Stepwise improvement of cardiopulmonary bypass for neonates and infants

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chapter 1

INTRODUCTION

The components of the cardiopulmonary bypass system, the prime volume and the techniques of perfusion are believed to have a significant impact on postoperative morbidity and even mortality in pediatric heart surgery. Complete repair of congenital heart defects is increasingly performed in neonates and small infants with a weight of ranging between two and five kilogram. The consequences of CPB are more pronounced because of the immaturity of their organs and the discrepancy between prime volume of the CPB system and patient blood volume. CPB results in a systemic inflammatory response syndrome (SIRS) [1]. SIRS is a nonspecific inflammation process that can lead to capillary leakage. Capillary leakage results in an extravascular fluid accumulation. When the extravascular fluid accumulation is severe the interstitial edema that occurs can lead to end organ dysfunction [1, 2]. The CPB system is seen as the main activator of the inflammatory response. However, several other factors play a role in the activation of the inflammatory response such as surgical trauma, thrombin activation, ischemia-reperfusion injury and blood-air contact [3-5]. The degree of hemodilution is another factor [6].

Miniaturization of all components of the bypass system leads to lower prime volumes, resulting in a reduced hemodilution factor [2, 5]. The extent of the dilution factor contributes to the capillary leakage due to complement activation. Böning et al. showed that a large prime volume leads to an increase in IL-6 production and tumor necrosis factor-α [6]. A Low prime volume results in less use of donor blood during and after CPB as the dilution factor affects postoperative blood loss ass well [7]. The disadvantages of donor blood are well known: the risk of virus and prion transfer, depression of the immune system, delayed haemolysis and the metabolic load, low pH, high glucose and potassium concentrations, of stored blood. It should be mentioned that also in fresh red blood cells (< 5 days) a low pH and a high glucose concentration is found [8]. This metabolic overload can be avoided by washing the donor red cells using a cell saver. Swindell et al. showed that washing of donor blood reduces potassium and lactate loads during CPB [9].

The aim of this thesis was to investigate several techniques or adaptations that were developed to reduce the deleterious effects of CPB in neonates and infants.

Ultrafiltration (UF) is widely used during and after CPB to reduce the total body water increase, to reduce the need for donor blood and to remove some inflammatory mediators [10, 11, 12]. There has to be a minimal volume in the venous reservoir to for optimal bloodflow; this limits the efficiency of UF performed during CPB. [10]. Zero-balanced ultrafiltration (Z-BUF) or dilutional ultrafiltration (DCUF) is developed especially to remove some proinflammatory mediators during CPB; fluid is added to the venous reservoir continuously [11, 13].
Modified ultrafiltration (MUF) is a technique described for the first time in 1991 by Naik and Elliott [10]. MUF was especially developed to diminish the effects of hemodilution thereby increasing hemoglobin and hematocrit values without the use of donor blood. MUF permits the return of the concentrated residual volume of the CPB system. MUF is performed after cessation of CPB, but before the administration of protamin. There are several techniques to perform MUF, arterial-venous, venous-venous or venous-arterial [14]. The arterial-venous method has the preference above the other techniques because warm oxygenized blood is presented to the lungs. This results immediately to a decrease in pulmonary vascular resistance and stabilizes hemodynamic conditions during the MUF procedure [15]. Other reported effects of MUF are an immediate rise in systolic blood pressure, improved ventricular function, as well as a decreased need for blood transfusion due to an increase of hematocrit and a decrease of postoperative bleeding [16].
We studied a group of 198 patients retrospectively on the effects of MUF on donor blood use and postoperative blood loss. We investigated whether MUF was able to reduce the use of donor blood and the influence of MUF on postoperative chest drain loss. This study is presented in chapter 2.

In chapter 3 and 4 we describe the anti-oxidative capacity of the CPB prime used for neonates. Pyles et al. described a decrease of the antioxidant capacity of plasma after CPB in children [17]. It has been reported that neonates and infants have a poor antioxidative capacity and a low iron binding capacity [18]. Transfusion of a relatively

small volume of fluid with a low antioxidant capacity decreases the ability of the plasma to catabolize reactive oxygen species [19]. Because of the relative large prime volume of the bypass system compared to the circulating volume of the patient, the composition of the prime therefore may play an important role in increasing the anti-oxidative capacity and thereby preventing reactive oxygen species (ROS) formation. ROS activates nuclear factor – κB, which is an important protein in the regulation of the acute phase response of inflammation. Nuclear factor – κB stimulates the production of, among others, IL-1, IL-6, and tumor necrosis factor-α [20]. We compared in vitro two different prime compositions, one prime solution based on human albumin and second prime solution based on fresh frozen plasma. Of both primes the total antioxidant capacity, as well as that of selected individual antioxidants was measured. We also measured the release of the important prooxidants non-protein bound iron and Hb/haem in both primes.

The CPB system is believed to be the main activator of the SIRS. Coatings of the different components of the bypass system are developed to reduce the contact activation between blood and the surface of the bypass system. Several coatings are commercially available: human albumin coating, heparin coatings, trillium coating and phosphorylcholine coating. A lot of controversies are found in the literature concerning coating of CPB systems. It is difficult to compare the different studies because of the differences in methods and composition of the study groups. In several studies children with a bodyweight of less then 5 kilogram are compared to children weighing more than 15 kilograms. Furthermore different coatings are used and the measured parameters are numerous. All over it appears that most coatings preserve platelets but do not completely inhibit the inflammatory response [21]. This is due to the fact that the CPB system is only one of the many triggers of the inflammatory response. Children undergoing major heart surgery without CPB compared with children undergoing heart surgery with the use of CPB are showing a simulair SIRS reaction [4]. The results of our prospective blind randomized study comparing uncoated to PHISIO® coated CPB systems in neonates and infants with very strict inclusion criteria on bodyweight, cyanoses and syndromes are described in chapter 5.

There is lack of information as to the interaction between the coating of the CPB system and medication. Mehta and colleagues describe the loss of several medications during time in an in vitro extracorporeal membrane oxygenation circuit [22].
The use of corticosteroids in pediatric cardiac surgery is controversial. Corticosteroids are sometimes used in pediatric cardiac surgery to reduce the pro-inflammatory mediators. The timing of administration seems to be important [23]. When corticosteroids are given before start the of CPB and during CPB, the concentration of proinflammatory cytokines has been reported to decrease [24]. For this reason corticosteroids are added to the prime in the same amount as the quantity that is given intravenously to the patient. We investigated whether dexamethasone concentration decreased during recirculation of the prime in an in vitro setting both with coated and with uncoated systems. The results are described in chapter 6.

Many of the questions that are described in this introduction section are also discussed in chapter 7 (review article).

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