Development of a Model for Albumin Priming in Pediatric Cardiopulmonary Bypass Circuits

by

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Abstract

Albumin is a plasma protein that is present in the native circulation of all humans, and plays a critical role in maintaining blood pressure through the colloid osmotic pressure (COP) it exerts within blood vessels. During cardiothoracic surgery, it is common practice to add albumin to the cardiopulmonary bypass circuit prime in an attempt to reduce the drop in colloid osmotic pressure of the circulation. While this is inarguably important, a universal protocol for finding the appropriate amount of albumin to add does not exist. The purpose of this project was to develop a model for the addition of albumin in the cardiopulmonary bypass circuits of pediatric patients, based on theoretical calculations and current clinical evidence.

This project began with an investigation as to the relationship between outcomes and albumin concentration in a cardiopulmonary bypass prime solution. Literature was reviewed that was both current and relevant to pediatrics, cardiopulmonary bypass circuit priming, albumin, colloid osmotic pressure, and edema. After a thorough exploration of the literature and accompanying data, it was evident that the need for an appropriate albumin concentration was supported, and the development of such a protocol for it was pursued.

The end result of this project produced a set of equations, built into a spreadsheet-based calculator, that could be integrated into the practice of pediatric perfusion to determine the appropriate amount of albumin to be added into the cardiopulmonary bypass prime. The implementation of the equations and calculator is expected to result in better outcomes of the pediatric population after cardiothoracic surgery.

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Table of Contents

List of Figures

List of Tables

1. Introduction

In the field of cardiac surgery, cardiopulmonary bypass is necessary for the majority of the procedures performed. Cardiopulmonary bypass involves connecting the circulation of a patient to an extracorporeal circuit that will assume the function of the heart and lungs for the duration of surgery. Prior to being connected to the patient's systemic circulation, the cardiopulmonary bypass circuit must be primed with a solution that will mix with the patient's blood at initiation of cardiopulmonary bypass. This is typically done with an isotonic crystalloid fluid, such as lactated Ringer's solution or PlasmaLyte, along with certain additives that are intended to minimize the physiologic disturbance to the patient. These additives typically include heparin, mannitol, sodium bicarbonate and albumin. Although each of these has their role and recommended dose, the role and dose of albumin is strongly debated.

Albumin is a naturally occurring plasma protein within the human body that is critical with regard to the maintenance of colloid osmotic pressure and transport compounds. It is added to the prime of a cardiopulmonary bypass circuit in an attempt to attenuate the drop in colloid osmotic pressure (COP) that would otherwise occur when the patient's circulating blood volume is diluted by the crystalloid prime volume [1]. If a significant drop in colloid osmotic pressure were to occur, it would result in a large fluid shift from the intravascular space into the interstitial space [1]. This fluid shift results in edema, and has been shown to lead to more severe outcomes, such as postoperative organ edema and dysfunction [1, 2, 3], extravascular lung water [1, 2, 4], and weight gain [5, 6,

7]. It can therefore be predicted that a deficit in circulating albumin would result, to some degree, in these adverse outcomes.

The practice of adding albumin to the prime of the perfusion circuit is still debatable, and the amount of albumin to add is vague. Cost, unknown efficacy, and widely varying patient parameters, such as blood volume and patient albumin concentration, complicate the potential for a universal practice of adding albumin to each prime. The potential for a universal practice is even further complicated in pediatric cases, where circuit volumes are proportionally much greater than patient blood volumes, creating a threat of extreme dilution of blood, as well as albumin. Pediatric patients also have a greater vascular permeability, and they often require hypothermia during cardiopulmonary bypass. All of these factors provide reason as to why an albumin dosing protocol in pediatrics is so complicated and simultaneously also so critical. The goal of this project was to explore the importance of albumin in a pediatric circuit prime, and attempt to develop a comprehensive model for albumin dosing in the priming of pediatric cardiopulmonary bypass circuits.

