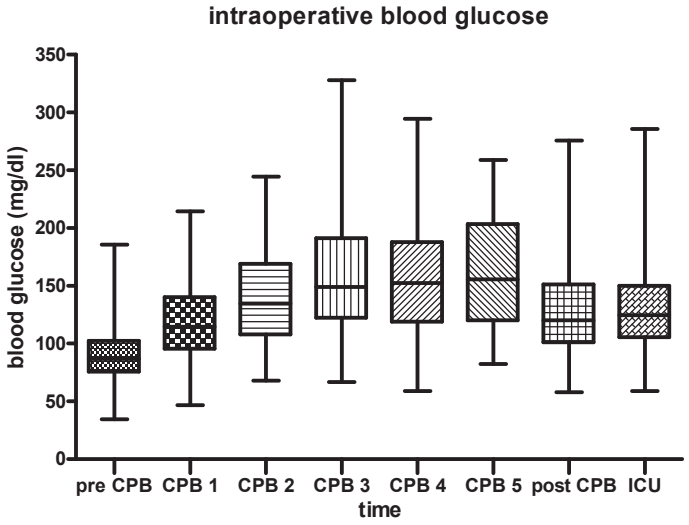

Figure 1. Intraoperative and ICU arrival blood glucose levels.

Table 3. Data of patients with hyperglycemia > 180mg/dl at ICU arrival.

Gender	Age	Weight (kg)		Aristotle Score	RACHS score	CPB time (min)	AOX (min)	CPB temp	DHCA/ ACP (min)	glc IC (mg/ dl)
M	1m3d	13.4	ASD	3	1	45	20	35.1		181.8
F	4d	2.5	Switch+ASD	13	4	148	93	26.2	4/0	196.2
M	3m3d	5.9	ALCAPA	10	3	224	156	25.8		185.4
M	14d	3.8	VSD,ASD,CoA,PDA	15	3	104	53	26.1	21/0	199.8
M	2m	2.5	PDA, AP-window, Atrial Septal Fenestartion.	9.8	2	65	30	28.4		201.6
M	1m16d	4.3	F4	8	2	156	94	28.6		219.6
M	5m2d	5.2	F4	8	2	85	45	30.7		190.8
M	6d	3.8	VSD+corr. Ao Arch	13	4	126	56	22.1		187.2
M	4d	3.4	Norwood	14.5	6	197	110	17.2	82/59	275.4
F	3m11d	5.4	F4+corr. Ao Arch	14	5	111	66	21.5	24/0	181.8
M	7d	3	Norwood	14.5	6	162	100	25.5	54/34	286.2
M	13d	3.1	ASD+PDA	6	1	102	45	29.3		196.2

ASD=atrial septal defect; Switch= arterial switch operation; ALCAPA= abnormal left coronary artery from the pulmonary artery; VSD= ventricular septal defect; CoA=aortic coarctation; PDA= patent ductus arteriosus; AP-window=aortic pulmonary window; F4= tetralogy of Fallot; corr. Ao Arch= correction aortic arch, RACHS= risk adjustment for surgery for congenital heart disease, CPB= cardiopulmonary bypass, AoX= Aortic crossclamping, DHCA= deep hypothermic cardiac arrest, ACP= antegrade cerebral perfusion, glc IC= blood glucose on Intensive Care arrival.

Table 4. Logistic regression analysis (blood glucose >180 mg/dl at ICU arrival as dependent variable)

	B	S.E.	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
					Lower	Upper
Weight (kg)	-0.358	0.144	0.013	0.699	0.527	0.927
Age (days)	-0.018	0.007	0.008	0.982	0.969	0.995
Aristotle Score	0.317	0.101	0.002	1.373	1.126	1.675
RACHS Score	0.633	0.223	0.004	1.884	1.217	2.916
CPB time (min)	0.006	0.003	0.07	1.006	1	1.012
AoX (min)	0.12	0.006	0.068	1.012	0.999	1.024
Gluc pre (mg/dl)	0.028	0.01	0.004	1.028	1.009	1.048
CPB temp (°C)	-0.296	0.066	0	0.744	0.654	0.846
DHCA	0.4	0.014	0.004	0.5	1.012	1.069

RACHS= risk adjustment for surgery for congenital heart disease, CPB= cardiopulmonary bypass, AoX= Aortic crossclamping, DHCA= deep hypothermic cardiac arrest, ACP= antegrade cerebral perfusion, glc IC= blood glucose on Intensive Care arrival. B=sample regression coefficient, S.E.= standard error, Sig.= two-sided P value or observed significance level, Exp(B)= exponentiation of the B coefficient, C.I.=confidence interval.

Table 5. Correlation analysis results of intraoperative blood glucose versus LOS, ICU days, extubation time and mortality.

Correlation	Spearman's rho	Significance (2-tailed)
Highest intraop Glc / ICU days	0.199	0.005
Highest intraop Glc / LOS	0.197	0.005
Highest intraop Glc / ICU glc	0.284	0.0001
Highest intraop Glc / Extubation time	0.259	0.0001
Highest intraop Glc / mortality	0.132	NS
> 140 mg/dl intraop glc / LOS	0.14	NS
> 140 mg/dl intraop glc / ICU days	0.102	NS
> 140 mg/dl intraop glc / extubation time	0.143	NS
> 140 mg/dl intraop glc / mortality	0.09	NS
> 180 mg/dl intraop glc / LOS	0.137	NS
> 180 mg/dl intraop glc / ICU days	0.147	0.038
> 180 mg/dl intraop glc / extubation time	0.203	0.015
> 180 mg/dl intraop glc / mortality	0.175	0.012

Table 6. Linear regression analysis results: Lower (<60 and <75mg/dl) and higher intraoperative blood glucose levels (>140 and >180mg/dl) versus LOS, ICU stay, mortality or extubation time.

					95% C.I.	
Linear Regression	B	Std Error	Beta	Sign.	lower	higher
<60mg/dl intraop glc / LOS	-1.949	4.285	-0.035	0.65	-10.399	6.501
<60mg/dl intraop glc / ICU days	0.154	1.863	0.006	0.934	-3.519	3.828
<60mg/dl intraop glc / extubation	1.715	2.2	0.071	0.437	-2.635	6.066
<60mg/dl intraop glc / mortality	-0.004	0.038	-0.009	0.91	-0.08	0.071
<75mg/dl intraop glc / LOS	1.884	2.711	0.063	0.488	-3.461	7.23
<75mg/dl intraop glc / ICU days	0.795	1.178	0.06	0.501	-1.529	3.118
<75mg/dl intraop glc / extubation	0.741	1.169	0.667	0.528	-1.572	3.053
<75mg/dl intraop glc / mortality	-0.025	0.024	-0.089	0.325	-0.072	0.024
>140mg/dl intraop glc / LOS	2.492	1.991	0.088	0.212	-1.435	6.418
>140mg/dl intraop glc / ICU days	-0.943	1.214	-0.77	0.438	-3.337	1.45
>140mg/dl intraop glc / extubation	1.258	0.852	0.124	0.142	-0.426	2.942
>140mg/dl intraop glc / mortality	0.023	0.018	0.9	0.199	-0.12	0.58
>180mg/dl intraop glc / LOS	2.45	2.05	0.84	0.233	-1.593	6.493
>180mg/dl intraop glc / ICU days	0.015	0.01	0.118	0.126	-0.004	0.062
>180mg/dl intraop glc / extubation	1.319	0.877	0.126	0.135	-0.414	3.053
>180mg/dl intraop glc / mortality	0.027	0.17	0.106	0.11	-0.006	0.06

B=sample regression coefficient, S.E.= standard error, Sig.= two-sided P value or observed significance level, Beta=standardized coefficient, C.I.=confidence interval.