2. Background

2.1 Role of Albumin in the Body

Albumin is the most abundant plasma protein in the human body, comprising 60% of the total protein content of plasma [8]. It provides many crucial physiological functions, including maintaining colloid osmotic pressure, and transporting hormones, fatty acids, bilirubin, calcium, and drugs [9]. Albumin is synthesized in the liver at a rate of about 0.2 grams per kilogram of body weight per day. The concentration of albumin in plasma of healthy adults ranges from 3.3 to 5.2 grams per deciliter, and there is a net balance between its synthesis and metabolism in the human body [9]. Extravascular colloid osmotic pressure in the liver regulates albumin synthesis, and the rate of metabolism is regulated by the plasma albumin concentration [10]. Albumin synthesis has been found to only increase two to threefold in times of maximum stimulus [10]. Normally, 40% of albumin is in the intravascular space, and 60% of albumin is in the extravascular space; however, the extravascular space contains much more volume than the intravascular space, and therefore, counterintuitively, has a lower concentration of albumin [8, 9]. Albumin normally does not permeate the endothelial barrier due to its large size (66,248 daltons), although any albumin that does leave the capillary is returned to the circulation via the lymphatic vessels [11, 12].

Arguably the most important function of albumin is to maintain colloid osmotic pressure, also referred to as oncotic pressure. Colloid osmotic pressure is the pressure exerted by plasma proteins (notably albumin) in the intravascular space, that tends to shift fluid out of the capillary and into the interstitial space [13, 14]. Colloid osmotic pressure

is one of the four Starling forces that together determine fluid movement across a capillary membrane (Table 1). The other Starling forces are hydrostatic pressure, interstitial fluid pressure, and interstitial fluid colloid osmotic pressure (Figure 1)[13, 15]. Together, these four pressures result in a net filtration pressure, which indicates the direction that fluid movement is driven [13, 15]. Net filtration pressure may be negative, indicating movement of fluid from the interstitial space into the capillaries, or positive, (indicating movement of fluid from the capillaries into the interstitial space) [14, 15]. Under typical conditions, the net filtration pressure is slightly positive [14].

Table 1: The Four Starling Forces [14].

	Hydrostatic Pressure	**Interstitial Fluid Pressure**	**Plasma Colloid Osmotic Pressure**	**Interstitial Fluid Colloid Osmotic Pressure**
Average value, mmHg	17.3	3.0	28.0	8.0
Fluid movement	Out of the vasculature	Into the vasculature	Into the vasculature	Out of the vasculature
Determined by	Blood pressure	Interstitial fluid and tissue compliance	Albumin and globulins	Albumin and other proteins

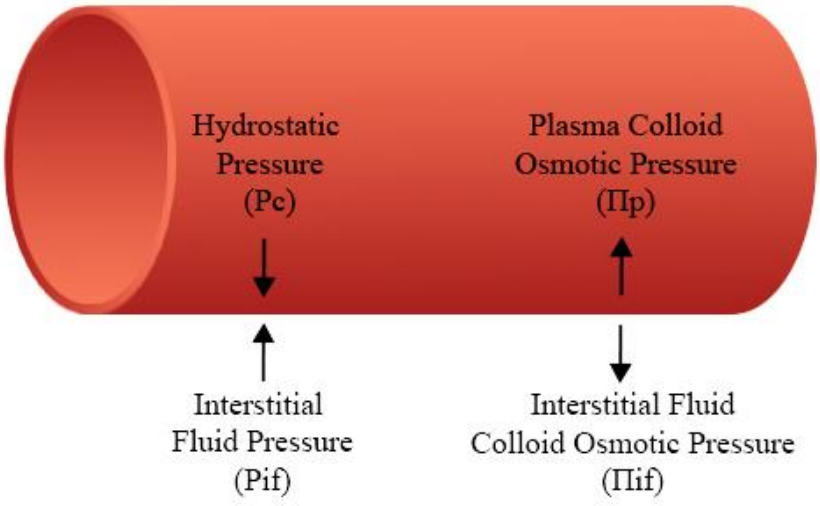

Figure 1: A Depiction of the Four Starling Forces.

Plasma colloid osmotic pressure is determined by the molecules or ions that are unable to pass through the pores of a capillary membrane. It acts to pull fluid out of the interstitial space, and into the intravascular space, and it is opposed by the colloid osmotic pressure of the interstitial fluid [15]. In healthy adults, the colloid osmotic pressure is approximately 28 mmHg, although some literature suggests that albumin can reach as low as 22 mmHg in healthy adults [16]. Albumin is responsible for approximately 80 percent of the plasma colloid osmotic pressure, while the remaining 20 percent of the plasma colloid osmotic pressure is provided by globulins, which are high molecular weight globular proteins [14]. A negligible amount of the plasma colloid osmotic pressure is created by fibrinogen, which is a glycoprotein that is converted into fibrin by thrombin and is essential for coagulation [14]. The contribution of each of these to the total COP is illustrated in Table 2.