DISCUSSION

This study shows that with a conventional (no insulin, no glucose) pediatric cardiac anesthetic approach there is little risk for intraoperative hypoglycaemia during pediatric cardiac surgery for congenital heart disease. In addition, severe hyperglycemia on ICU arrival was uncommon, but younger patients, lower weights, complex operations, high pre-CPB blood glucoses and DHCA representing a higher risk for hyperglycemia on ICU arrival.

Comparable with the paper of DeCampli et al. [14] significant higher glucose levels on ICU arrival were observed in patients age < 30 days compared to those older than 30 days, and in patients weighing 5 kilos or less compared to those weighing more than 5 kilos.

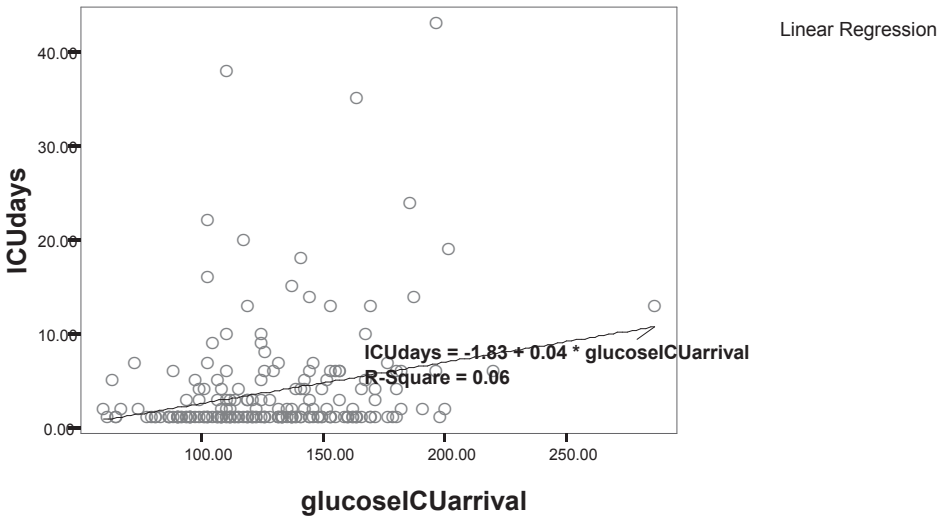

Figure 2. Blood glucose levels at ICU arrival versus ICU days.

Balancing between perioperative hypoglycaemia and hyperglycemia

Our study did not support the hypothesis that lower- or higher intraoperative blood glucose levels would be associated with a longer duration of postoperative hospitalisation.

According to the results of Polito et al.[2] 23% of our patients are at greater risk for adverse outcome (mortality and composite morbidity variable) because of an intraoperative glucose level < 75 mg/dl (4.1 mmol/l). Our results do not support this, patients whose minimum intraoperative glucose level was < 75 mg/dl or even < 60 mg/dl did not show any association with LOS, ICU stay, extubation time or mortality. Avoiding lower glucose levels (< 75 mg/dl) can only be achieved by administrating glucose containing fluids in the pre CPB period, which will increase the occurance of hyperglycemic periods [15].

Twenty-eight percent of our patients had at least one intraoperative glucose level > 180 mg/dl (10 mmol/l) and 64% had at least one episode of blood glucose levels > 140 mg/dl which, in accordance to the results of Polito et al.[2], is not associated with adverse events.

On the other hand various other reports have shown an association between postoperative hyperglycemia and extubation time, LOS, mortality [1,3,4]. We also found a weak association between blood glucose levels at ICU arrival and ICU days.

Factors influencing blood glucose levels during cardiac surgery

Stress, steroids and administration of glucose are conditions that are associated with hyperglycemia in the neonate. High circulating levels of cortisol and catecholamines

(adrenaline and noradrenaline) have the reverse action to insulin, rendering the baby insulin resistant and catabolic, and in addition the latter directly suppress insulin release. Since all patients received 30mg/kg methylprednisolone iv before going on CPB and since steroids use in pediatric cardiac surgery is still controversial [20,21], additional benefit in preventing hyperglycemia might be achieved by withholding steroids in pediatric cardiac surgery.

High doses of opioids (sufentanil 10mcg/kg) attenuate the physiologic response to stress in infants undergoing cardiac surgery [16-18]. High doses of sufentanil together with non-glucose iv fluids contributed to the high percentage (95%) of our patients that had glucose level < 180 mg/dl (10 mmol/l) on arrival at ICU. The NICE-SUGAR study [6], blood glucose target of < 180 mg/dl (<10 mmol/l) resulted in lower mortality in adult patients than did a more strict target, endorsed the concern that glycemic control in the peri-operative period could place patients at risk for hypoglycemia and hereby enhance the risk for adverse outcome and mortality. In our study we observed an overall 30 days postoperative mortality of 1.5% (3/204), if we only take into account the patients $\leq$ 10 kg then mortality would be 3/131 (2.3%), were the now reported mortality in the European Association for Cardio-thoracic Surgery and the Society of Thoracic Surgeons Congenital Heart Surgery Database is 4% [19].

Since only 3.5% of our patients who did not undergo DHCA had blood glucose levels > 180 mg/dl on arrival at ICU, a conventional (no insulin, no glucose) anesthetic management seems sufficient in the vast majority of patients (96.5%) [6]. But special attention should be paid to neonates who need DHCA for surgical repair and are at an increased risk of postoperative hyperglycemia (5 out of 9 DHCA patients had blood glucose levels > 180 mg/dl at ICU arrival). In these patients a more strict intraoperative glycemic target ((90-140 mg/dl; 5-7.7 mmol/l) [5], (110-126 mg/dl; 6.1-7 mmol/l) [2]) might be useful, requiring insulin infusions and Real-Time continuous glucose monitoring [8].

High dose opioids may influence extubation time, but even with high dose opioids all of the 142 pediatric patients in our study, that did not received additional sedations, were all extubated within 21.1 hours after arrival at ICU.

Limitations

This is a non-blinded retrospective study. Because of logistic problems at our ICU 30% of our patients had to be transported to another department for which they received additional sedation, the reason for additional sedation whether it was for transportation or for medical reasons was not traceable.

CONCLUSIONS AND RECOMMENDATIONS

Since the optimal intraoperative blood glucose target range in pediatric patients during cardiac surgery for congenital heart disease remains unclear, a conventional intraoperative high dose opioids and withholding glucose in intravenous fluids permits for a safe and moderate glucose control during pediatric cardiac surgery for congenital heart disease".

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Chapter 10

General discussion, conclusions and prospects

Postoperative multiple organ dysfunction is a major contributor to morbidity and mortality for patients who underwent cardiac surgery. Risk factors in this regard are divers and generally include infection, non- infectious inflammatory conditions, tissue trauma, burn injury, ischemia, toxin exposure and immune system activation [1]. In neonatal and infant congenital heart surgery, the early mortality and morbidity significantly improved during the last decades [2]. Multivariate analysis of the data collected in the European Association for Cardiothoracic Surgery (EACTS) Congenital Database between 1999 and 2008 confirmed that lower body weight, higher Aristotle Basic Score (ABS), longer CPB time, longer aortic cross-clamp time, longer circulatory arrest time and univentriculair physiology are risk factors for hospital mortality[3]. Higher ABS as well as longer CPB time and circulatory arrest time are associated with an increased rate of complications [3]. Attempts to reduce postoperative CPB related morbidity primarily focused on suppressing of the systemic inflammatory response to the extracorporeal circuit. The aim of this thesis was to investigate the results of specific innovations that were tested and implemented in our institution to harness deleterious effects of neonatal and infant CPB. These specific innovations concerning optimization of temperature management, circuit minimization and blood salvage, regulation of colloid oncotic pressure and glycemia control, are addressed in more detail in the following sections. Finally, general conclusions are formulated and future prospects are presented.