Table 2: The Effect of Different Plasma Proteins on Colloid Osmotic Pressures [14].

	g/dL	Πp (mmHg)
Albumin	4.5	21.8
Globulins	2.5	6.0
Fibrinogen	0.3	0.2
Total	7.3	28.0

2.2 Low Albumin Levels Lead to Edema

The focus of this review is to define the importance of a proper albumin concentration, which directly correlates to an appropriate colloid osmotic pressure, and prevention of edema. By understanding the process of edema formation and the adverse results that follow, it becomes clear that maintenance of an appropriate albumin concentration is the most effective method in preventing edema formation.

Under normal physiologic conditions, there should be a minimal net movement of fluid into the extravascular space that the lymphatic vessels will return to the venous system [17]. However, in cases where there is a deficit or dilution in plasma proteins and the colloid osmotic pressure is compromised, or permeability of the capillary membrane is increased by inflammation, a greater fluid shift into the extravascular space is favored. When this fluid shift into the extravascular space is greater than normal, the lymphatic system cannot drain it appropriately, and edema results [13]. This is commonly seen during and after cardiopulmonary bypass, when there is a dilution of albumin resulting in a compromised colloid osmotic pressure, and the inflammatory response causes increased vascular permeability.

Edema is a concern because it is commonly associated with fluid loss from the vascular system, leading to decreased blood pressure and possibly underperfusion of tissues. This sequela challenges the fluid balance in these individuals, who need to take in fluid to replace that which is lost to the edematous tissue. Edema that develops within the pericardium or pleural space might also disrupt organ function, with serious consequences [18].

2.3 Human Albumin Preparations and Uses

Human albumin has been utilized clinically for over 60 years, for a variety of reasons [19]. It is typically prepared from pooled human plasma, which is then concentrated through an alcoholic precipitation process, and then pasteurized to at least 60°C for a minimum of 10 hours to inactivate pathogens [19]. Sodium octanoate and acetyltryptophan are added as stabilizers for this process [9]. Typically, 12.5 grams of albumin is mixed with saline, to make an iso-oncotic 5% solution (250 mL), or a hyperoncotic 25% solution (50 mL) [9]. These solutions are sold for use in cases of hypovolemia, hypoalbuminemia, and cardiopulmonary bypass priming, as described in the next section.

There are few contraindications for administering human albumin. One definite contraindication would be a patient allergy against the added stabilizers or solubilizing agent [9]. Hypervolemia is also a contraindication, as albumin increases intravascular volume and could risk fluid overload and subsequent hypertension [9]. Other

contraindications include pulmonary edema in the presence of congestive heart failure, and hypocoagulopathy resulting from dilution [9].

The pasteurization of albumin minimizes the risk of any possibility of transfusion reaction. Incidence of acute reactions to albumin infusions has been reported to be 1 in 6600, and the incidence of severe, or potentially life-threatening acute reactions has been reported to be 1 in 30,000 [8]. In 2004, Pillonel *et al.* estimated the risk of infection with human albumin to be as low as 1 in 325,000 [20]. In the 10 years between 1990 and 2000, 112 million units of albumin were transfused worldwide, with no reported fatalities due to albumin [12]. Therefore, the risk of transfusion is relatively low, and should not be considered significant enough to deter one from administering albumin to reduce dilution of albumin from the cardiopulmonary bypass prime.