TEMPERATURE MANAGEMENT DURING CPB

In pediatric heart surgery, technical developments and enhanced surgical skills allowed for reduction of depth of hypothermia in most procedures. Previously, intracardiac repairs were mostly performed with moderate (28 - 30 °C) to profound (< 25 °C) systemic hypothermia with exception for short procedures that utilized mild (30 - 32 °C) hypothermia. Systemic hypothermia reduces tissue metabolic rate and oxygen demand and is used to protect the myocardium, the brain and other organs against potential ischemic insult [4, 5]. Systemic hypothermia allows lowering the arterial blood flow that may be used to promote better visibility in the operation field and that is assumed to result in less blood trauma. On the other hand, a generalized inflammatory response is often a dominant feature of hypothermic bypass [6, 7]. Chapter 2 presents the results of our study on clinical outcome of pediatric patients, operated with short aorta occlusion time with mild (32 °C) or moderate (28 °C) hypothermic CPB [8]. Our study documented no difference in organ preservation depending on the type of hypothermia used during VSD closure in pediatric patients. The chosen temperatures did not impair the adequacy of CPB. There was no difference in technical complexity of the operation. Moreover, the clinical outcome of the patients did not depend on the type of hypothermia. Our results

correlate with the results of Eggum and associates, who did not measure any differences in levels of inflammatory mediators between pediatric patients operated with mild or with moderate hypothermia, with exception for an enhanced interleukin-8 response in the moderate hypothermia group [9].

Based upon the results of our study, mild hypothermia has been applied in the wide spectrum of corrective operations for congenital heart problems in pediatric patients in our institution.

CIRCUIT MINIMIZATION AND BLOOD SALVAGE

One of the measures to reduce the inflammatory response caused by CPB is to reduce both the blood contact surface area of the circuit as well as the priming volume [10, 11, 12]. In neonates and small children, the CPB circuit surface and the priming volume are relatively large in relation to the size and blood volume of the patient. Therefore, the use of allogeneic blood products is often inevitable to maintain an optimal hematocrit during the bypass. On the other hand, the deleterious effects of allogeneic blood transfusion are well documented in adult patients and Silliman et al. have shown that blood transfusion is a major contributing factor for multiorgan failure [13]. In Chapter 3 and 4 we investigated the effects of CPB circuit reduction, residual volume salvage and intraoperatieve blood salvage on allogeneic transfusion requirements in neonates and infants undergoing cardiac surgery. Our results showed that transfusion of homologous blood product during and after infant cardiac surgery can be efficiently diminished by minimization of the CPB circuit and cell saving of the residual volume after operation [14]. Especially, minimization of the CPB circuit (priming volume reduction from 700 ml, to 450 ml and further down to 330 ml) significantly reduced the demand of homologous blood products, both red blood cell concentrate and fresh frozen plasma, during the operation. As an advantage, patients were exposed to a decreased number of donors as well. Additionally, there was a significant reduction in the homologous blood products transfusion postoperatively due to the use of the cell saving product obtained by the processing of the residual CPB volume. To realize the benefits of this blood conservation policy the availability of the cell saving product as soon as possible after the cessation of CPB, the amount of the product and the commitment of the team to the policy goals are of crucial importance.

The results of our retrospective audit encouraged the prospective trial on further circuit reduction and adjuvant intraoperative blood salvage in neonates and infants (Chapter 4). For a long time blood salvage was considered to be not applicable in pediatric patients due to the technical limitations to wash and hemoconcentrate small volumes of salvage blood (<300 ml). More recently, new autotransfusion devices allow

efficient blood salvage in small children by employing small volume centrifugal bowls (<100 ml) and dedicated pediatric systems. Prospective studies addressing the effects of intraoperative cell salvage in adult cardiac surgery have been performed since the late seventies, showing that intraoperative and postoperative cell salvage is effective, safe and that autotransfusion of washed cells is not associated with clinically significant derangement of clotting profiles [15], although activation of platelets and leucocytes was found in the salvage blood [16]. In our institution, cell salvage of the residual circuit volume was successfully introduced in adult cardiac surgery and intraoperative cell salvage was subsequently combined with it as a routine blood conservation measure [17]. It is obvious that intraoperative blood salvage is not equally useful for all types of surgery and its effectiveness strongly depends on the ability to collect shed blood from the operating field, the hematocrit of collected blood as well as on the local re-transfusion policy. In the prospective non-randomized study, we determined the impact of intraoperative blood salvage, as an additional blood conservation technique, on allogeneic blood products transfusion in infant patients undergoing elective cardiac surgery [18].

Our results demonstrated that intraoperative cell salvage significantly enhanced the amount of salvage product available for transfusion. Consequently, significantly more patients received salvage product in the postoperative period and the frequency of allogeneic blood transfusion was significantly reduced as well as the mean transfused volume. We did not observe any adverse effects of salvage product transfusion in terms of increased postoperative bleeding, derangement of clotting pathways or enhanced transfusion of platelet concentrate and FFP.

The intraoperative blood salvage had the benefit of reducing postoperative allogeneic blood transfusion, but was not cost effective (the cost made to collect shed blood was higher than the financial savings associated with the reduction of allogeneic blood transfusion).

Further benefit would be enhanced by prolongation of the acceptable transfusion time for salvage product, strict application of a postoperative transfusion protocol with the salvage product as the first line transfusion therapy and adjustment of the transfusion trigger.

The latest miniaturizations of a CPB circuit enable to perform bloodless open heart surgery in selected pediatric patients [19]. Still, the asanguineous prime composition for neonates and infants is not yet a routine clinical practice. In keeping with safety standards and institutional protocols, we finally achieved the CPB circuit reduction from 700 ml to 300 ml during the past years (from 1997 until 2006). In Chapter 5, we present a retrospective analysis of the effect of stepwise miniaturization of CPB circuit on homologous blood requirement during the neonatal and infant CPB. The incidence of RBC transfusion in the priming decreased from 100% to 94% and during the CPB from

100% to 80% [20]. Moreover, the volume of peri- and postoperative transfusion of fresh frozen plasma and platelet concentrate was significantly higher in the group with the largest CPB circuit. This group also had the lowest platelet counts after bypass compared to the other groups. Neonates operated with the smallest CPB circuits stayed significantly shorter in the ICU and were extubated sooner. Those improved clinical outcomes indicate superior postoperative cardiopulmonary function of neonates operated with the use of a minimized CPB circuit [12, 21]. We could conclude that miniaturization of the CPB circuit size reduced the overall use of blood products. This facilitates a decreased patient inflammatory response. Still, our CPB circuit with the volume of approximately 300 ml (the circuit type that was used during the trial) was higher than reported by others [21, 22] and required further reductions.

As the concept has emerged that bloodless CPB for small children could be safely and successfully performed, a specific centre - related program is required to achieve this objective. As discussed in Chapter 6, the institutional guidelines must consider reduction of CPB circuit, enhancement of preoperative patient hematocrit, evaluation of acceptable safe CPB hematocrit and assessment of expected reduction of blood transfusion during CPB [23].

Accordingly, with the recommendations from our studies, we now routinely use intraoperative blood salvage together with residual volume proceeding during pediatric cardiac surgery. Introduction of a dedicated cell-saving device with small pediatric centrifugal bowl of 55 ml allows us to obtain a useful salvage product from the reduced amount of blood loss and the minimal residual volume. We additionally redesigned our CPB circuit and incorporated the new type of oxygenator with integrated arterial filter. This rendered the reduction of CPB priming volume down to 250 ml for the smallest patients. The impact of those innovations on the transfusion of allogeneic blood products during pediatric cardiac surgery will be evaluated in future audits.

The future volume reduction together with the implementation of a safe hematocrit strategy may render asanguinouse neonatal CPB.

REGULATION OF COLLOID OSMOTIC PRESSURE DURING CPB

Minimization of CPB circuit and elimination of allogeneic blood from the priming solution to diminish inflammatory response to CPB do not solve completely the problem of fluid extravasation and body weight gain after CPB. Dilution depended decrease of plasma colloid osmotic pressure (COP) favours a fluid shift from the intravascular space into the interstitial space that consequently augments total body water and enhances the risk of multiple organ failure [10].

A meta-analysis of controled adult trials by Russell et al. [24] concluded that albumin added to the priming of the CPB favourably influenced COP, on-bypass positive fluid balance, postoperative weight gain, and colloid usage. Although the impact of the priming components and volume have significant effect on neonates and infants [25, 26], there is no consensus about the choice of the priming formula and intravascular volume replacement regime as well as the optimal level of COP. Chapter 7 presents study results on the risk factors for low COP during infant CPB [27]. In our institution, priming of infant CPB circuit constituted of different colloidal solutions, the COP values were routinely measured and human albumin solution was administrated during the bypass to manage COP at appropriate level. Extensive variations of COP values of the priming and during the infant CPB motivated us to audit clinical and laboratory data to recognize the patients prone to low COP at the end of bypass. We also validated the existing protocol to propose the future adjustments of infant priming composition and COP regulation strategy. Results of our study demonstrated that pre-bypass crystalloid dilution during induction as well as return of the crystalloid cardioplegic solution into the circulation should be avoided as the significant risk factors for low COP during the bypass. Additionally, we concluded that priming COP and COP management strategy during bypass should be tailored to individual patient demand, as the existing regulatory protocol was not adequate.

In a prospective randomized study (Chapter 8), we evaluated the influence of two different COP regulatory strategies on post bypass body weight gain, fluid balance and clinical outcomes [28]. Results of our study permit the conclusion that the priming for neonatal and infant CPB with a 5% albumin solution (achieved by addition of 20% albumin into the priming volume to acquire a concentration of 5 g per 100 ml), better counteracts the preoperative decrease in patient colloid osmotic pressure than priming with an albumin dose of 0.5 g/kg body weight. Additional supplementation of human albumin during the CPB to maintain colloid osmotic pressure at least at 18 mmHg preserves the plasma albumin concentration within the physiological range and stabilizes the colloid pressure during the bypass better than regulatory strategy with target at 15 mmHg. The lower postoperative plasma lactate concentration and the shorter duration of mechanical ventilation in the high colloid osmotic pressure group suggests a clinical benefit of this new strategy in neonates and infants, even though there were no significant differences between the study groups with regard to postoperative body weight gain.

The new strategy of COP regulation during CPB already has been implemented and the effort to avoid any additional perioperative crystalloid dilution intensified.

INTRAOPERATIVE GLYCEMIA CONTROL

Infants often have reduced glycogen reserve and especially under the physiological stress and insulin therapy they may be at risk for developing hypoglycemia [29]. Study results of Polito et al. reported on adverse outcomes and intraoperative glucose levels during complex congenital heart surgery in children [30]. Therefore, we audited our pediatric cardiac perioperative management and the blood glucose levels in 204 consecutive children during open cardiac surgery for congenital heart defects, exploring the association between blood glucose and complexity of congenital heart disease, and preoperative patient characteristics. Younger age, lower body weight and lower CPB temperature were associated with postoperative hyperglycemia, as were higher pre CPB blood glucose level, higher Risk Adjustments Congenital Heart Surgery (RACHS) scores and Aristotle severity scores. Still, a conventional (no insulin, no glucose) anaesthesia management was sufficient in the vast majority of patients (95%) to control the glucose level within the normal ranges [31].

Therefore, this strategy concerning the glucose control during CPB is continued.

GENERAL CONCLUSIONS

In the past two decades, different technological as well as procedural innovations were implemented in CPB to improve its quality. The efficacy of those innovations was validated in clinical trails and the results of our studies demonstrated that implementation of novel concepts in CPB produced measurable improvement of its quality, although not always a significant benefit in terms of patient outcome could be detected.

Minimization of the circuit together with the avoidance of allogeneic blood during the CPB showed the most positive impact on postoperative course in the neonates and infants undergoing cardiac surgery. The pursuit for asanguineous neonatal and infant CPB will be continued, as new, extremely small devices will be developed and implemented in clinical practice. Conditional innovations presented in the thesis may be regarded as the "fine tuning" of CPB strategy, but their additional value must be not underestimated. All those steps are essential in optimisation of CPB and tailoring of the individual strategy for every single patient in the ongoing process of quality improvement.

Performing clinical research concerning CPB, we realized that some of our studies demonstrated typical limitations representative for pediatric CPB trials. Publications in peer-reviewed journals often disclose that they are; single centre, not randomized, retrospective and observational. Moreover, the study groups frequently comprise a small number of cases so a reliable statistical assessment may be extremely difficult. Reasons for that are obvious for anyone involved in a pediatric clinical trial. Most institutions, if

not all, performing pediatric cardiac surgery with CPB have a caseload that does not match numbers required for clinical trials and therefore any method of risk adjustment for congenital heart disease is highly challenging. Inclusion of patients in randomized trials and obtaining of signed informed consent from the parents or guardians is a difficult task that limits the enrolment of patients. Logistics of the chain of care often requires a cooperative effort of different professionals with their own departmental protocols that must be temporally adjusted or abandoned for the study protocol. Even systematic literature studies on pediatric cardiac surgery related subjects are difficult to conduct as the specific institutional policies frustrate the comparison of the study results.

Being aware of the existence of limiting factors that influence the results of pediatric clinical trails we need to view proposed innovations with caution. We need to choose carefully the innovations that we consider applicable, safe and potentially beneficial for patients under local institutional circumstances. Only a continuous scrupulous audit of local results could objectively assess the efficacy of the innovations made.

Continuous quality improvement of CPB is a process that is not yet completed. With active involvement of industrial partners, technological progress can be achieved in the nearby future. Optimisation of the collaborative effort of all professionals involved in the multidisciplinary application of CPB is a prerequisite for further improvement in the pediatric cardiac surgery.

PROSPECTS

More profound understanding of specific CPB aspects that was obtained during the clinical trails presented in this thesis consequently led to the initiation of new research to improve the clinical outcomes. Continuous quality improvement strongly depends on the adequate and reliable data collection system as well as the distinctive definition of influential variables and measurable outcomes relevant for the process. These requirements apply to the improvement of the CPB process as well. Therefore, we will persist in our efforts to expand the existing data collection system with new monitoring possibilities, as for example the Near Infra Red Spectroscopy (NIRS). This technique allows us to collect data on the regional oxygenation in relation to the level of dilution during the CPB as well as the abnormal blood flow patterns during the operation. We expect that additional information provided by the NIRS will support us in the pursuit of asanguineous neonatal and infant CPB.

Recently, manufacturers and the users of pediatric CPB equipment concluded that industrial process of minimization has reached its limits. Without new technological discoveries, further reduction of CPB circuit elements seems not possible. Therefore, rethinking and redesigning of concepts of CPB circuit to reduce the total system volume

is indicated. With use of the advanced last generation neonatal and infant oxygenators, with integrated arterial filter, we still will be able to reduce our circuit.

To diminish deleterious effects of allogeneic blood transfusion during the CPB, the efficacy of pre- washing of red blood cells concentrate in a cell saving device is already studied. Additionally, the relevance of the electrolytes balanced washing solutions would be evaluated. However, this innovative approach requires a clinical audit to confirm it relevance for the quality improvement in CPB.

Furthermore, the ongoing progress of the surgical skill and development of the advanced monitoring techniques, make the normothermic CPB for complex cardiac corrections a realistic possibility. This eventually will require new myocardial protective strategies, as for example minimal warm cardioplegia. To determine the quality improvement related to this innovation the reliable marker for the myocardial impairment is required. Additionally, inter -institutional benchmarking would be purposeful to recognize the beneficial value of different operative en protective strategies.