Without the presence of any contraindications and minimal risk of transfusion reaction, perhaps the most prevalent deterrent for administering albumin is cost, as human albumin is the most expensive non-blood plasma substitute that may be used to treat hypovolemia [9]. The cost of albumin (both the 5% solution and the 25% solution) from three different hospitals was obtained (Table 3). These data provide an insight into the cost of albumin to the institution, as well as the amount that the patient is charged. Any perception that the cost of albumin is a discouragement to administering the full and appropriate amount is ill-considered, and potentially harmful to the patient. While the full cost of pediatric cardiac surgery varies widely, a 2014 publication by Pasquali *et al.* used data from 12,718 patients from 27 hospitals to report that the typical cost of a pediatric cardiac surgical procedure ranged from $25,499 for an atrial septal defect repair, to $165,168 for a Norwood procedure [21]. Relative to the total cost of surgery, the cost of

albumin is small and its potential benefits make it justified. Thus, cost should not be considered as a discouragement for adding albumin to the cardiopulmonary bypass prime.

Table 3: The Cost of Albumin Across Different Institutions [22, 23].

	Institution 1	Institution 2	Institution 3	Average
Cost to Institution				
25% albumin, 12.5 g unit	$44.90	$43.25	$43.55 $43.25*	**$43.74**
5% albumin, 12.5 g unit	$42.74	$41.00	$43.25*	**$42.33**
25% albumin, per gram	$3.59	$3.46	$3.48 $2.46*	**$3.25**
5% albumin, per gram	$3.42	$3.28	$3.46*	**$3.39**
Charge to Patient				
25% albumin, 12.5 gram unit	$233.79	$437.61	$370.71 $159.82*	**$300.48**
5% albumin, 12.5 gram unit	$176.52	$421.88	$157.67*	**$252.02**
25% albumin, per gram	$18.70	$35.01	$29.60	**$27.77**
5% albumin, per gram	$14.12	$33.75	$12.56*	**$20.14**

Note: * indicates price for a bag unit; the remaining amounts are for bag units.

Human albumin is utilized in medical practice for a variety of reasons, such as hypovolemia, hypoalbuminemia, and as a prime component for a cardiopulmonary bypass circuit. Hypovolemia, or a state of decreased blood volume, may be treated with albumin as it increases the colloid osmotic pressure, pulling volume from the interstitial space. Hypoalbuminemia (a concentration below 3.5 grams of albumin per deciliter) may

be caused by redistribution of albumin into the interstitial space or by catabolism, both of which are seen with sepsis, infection, and trauma [9].

In the practice of cardiac surgery, human albumin is vital and is utilized regularly in the cardiopulmonary bypass circuit prime. For circuits that are not coated with a biocompatible material such as heparin, blood contact causes activation of the inflammatory system, and further activation of platelets, the complement cascade, the clotting cascade, and cellular adhesion [24]. The addition of albumin in these circuits provides a coating, or layer, that reduces the activation and adhesion of platelets, as well as a decreased adsorption of fibrinogen [25]. The degree of this effect, however, remains unknown. In a study published in 2001, Boks *et al.* analyzed this effect, via the associated pressure drop across the membrane oxygenator. It was found that whether adding 2 grams of albumin (n = 20), 20 grams of albumin (n = 20), or no albumin (n = 20) to 1,600 mL of a colloidal prime, resulted in no statistical difference in oxygenator resistance or β-thromboglobulin levels (indicative of platelet activation) between groups [25]. Additionally, as will be discussed in Section 2.5, studies by Palanzo *et al.* and Myers *et al.* found a more preserved platelet count was achieved with an albumin prime than with a crystalloid prime.

With the effect of albumin on platelet activation and adhesion still not defined, and many manufacturers now precoating cardiopulmonary bypass circuits, the more significant reason for adding albumin to the prime is to maintain a normal colloid osmotic pressure of the patient upon initiation of bypass. Without the addition of albumin, the cardiopulmonary bypass circuit prime dilutes the plasma proteins of the circulation, greatly reducing colloid osmotic pressure, allowing movement of fluid out of the vascular

space and into the interstitial space. This movement has the potential to result in postoperative weight gain [5, 6, 7], pulmonary edema [1, 2, 4], and multiple organ dysfunction [2].

2.4 Specific Considerations for Use of Albumin in Pediatric Perfusion

While adults are susceptible to adverse effects from a hypo-oncotic cardiopulmonary bypass prime, pediatric patients present with an increased risk for severe adverse outcomes, as they are more prone to fluid shifts and edema. Factors that contribute to this increased sensitivity are pediatric physiology, hemodilution due to large circuit sizes, inflammatory response leading to increased vascular permeability, and hypothermia [18].