Attention to these future prospects will enable an excellence in the field and achievement of the optimal results.

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Chapter 11

Summary / Samenvatting

Acknowledgement

Curiculum vitae

List of publication

Portofolio

Summary

Chapter 1 contains the introduction to the thesis and presents the idea of innovation in cardiopulmonary bypass as a continuous quality improvement process. It describes specific aspects of cardiopulmonary bypass that are in the focus of this thesis and presents latest innovations introduced to attenuate the deleterious effects of it.

Chapter 2 compares the clinical results between two groups of pediatric patients, operated with short aorta occlusion times and mild or moderate hypothermic cardiopulmonary bypass, to assess the effect of temperature management on the clinical outcome. Although, moderate hypothermia of 28 °C was widely accepted in cardiac surgery with cardiopulmonary bypass, several studies suggested that normothermic or "tepid" bypass techniques might improve the clinical outcomes for patients undergoing cardiac operations. To assess the effect of bypass temperature management strategy in pediatric patients undergoing correction of ventricular septal defect, 26 patients with body weight under 10 kg were randomly assigned to two treatment groups: Group 1, mild hypothermia, patients cooled to nasopharyngeal temperature of 32 °C during the bypass; or Group 2, moderate hypothermia of 28 °C. Hematologic data after bypass and protamine administration revealed a significantly longer activated partial thromboplastin time in the 32 °C group; however, the difference in blood loss did not reach significance. This study showed that both perfusion temperatures equally well facilitated cardiopulmonary bypass for this type of intracardiac surgery.

Chapter 3 evaluates the effects of cardiopulmonary bypass circuit reduction and salvage of red blood cells from the residual volume after the procedure on allogeneic transfusion requirements in infants undergoing cardiac surgery. The retrospective observational study included 148 consecutive infants between 1 to12 months of age, with a body weight less than 10 kg, who underwent an elective cardiac operation between 1997 and 2005. Patients were divided into three groups depending on the circuit prime volume used during the operation; 700 ml (Group 1), 450 ml (Group 2) and 330 ml (Group3). In Group 1 residual volume after perfusion was fully discarded and in Group 2 and 3 was processed in cell saving device.

Reduction of the circuit volume significantly diminished transfusion of homologous blood products in the prime and during the bypass. Total perioperative use of red blood cells concentrate was reduced from 1.9 units to 1.1 units ($p<0.0001$) and fresh frozen plasma from 1.8 units to 0.8 units ($p<0.0001$). Despite of the cell salvage product availability there were no significant differences between the groups in amount of homologous red blood cells transfused directly after the cessation of bypass. However, the cell salvage product transfused in the Intensive Care Unit significantly ($p=0.02$) diminished use of homologous red blood cells. Therefore, we concluded that consequent minimization of the bypass circuit was extremely effective in reduction of homologous blood

products transfusion requirements. Cell salvage product from residual volume reduced homologous blood transfusion in the postoperative period, but intraoperatively, had no effect on allogeneic transfusion demand.

Chapter 4 presents the results of the prospective non-randomized study undertaken as the continuation of the retrospective audit described in Chapter 3. The impact of intraoperative cell salvage on the allogeneic blood products transfusion requirements in infant patients undergoing cardiac surgery with cardiopulmonary bypass was studied in two consecutive cohorts (122 patients). The first cohort underwent between January 2004 and July 2005 procedures with only blood salvage from the residual volume. The second cohort consisted of patients operated on from August 2005 until December 2006, with additional use of intraoperative cell salvage. Additional intraoperative cell-salvage significantly enhanced the amount of cell saving product available for transfusion (183 ± 56 vs. 152 ± 57 mL, $p = 0.003$) and significantly more patients received the cell saving product postoperatively. We did not observe any adverse effects of intraoperative cell-salvage. Accordingly, we stated that intraoperative cell-salvage, employed as an adjuvant technique to the residual volume salvage in infants undergoing first time cardiac surgery with cardiopulmonary bypass, was a save method of reducing the use of allogeneic blood in postoperative period, but was not cost effective.

Chapter 5 summarizes in a retrospective analysis the effect of stepwise miniaturization of the cardiopulmonary bypass circuit on homologous blood requirement during neonatal and infant cardiac surgery. All patients, between 1 to12 months of age and weighing less than 10 kg, who underwent an elective first time open heart operation at the Erasmus MC, between January 1997 and July 2008, were included in the study. Our results demonstrate that consequent reduction of the circuit size was a right step towards the transfusion – free cardiac surgery. By downsizing the oxygenator and reducing the circuit tubing length, we significantly reduced the priming volume and subsequently the total use of blood. The incidence of homologous blood transfusion in the priming was decreased from 100% to 94% and during the bypass from 100% to 80%. Still, there were additional measures needed to obtain asnguineous cardiopulmonary bypass for neonatal and infant patients.

Chapter 6 reflects upon the most relevant requirements for success of asanguineous neonatal and infant cardiopulmonary bypass: an acceptable level of hemodilution during the bypass, the preoperative patient hematocrit value and the volume of cardiopulmonary bypass circuit. It presents an assessment of practical measures that were adapted in our institution to achieve an asanguineous CPB for neonatal and infant patients. The reduction of the prime volume together with an adequate level of hemo-

dilution during the bypass are simple and safe techniques to reduce allogeneic blood transfusion in neonatal and infant open heart surgery. Adherence to institutional guidelines and multidisciplinary efforts undertaken in the pre- and postoperative period are of a great importance concerning the bloodless CPB and should be seriously pursued by all involved caregivers.

Chapter 7 contains the results of the clinical and laboratory data audit that was performed to identify the risk factors for low colloid osmotic pressure at the end of cardiopulmonary bypass. Data of 73 consecutive infant patients with body weight less than 10 kg, who underwent elective, first time open heart surgery between March 2005 and December 2006 were examined. Univariate and multivariate analysis of risk factors for low colloid osmotic pressure (< 15 mmHg) was performed. Forty-eight percent of patients had low colloid osmotic pressure at the end of bypass. The significant univariate predictors of low oncotic pressure at the end of bypass were: lower patient weight, lower oncotic pressure before start of bypass, lower priming oncotic pressure and larger volume of cardioplegia received into the circulation. After multivariable analysis lower patient's oncotic pressure before bypass remained the only significant predictor for low oncotic pressure at the end of bypass.

Therefore, pre-bypass crystalloid dilution during induction should be avoided as this is the most important cause of low oncotic pressure during the bypass. Oncotic pressure of the priming and management strategy during the bypass should be adapted to the individual patient demand.

Chapter 8 continues the subject of oncotic pressure regulation during the neonatal and infant cardiopulmonary bypass. In neonatal and infant cardiac surgery with cardiopulmonary bypass hemodilution with reduction of plasma albumin concentration and low colloid oncotic pressure are the main factors associated with tissue edema and postoperative weight gain. The aim of this study was to evaluate the influence of two different oncotic pressure regulatory strategies on post bypass body weight gain, fluid balance and clinical outcomes.

The oncotic pressure regulatory strategy for neonatal and infant cardiopulmonary bypass, based upon the 5% concentration of albumin in the priming and a pressure target at 18 mmHg during the bypass, better preserved the plasma albumin concentration within the physiological range and stabilized the colloid pressure than the standard strategy (0.5 g/kg albumin in the priming, bypass pressure target at 15 mmHg). Nevertheless, to ameliorate the outcome of neonatal and infant cardiopulmonary bypass the clinical relevance of these results should be further investigated in relation to the inflammatory response mechanisms.

Chapter 9 provides the information about the study results related to the glycemia control during pediatric cardiac surgery for congenital heart diseases. Many studies are reporting that the occurrence of hyperglycemia in the postoperative period is associated with increased morbidity and mortality rates in children after cardiac surgery for congenital heart disease. This study sought to determine blood glucose levels in standard pediatric cardiac anesthesiological management without insulin infusion. The study population consisted of 204 consecutive pediatric patients aged from 3 days to 15.4 years undergoing open cardiac surgery for congenital heart disease between June 2007 and January 2009. Younger age, lower body weight and lower cardiopulmonary bypass temperature were associated with hyperglycemia at Intensive Care Unit arrival, as well as were higher pre - bypass blood glucose level and higher RACHS and Aristotle severity scores. A conventional (no insulin, no glucose) anesthetic management seems sufficient in the vast majority of patients (95%). Still, intensive monitoring is indicated, especially in small neonates with complex congenital heart surgery, in whom insulin treatment may be contemplated.

Chapter 10 contains the discussion and conclusions to this thesis.
The findings of this thesis were that minimization of the circuit together with the avoidance of allogeneic blood during the cardiopulmonary bypass showed a positive impact on postoperative course in the neonates and infants undergoing cardiac surgery. In the future, the pursuit for asanguineous neonatal and infant CPB will be continuing. With involvement of industrial partners, technological progress can be easily achieved. Still, the further optimization of collaboration between all professionals involved in the multidisciplinary effort of cardiopulmonary bypass should be an additional goal of improvement and should receive the required attention.

SAMENVATTING

Hoofdstuk 1 bevat de inleiding van dit proefschrift en beschrijft innovatie van cardiopulmonale bypass (CPB) als een continu proces van kwaliteitsverbetering. Specifieke aspecten van CPB die de focus van dit proefschrift vormen, worden toegelicht, alsmede de nieuwste innovaties om de schadelijke effecten van de CPB te verminderen.

Hoofdstuk 2 vergelijkt de klinische resultaten tussen twee groepen van pediatrische patiënten, geopereerd met korte aorta occlusietijden met milde versus matige hypothermie tijdens de CPB. Hoewel matige koeling van 28 °C tijdens CPB algemeen werd geaccepteerd binnen de hartchirurgie, suggereerden verschillende studies dat normotherme bypasstechnieken of milde hypothermie de klinische uitkomsten voor patiënten mogelijk verbeteren. Om het effect van de bypasstemperatuur management strategie op klinische uitkomsten te bestuderen bij pediatrische patiënten, die een correctie van ventrikelseptumdefect ondergaan, werden 26 patiënten met een lichaamsgewicht onder de 10 kg toegewezen aan een van twee behandelgroepen: Groep 1, lichte koeling tot een nasofaryngeale temperatuur van 32 °C tijdens de bypass, of Groep 2, matige koeling van 28 °C. Hematologische parameters na het beëindigen van CPB en na protamine toediening toonden een significant langere geactiveerde partiële tromboplastinetijd in Groep 1, maar het verschil in bloedverlies tussen de groepen was niet significant. Conclusie van deze studie is dat beide perfusietemperaturen adequate condities voor uitvoering van de cardiopulmonale bypass faciliteren, voor dit type van intracardiale chirurgie.

Hoofdstuk 3 evalueert de effecten van reductie van het cardiopulmonale bypass circuit en het bewerken van het CPB circuit restvolume, op allogene transfusiebehoefte van zuigelingen die hartchirurgie ondergaan. In deze retrospectieve observationele studie werden 148 opeenvolgende zuigelingen tussen 1 tot 12 maanden oud en met een lichaamsgewicht van minder dan 10 kg werden geincludeerd. Alle patiënten ondergingen een electieve hartoperatie tussen 1997 en 2005. Patiënten werden verdeeld over drie groepen, afhankelijk van het circuitvolume dat werd gebruikt tijdens de operatie; 700 ml (Groep 1), 450 ml (Groep 2) en 330 ml (Group3). In Groep 1 werd het restvolume na perfusie volledig verwijderd terwijl in Groep 2 en 3 het restvolume werd verwerkt in het autologe bloedtransfusie-apparaat. De vermindering van het volume van het circuit was geassocieerd met een aanzienlijke reductie van transfusie van homologe bloed producten in de priming en tijdens de bypass: Totaal gebruik van rode bloedcellen concentraat tijdens operatie daalde van gemiddeld 1,9 eenheden naar 1,1 eenheden ($p < 0,0001$) en van vers ingevroren plasma van 1,8 eenheden naar 0,8 eenheden ($p < 0,0001$). Ondanks de beschikbaarheid van het autologe product waren er geen signifi-

cante verschillen tussen de groepen in de hoeveelheid van homologe rode bloedcellen transfusie direct na de beëindiging van CPB. Echter, autologe product transfusie in de Intensive Care Unit was geassocieerd met significant minder gebruik van homologe rode bloedcelproducten. Geconcludeerd werd dat minimalisering van het cardiopulmonale bypass circuit zeer effectief was in het verminderen van de behoefte aan homologe bloedproductentransfusies. Het autologe product uit restvolume verlaagt homologe bloedtransfusie in de postoperatieve periode, maar intra-operatief had het geen effect op de allogene transfusie vraag.

Hoofdstuk 4 bevatte prospectieve niet-gerandomiseerde studie die werd verricht als voortzetting van de retrospectieve audit beschreven in hoofdstuk 3. De impact van intraoperatieve autologe bloedbewerking op de allogene bloedproducten transfusie behoefte van de patiënten die hartchirurgie met CPB hebben ondergaan werd onderzocht in twee opeenvolgende cohorten (totaal 122 patiënten). Het eerste cohort onderging tussen januari 2004 en juli 2005 procedures met alleen cel-salvage van het restvolume. Het tweede cohort bestond uit patiënten geopereerd vanaf augustus 2005 tot december 2006, met extra gebruik van intraoperatieve autologe bloedbewerking techniek. Aanvullende autologe bloedbewerking was geassocieerd met een significant hoger volume van het autologe product beschikbaar voor transfusie (183 ± 56 versus 152 ± 57 ml, p = 0,003); aanzienlijk meer patiënten ontvingen het autologe product postoperatief. Er werden geen nadelige gevolgen gevonden als gevolg van de intraoperatieve bloed bewerkingstechniek. Daarom werd geconcludeerd dat intraoperatieve autologe bloedbewerking, toegepast als een adjuvante techniek op de bloedbewerking van het restvolume uit de CPB circuit, een veilige methode is om het gebruik van allogene bloedtransfusie in de postoperatieve periode te verminderen. Deze methode bleek helaas niet kosteneffectief.

Hoofdstuk 5 betreft een retrospectieve analyse van het effect van stapsgewijze miniaturisatie van CPB circuit op homoloog bloed gebruik tijdens hartchirurgie van neonaten en zuigelingen. Alle patiënten, tussen 1 tot 12 maanden oud en met het lichaamsgewicht minder dan 10 kg, die een electieve primaire open hartoperatie in het Erasmus MC ondergingen tussen januari 1997 en juli 2008, werden in de studie opgenomen. Onze resultaten tonen aan dat reductie van het CPB circuit, een goede stap is richting de transfusie – vrije hartchirurgie. Door de keuze van de kleinste oxygenator en het reduceren van de lengte van CPB circuitlijnen, wordt een significante vermindering van het vulvolume bereikt en een vermindering van het totale bloedgebruik. De incidentie van homologe bloedtransfusie in de priming werd verlaagd van 100% naar 94%, en tijdens de cardiopulmonale bypass van 100% naar 80%. Toch blijven aanvullende maat-

regelen nodig om bloedvrije cardiopulmonale bypass te verkrijgen voor neonatale en zuigelingen patiënten.