Pediatric patients have a slightly different physiology than adult patients, and thusly causes them to be sensitive to the effects of a hypo-oncotic cardiopulmonary bypass prime. These factors include an overall physiologic immaturity, increased metabolic demand, and a high vascular permeability. Their immature myocardium makes them more vulnerable to myocardial injury, especially in the face of their innate increased metabolic demand, which requires an increased cardiac index [26]. Their increased vascular permeability allows for fluid to shift into the interstitial space more easily, especially during times of low colloid osmotic pressure. These physiologic factors make a pediatric patient more prone to edema during bypass. It is also important to mention that pediatrics have a proportionally larger blood volume per weight than adults do. This higher proportional blood volume results in a higher blood volume per weight, and affects the total blood volume. This information is provided in Table 4.

Table 4: Blood Volume per Weight for Different Pediatric Patient Sizes [27].

Patient Weight (kg)	<10	11-20	21-30	31-40	>40
Blood Volume (mL/ kg)	85	80	75	70	65

Another difference between adult and pediatric perfusion is the extreme temperature manipulation typically utilized in pediatric surgery, due to the level of complexity that congenital defect repairs involve. Commonly, deep hypothermia with circulatory arrest is used. Such temperature changes imposed upon the human body are correlated with edema formation [28] via activation of the complement cascade and prompt leukocyte degranulation. Each of these results in endothelial injury, and therefore increased capillary permeability [28]. An increased capillary permeability allows for fluid to shift more easily into the interstitial space, especially in a low colloid osmotic pressure environment. Hypothermia also induces vasoconstriction and an increased viscosity of the blood, causing an increased hydrostatic pressure, and a higher tendency for fluid to be pushed through to the interstitial space [29].

Vascular permeability is also thought to be increased in pediatrics due to capillary leak syndrome, a phenomena where an immune response is elicited due to the trauma of surgery, exposure to the cardiopulmonary bypass circuit, and ischemic-reperfusion injury, resulting in vascular excavation and edema [30]. This sequelae is caused by an increase in cytokines and complement proteins, and activation of the clotting cascade, neutrophils, and endothelial cells, increasing the vascular permeability to macromolecules [30]. The

mechanism of capillary leak syndrome is still being investigated, and the significance of its effects are still debatable.

If albumin can cross the capillary wall during times of increased capillary permeability in children, it could actually potentiate edema and would greatly affect the strategy of maintaining serum albumin concentration. However, recent studies investigating edema after bypass have found that the interstitial edema consisted of fluid and electrolytes, and there was no increase in protein concentration of the interstitial space [31, 32]. In a 2002 study by Tassani *et al.*, albumin in the intravascular space of adults undergoing coronary artery bypass grafting with cardiopulmonary bypass was tracked using Evans blue dye, a dye which firmly binds to up to 1000 binding sites on albumin [31]. It was found that the escape rate (the rate at which a substance crosses between the endothelial cells of the capillary) of Evans blue dye (and consequently albumin) was not increased after bypass [31]. Tassani *et al.* published a similar study in 2007, tracking albumin extravasation with Evans blue dye in neonates, and again, there was no increase in the escape rate of Evans blue dye after bypass [32].

Perhaps the most relevant complication that arises with pediatric perfusion is the large size of a circuit's prime volume relative to the patient's blood volume, which can lead to hemodilution. While pediatric circuits are minimized as much as possible to reduce prime volume, the volume still may be as much as 100 percent of the patient's estimated blood volume. Table 5 provides a sample circuit selection that an institution may use, based on patient weight. Using this information, Figure 2 was created, using the patient volumes from Table 4, and illustrates the percent of hemodilution (prime volume/ patient volume) that takes place across patients under 70 kg. For patients of a smaller

weight (and therefore a lower blood volume), it is crucial to be aware of the dilution that takes place due to the prime volume. This proportional disparity of volumes also allows for a relatively higher amount of exposure of the blood to the extracorporeal circuit, which invokes a strong inflammatory response and subsequent capillary leakage.

Table 5: A Sample Circuit Selection for Pediatrics Based on Weight [33].