Hoofdstuk 6 beschrijft de meest relevante factoren voor succesvolle bloedvrije cardiopulmonale bypass bij kinderen die hartchirurgie ondergaan: een acceptabel niveau van hemodilutie tijdens de bypass, de waarde van preoperatief hematocriet van de patiënt, en het volume van de cardiopulmonale bypass circuit. Het presenteert een evaluatie van de praktische maatregelen die werden toegepast in onze instelling om een bloedvrije CPB bereiken voor neonatale en zuigelingen patiënten. De vermindering van het priming volume gekoppeld aan een adequaat niveau van hemodilutie tijdens de bypass zijn eenvoudige en veilige technieken om allogene bloedtransfusies te beperken. Naleving van de institutionele richtlijnen en multidisciplinaire inspanningen in de pre- en postoperatieve periode zijn van groot belang om bloedeloze CPB waar te kunnen maken en moeten serieus worden nagestreefd door alle betrokken zorgverleners.

Hoofdstuk 7 beschrijft de in ons instituut uitgevoerde audit van klinische- en laboratoriumgegevens die als doel had om risicofactoren te identificeren voor lage colloïd osmotische druk aan het eind van CPB in kinderen met een lichaamsgewicht van minder dan 10 kilo. Gegevens van 73 opeenvolgende pediatrische patiënten met een lichaamsgewicht minder dan 10 kg, die electieve, primaire open hartchirurgie ondergingen tussen maart 2005 en december 2006 werden onderzocht. Univariate en multivariate analyse van risicofactoren voor lage colloïd osmotische druk (<15 mmHg) aan het einde van CPB werd uitgevoerd. Achtenveertig procent van de patiënten had een lage colloïd osmotische druk aan het eind van CPB. De significante univariate voorspellers van lage osmotische druk aan het eind van CPB zijn: een lager lichaamsgewicht, een lagere osmotische druk voor aanvang van CPB, een lagere osmotische druk van de priming, en een groter cardioplegievolume. Na multivariate analyse, bleek de lagere colloid osmotische druk voor de bypass de enige onafhankelijke voorspeller voor een lage colloid-osmotische druk aan het eind van CPB. Derhalve dient pre-bypass kristalloïde verdunning tijdens de inductie te worden vermeden. Colloid-osmotische druk van de priming en de managementstrategie van colloid-osmotische druk tijdens de bypass dient aangepast te worden aan de individuele patiënt.

Hoofdstuk 8 borduurt voort op het onderwerp van colloid-osmotische druk regulatie tijdens de neonatale en zuigelingen CPB. Bij neonatale en zuigelingen hartchirurgie met cardiopulmonale bypass, zijn hemodilutie met een reductie van plasma albumine concentratie en een lage colloïd osmotische druk zijn de belangrijkste twee factoren die weefseloedeem en postoperatieve gewichtstoename voorspellen. Het doel van deze studie was om de resultaten te evalueren van twee verschillende colloid-osmotische

druk regulatie strategieën op post-CPB gewichtstoename, vochtbalans en klinisch eindresultaat. De colloid-osmotische druk regulatie strategie voor neonatale en zuigelingen cardiopulmonale bypass, gebaseerd op de concentratie van 5% van albumine in de priming en een osmotische druk target op 18 mmHg tijdens de bypass, resulteert in een betere handhaving van de plasma-albumine concentratie binnen de fysiologische grenzen en stabiliseert de colloïd druk beter dan de standaard strategie (0,5 g / kg albumine in de priming, druk target bypass bij 15 mmHg) . Desalniettemin, dient de klinische relevantie van deze resultaten verder te worden onderzocht in relatie tot de inflammatoire respons mechanismen, met het uiteindelijke doel om de klinische uitkomsten te verbeteren.

Hoofdstuk 9 betreft een studie naar bloedsuiker controle tijdens hartchirurgie voor aangeboren hartziekten bij kinderen. De literatuur suggereert dat het optreden van hyperglycemie in de postoperatieve periode is geassocieerd met een verhoogde morbiditeit en mortaliteit bij kinderen na een hartoperatie voor aangeboren hartafwijkingen. De studie beschreven in hoofdstuk 9 onderzocht de bloedsuikerspiegel tijdens standaard pediatrisch cardio - anesthesie management zonder insuline-infusie. De onderzoekspopulatie bestond uit 204 opeenvolgende pediatrische patiënten in de leeftijd van 3 dagen tot 15,4 jaar die een open hart chirurgie voor aangeboren hartafwijkingen ondergingen tussen juni 2007 en januari 2009. Jongere leeftijd, een lager lichaamsgewicht en een lagere cardiopulmonale bypass temperatuur waren geassocieerd met hyperglycemie bij aankomst in de Intensive Care Unit, evenals hogere pre - bypass bloedsuikerspiegels en hogere RACHS en Aristoteles scores. Conventioneel (geen insuline, geen glucose) anesthesie management lijkt voldoende in de overgrote meerderheid van de patiënten (95%). Desalniettemin is intensieve monitoring aangewezen, met name in kleine neonaten die een complexe aangeboren hartoperatie ondergaan, en bij wie behandeling met insuline kan worden overwogen.

Hoofdstuk 10 bevat de discussie en conclusies van dit proefschrift. De belangrijkste bevindingen van dit proefschrift zijn dat minimalisatie van het circuit samen met het vermijden van allogene bloed tijdens de cardiopulmonale bypass een positief effect hebben op het postoperatieve beloop in de pasgeborenen en zuigelingen die cardiale chirurgie ondergingen. In de toekomst zal het nastreven van bloedloze neonatale en zuigelingen CPB verder worden voortgezet. Met betrokkenheid van de industriële partners kan de technologische vooruitgang gemakkelijk worden bereikt. Essentieel is de verdere optimalisatie van de samenwerking tussen alle professionals betrokken bij de multidisciplinaire inspanning, om uiteindelijk een optimaal CPB beleid te realiseren, dat is toegespitst op de individuele eigenschappen van de patiënt.

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During the writing of the thesis I often thought about my professional "past and present" and many different situations and people that influenced my career. Some of those people were very helpful and stimulated me to pursue my scientific goals, some were discouraging and always negatively critical and the others were merely indifferent. Nevertheless, I am very thankful to all of them. The interaction with them taught me to ask the right questions and looked for the adequate answers and solutions.

To me, the scientific involvement means to understand the surrounding world, to search for the significant patterns in it and to use the acquired knowledge for solving the problems. Because of that I appreciate contact and interaction with all living creatures and nature elements throughout my whole life.

This thesis is the product of a teamwork that facilitated all clinical research. Therefore, I would like to express my gratitude to all cardiac surgeons, anesthetists, perfusionists, personnel of an Operation Room and Intensive Care Unit for their cooperation during the various studies.

However, the names of two special persons, who played the key role in the performing of the studies and writing of the thesis, must be individually mentioned.

I would like to thank my promoter Prof. Ad Bogers for asking me to consider the option of the thesis writing. He ignited the spark. Without his enduring support and counsel in the whole process I would not have been able to reach the finish so straightforward.

To my co-promoter, Hanneke Takkenberg, I am grateful for her advice, comments and help with all the publishing work.

Although, this thesis may be seen as a final achievement in my scientific career, I still expect in the future an opportunity to perform more research work to improve the quality of pediatric crdiopulmonary bypass.

CURRICULUM VITAE

Hanna Dorota Golab (maiden name: Schwarz) was born on 9th November 1956 in the industrial city of Gliwice in the south of Poland. After finishing primary school she continued her education at the 2nd Liceum in Gliwice, where above the general courses she took the facultative ones in mathematic, physic and biology. Having past the final examination "cum laude" she was awarded the free entrance to any polish university of her choice. As she was hesitating between the biology studies or mathematics, the decision to study bio – electronics with specialization in medical electronic devices was a logical one. In 1980 she obtained her Master of Science Degree in Electronics and graduated as a certified Engineer at the Silesian University of Technology in Gliwice. Her graduation work was related to the Doppler measurements of the blood flow in the blood vessels. This field of the interest brought her in contact with the medical professionals and a clinical research. She started her employment as an engineer in the Thoracic and Vascular Surgery Department of University Hospital of Silesian Medical University in Zabrze and afterward she moved to the department of Cardio - Thoracic Surgery of the same hospital. From the beginning, she was involved with the development and utilisation of extracorporeal circulation systems, at first as a technical specialist and gradually as a perfusionist. She followed "in service" perfusion education in Poland, and additionally she took the scholarships in England and the Netherlands. In 1986 she was a member of the team of Prof. Z. Religa that performed the first human heart transplantation in Poland.