Oxygenator	Weight (kg)	Prime Volume (mL)	Flow (ml/min)
Sorin KIDS D 100	<4	215	Up to 700
Capiox Terumo FX 05	4-12	300	Up to 1500
Maquet Quadrox-i Pediatric	12-22	500	Up to 2800
Capiox Terumo FX 15	22-60	(20-40) 600 (40-60) 750	Up to 4000
Capiox Terumo FX 25	>60	900-1000	Up to 7000

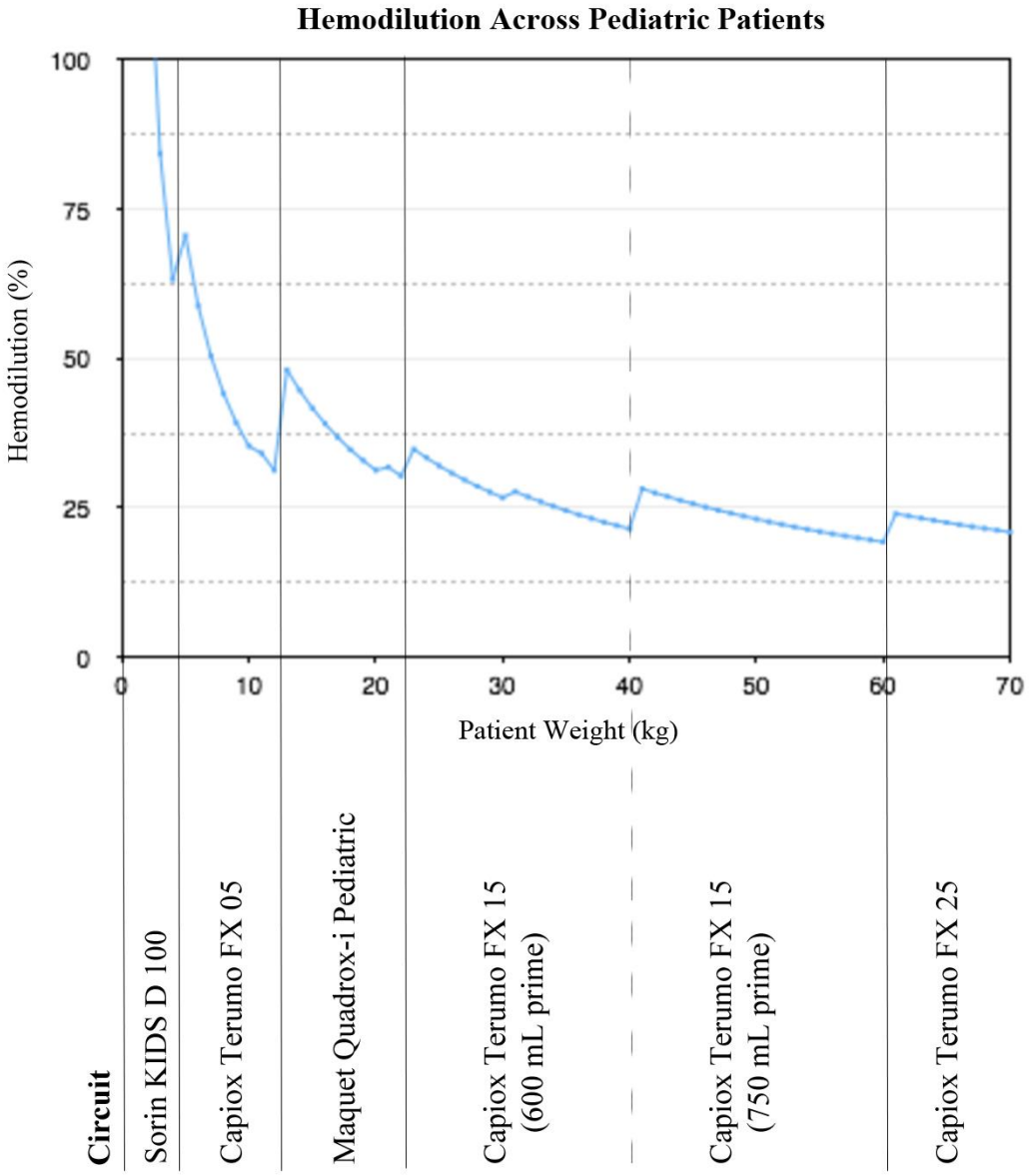

Figure 2: Percentage of Hemodilution by Different Circuits by Patient Weight.

It is important to define the reference ranges for colloid osmotic pressure and albumin in pediatrics. Currently, the reference range for colloid osmotic pressure in pediatrics has not been well defined; however, Sussmane *et al.* attempted to quantify the colloid osmotic pressure in healthy infants (1 month to 11 months old). With a 95%

confidence interval, the COP for healthy infants was found to be between 24.3 and 26.0 mmHg, and had no correlation to gender or body weight [16]. With regard to albumin, the normal reference range for adults is 3.5 to 5.5 grams per deciliter; however, the normal range in pediatrics differs slightly by age, as shown in Table 6.

Table 6: The Normal Range of Albumin for Different Ages [34].

Age	0 to 30 days	1 to 3 months	4 to 11 months	Over 12 months
Albumin Reference Range (g/dL)	2.9 to 5.5	2.8 to 5.0	3.9 to 5.1	3.7 to 5.5

2.5 Clinical Outcomes Associated with Low Albumin Levels

As mentioned in previous sections, low levels of albumin encourage fluid shifts into the interstitial space, which results in edema formation. Both hypoalbuminemia and the resulting edema formation have been a topic of exploration within the scientific community, and many studies have found evidence to show the adverse outcomes of patients with inappropriate albumin concentrations (and an improper colloid osmotic pressure) including weight gain, edema, platelet count, and organ dysfunction.

One indication of a positive fluid shift and subsequent edema is weight gain on bypass, as the fluid that would be in the intravascular space and exposed to glomerular filtration and excretion by the kidneys, is now in the interstitial space. In 2008, Loeffelbein *et al.* found that weight gain was significantly lower (2% ± 4.4 versus 8% ± 8.0) in infants and neonates that had a human albumin prime (n = 10, COP of 27.9 ± 4.87,

versus patients that had a fresh frozen plasma prime (n = 10, COP of 5.8 ± 1.32) [5]. Eising *et al.* found in 2001 that utilizing a priming solution with a low COP (0 mmHg) as opposed to a high COP (48 mmHg) resulted in a slight weight gain [1]. Yu *et al.* found that a CPB prime of 5% albumin as opposed to a prime of 3% albumin saw a reduced fluid balance after bypass [6]. Aukerman *et al.* found that the amount of albumin in the prime volume significantly predicted weight gain in pediatric patients on postoperative days 1, 2, and 3 [7].

While platelet count is not necessarily associated with colloid osmotic pressure or edema, it is still an outcome that is commonly investigated with albumin concentration. As mentioned in Section 2.3, albumin has been thought to reduce platelet activation caused by exposure to the foreign surface of the cardiopulmonary bypass circuit. This potential is significant, as platelet activation may result in thrombosis and excess bleeding [35]. Both Palanzo *et al* [36]. and Myers *et al.* [37] found that adding as little as 0.0375 grams of albumin per every 100 mL of prime significantly lowered platelet count drops due to bypass. While these studies indicate a significant effect of albumin on platelet count, Boks *et al.* found no change in the pressure drop across the membrane oxygenator, indicating none to little platelet activation [25]. Therefore, the potential for albumin to mitigate platelet activation should be further explored.

General consequences that may result from edema formed during CPB include delayed chest closure due to myocardial edema [38], prolonged circulatory and respiratory support [39], and organ dysfunction [1, 2]. Edema formation may also be specific to certain tissues. Myocardial edema has been shown to result in decreased myocardial function (both systolic and diastolic) and although the main mechanism for

myocardial edema is thought to be reperfusion injury, colloids and highly oncotic cardioplegic solutions have been shown to reduce myocardial edema and attenuate cardiac dysfunction [3]. Eising *et al.* found that a hyper-oncotic prime significantly improves cardiac output, both two and four hours post-operatively [1]. Pulmonary edema is also thought to be mainly due to reperfusion injury and inflammatory reactions, as the lungs come into contact with the entire cardiac output, and thus, more inflammatory mediators [40]. In 2001, Eising *et al.* found that a hyperoncotic cardiopulmonary bypass prime prevented extravascular lung water (EVLW) accumulation; however, pulmonary function was unchanged with a hyperoncotic prime [1]. Hoeft *et al.* found that EVLW in a crystalloid prime increased 60% from baseline, while an albumin prime resulted in minimal EVLW [4]. Other adverse outcomes that were found with a lower COP cardiopulmonary bypass prime included a higher plasma lactate concentration, and longer duration of mechanical ventilation [41].