Since 1988 till present she works in the Department of Cardio-Thoracic Surgery of Erasmus MC, University Hospital of Rotterdam, in the position of certified clinical perfusionist and scientific researcher. In 1990 she was certificated as an "Erkend Klinisch Perfusionist" by the Dutch Society for Extracorporeal Circulation (NeSECC). The certification was based upon the research study"Clinical comparison on arterial line filters: Bently 1025 C and Swank HF 6000 used during cardiopulmonary bypass for CABG operations." In 1996 the Dutch Hospitals Association (NVZ) and the European Board of Cardiovascular Perfusion registered her as a Clinical Perfusionist.

She is an active member of the NeSECC and between 2002 and 2006 she chaired the Scientific Committee of this perfusion organisation. From 1995 till present she teaches the subjects of perfusion technology at the national Perfusion Education Program in LUMC in Leiden.

LIST OF PUBLICATIONS

1. Golab HD, Scohy TV, Jong de PL, Kissler J, Takkenberg JJM, Bogers AJJC. Relevance of colloid oncotic pressure regulation during neonatal and infant cardiopulmonary bypass: a prospective randomised study. Eur J Cardiothorac Surg. 2010; Nov 3. [PMID: 21055963]
2. Scohy TV, Golab HD, Egal M, Takkenberg JJM, Bogers AJJC. Intraoperative Glycemic Control during Pediatric Cardiac Surgery for Congenital Heart Disease: Does it really make a difference? Pediatric Anaesthesia 2010; submitted
3. Golab HD, Takkenberg JJM, Bogers AJJC. Specific requirements for bloodless cardiopulmonary bypass in neonates and infants; a review. Perfusion. 2010; 25: 237-43
4. Golab HD, Bogers AJ. Small, smaller, smallest. Steps towards bloodless neonatal and infant cardiopulmonary bypass. Perfusion 2009; 24: 239-42
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11. Golab HD, Bos E, Quaegebeur J, Hess J, Wijers MJ. Clinical experience in the Low-Flow perfusion technique for neonates. Proceedings of 4th European Congress on Extra-Corporeal Circulation Technology, Noordwijk June 1991
12. Golab HD. Clinical comparision on arterial line filters Bentley 1025C and Swank HF 6000 used during CPB for CABG operations. The NeSECC Journaal 1990; 3: 16- 19

13. Gołab K, Gołab H, Dobosz J. Ultrasonic evaluation of blood flow in arteriovenous fistulas for the purpose of hemodialysis. Wiad Lek. 1984; 37:1665-8, (in Polish)
14. Schwarz H, Wos S, Bochenek A. Diagnostic value of ultrasonic methods used in peripheral vascular diseases. Polski Przeglad Chirurgiczny 1982; 11: 817-822 (in Polish)

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Golab Hanna Dorota
Erasmus MC Department: Cardiothoracic Surgery
Research School: COEUR

PhD period: 2006 - 2010
Promotor(s):Prof. dr. A.J.J.C. Bogers
Supervisor: Dr. J.J.M. Takkenberg

1. PhD training	Year	Workload Hours/ECTS
General courses		
- PAOG Erasmus "Effective presentation in English"	5 en 11.11.1998	20
- PAOG Erasmus" How to write a readable scientific article"	10.03 -29.04.1998	40
- PAOG Erasmus "Statistic methods in health sciences"	21.11 – 12.12.1998	20
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek'	10 - 14.11.2008	40
- LUMC "Training competentiegericht onderwijs geven"	16.05.2008	10
- LUMC "Cursus werkbegeleiding voor klinisch perfusionisten"	14 -15.02.2001	20
Specific courses (e.g. Research school, Medical Training)		
- COEUR : Congenital Heart Disease	05 - 06.02.2009	1.5
- COEUR: Intensive Care Research	17 - 18.09.2009	1.5
- Righospitalet European Pediatric Perfusion Course, Kopenhagen	27 - 28.11.2008	1.5
-		
Seminars and workshops		
- COEUR :Tetralogy of Fallot	25.01.2008	0.4
- COEUR: Surgical and percutaneous aortic valve implantation; indications, techniques and follow-up	30.01.2009	0.4
- Pediatric Perfusion Workshop , Munchen	22 - 23.10.2010	1
- Symposium "Over hartkleppen en hartpompen", Utrecht	10.09.2009	0.4

1. PhD training	Year	Workload Hours/ECTS
Presentations		
- "Effects of cardiopulmonary bypass circuit reduction, residual volume salvage and intraoperative cell salvage on allogeneic transfusion requirements in infants undergoing cardiac surgery." 10th International Cardio-surgical meeting in Gdansk	18.01.2008	3
- "Small, smaller, smallest; relevance of cpb circuit downsizing for neonates and infants". Themadag Kinderhartchirurgie Opleiding tot Klinisch Perfusionist, Leiden	05.10.2009	3
- "Bloodless cardiopulmonary bypass for neonates and infants; state of the art in cardiovascular perfusion" NeSECC 35th Anniversary Jubilee Symposium, Nunspeet	05.02.2011	3
(Inter)national conferences		
- 12th International Symposium on perfusion, Brussels	02.10.2010	1
- 5 International Conference Pediatric Mechanical Circulatory Support Systems and Pediatric Cardiopulmonary Bypass, Dallas	27 - 30.05.2009	1
- Onderwijsconferentie "Over meesters en gezellen; vakbekwaamheid in praktijk", LUMC	24.05.2009	1
- Wetenschappelijke bijeenkomst NeSECC "Cardiac assist", Amsterdam	15.05.2009	1
- 10th International Cardio surgical meeting in Gdansk	18 -19.01.2008	1
- 11th International Symposium on perusion, Brussels	18.10.2008	1
- Wetenschappelijke bijeenkomst NeSECC "Opleiding en juridische aspecten van het vakgebied van de klinisch perfusionist", Leiden	24.11.2007	1
- Wetenschappelijke bijeenkomst NeSECC "Reductie van donorbloedgebruik in de cardiochirurgie", Breda	21.04.2007	1

1. PhD training	Year	Workload Hours/ECTS
- Wetenschappelijk bijeenkomst NeSECC "Gebruik van de antifibrinolitica tijdens CPB; de plaats van aprotinine." Nieuwegein	07.06.2006	1
- The 30th Anniversary Internarional Symposium NeSECC, Ermelo	04 - 05.02.2006	1

2. Teaching	Year	Workload Hours/ECTS
Lecturing		
- Teacher "Opleiding tot Klinisch Perfusionist", Directoraat Onderwijs en Opleidingen, LUMC	1996 – present	30/y
- Teaching activities "Opleidingsinstituut Erasmus MC" Nursing School.	2000 – present	10/y
- Teaching 3rd year medical students (minor Congenital Cardiology Erasmus MC)	2010	5
Supervising practicals and excursions, Tutoring		
- Practical supervisor of perfusionists in training in Erasmus MC	1995 - present	50/y
Supervising Master's theses		
- Supervisor of research project and final research paper for the School of Clinical Perfusionists, LUMC	1995 - present	16/y
Other		
- Reviewer "European Journal of Cardiothoracic Surgery"	2007- present	1
- Reviewer "Interactive Cardio Vascular and Thoracic Surgery"	2007- present	0.6
- Reviewer "Perfusion"	2008 - present	0.6

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