These various findings generally support that a deficit of albumin in the prime is correlated with adverse clinical outcomes, especially in pediatrics. Thus, it is surprising that there is not a generally accepted manner of dosing albumin in the circuit prime of this patient population. Together, these support the development of a model that encourages appropriate albumin dosing in circuits. Table 7 summarizes publications related to low albumin levels and clinical outcomes.

Table 7: Articles Related to Albumin Levels and Clinical Outcomes.

Article Author	Article title	Year published	Population
Loeffelbein *et al.* [5]	High colloid oncotic pressure priming of cardiopulmonary bypass in neonates and infants: implications on haemofiltration, weight gain and renal function	2007	n = 20 Pediatric, ages 3 days to 513 days
Eising *et al.* [1]	Does a hyperoncotic cardiopulmonary bypass prime affect extravascular lung water and cardiopulmonary function in patients undergoing coronary artery bypass surgery?	2001	n = 20 Adult, CABG
Yu *et al.* [6]	Effect of different albumin concentrations in extracorporeal circuit prime on perioperative fluid status in young children	2008	n = 151 Pediatric, ages 2 months to 36 months
Aukerman *et al.* [7]	The relationship between extracorporeal circuit prime, albumin, and postoperative weight gain in children	1998	n = 76 Pediatric, under 4 years of age
Palanzo *et al.* [36]	Albumin in the cardiopulmonary bypass prime: how little is enough?	1999	n = 80 Adult
Myers *et al.* [37]	Use of autologous blood as part of the perfusate for cardiopulmonary bypass: a priming technique	2002	n =178 Adult
Boks *et al.* [25]	Is the use of albumin in colloid prime solution of cardiopulmonary bypass circuit justified?	2001	n = 60 Adult
Hoeft *et al.* [4]	Priming of cardiopulmonary bypass with human albumin or Ringer lactate	1991	n = 20 Adult, CABG
Golab *et al.* [41]	Relevance of colloid oncotic pressure regulation during neonatal and infant	2011	n = 70 Pediatric, weight < 10 kg

2.6 Problem Statement

Theoretically, maintaining a normal colloid osmotic pressure benefits patient outcomes by countering edema formation, and/or inhibiting vascular overload. Postoperative edema in neonates after cardiopulmonary bypass has been reported to be between 37% [42] and 54% [43], an outcome that may be prevented with appropriate albumin dosing. However, no universal protocol exists for calculating the amount of albumin to add to pediatric cardiopulmonary bypass circuit primes, resulting in inconsistent and potentially harmful practice. The goal of this project was to develop a predictive model for determining how much albumin should be added to the circuit prime of pediatric patients.

3. Methods

3.1 Overview

The goal of this project was to develop a model to provide appropriate albumin dosing in pediatric patients during cardiopulmonary bypass. This was done by creating a set of equations that were then integrated to create a calculator for use by perfusionists, to provide dosing information to either maintain the patient's pre-bypass albumin concentration, or to achieve a specified albumin concentration. Table 8 provides information about the variables that are used in the equations presented throughout this section.

Table 8: Variables Designated for Equation Development.

Variable	Units	Definition
X	g	Amount of albumin to be added to achieve concentration desired.
$A_{diluted}$	g/dL	Albumin concentration after dilution with the prime volume.
$A_{patient}$	g/dL	Albumin concentration of the patient before bypass.
A_{goal}	g/dL	Albumin concentration desired.
V_{prime}	mL	Volume of the cardiopulmonary bypass circuit prime.
$V_{patient}$	mL	Volume of the patient, which can be found by multiplying the weight of the patient by appropriate the blood volume found in Table 4 of Section 4.5.

3.2 Dilution of Albumin

When albumin is not added to the prime, the albumin in the body is diluted. Equation (1) can be used to calculate the albumin concentration after the addition of circuit prime. This equation takes into account patient blood and prime volumes ($V_{patient}$ and V_{prime}, respectively) and albumin concentration ($A_{patient}$):

$$A_{diluted} = (A_{patient} * V_{patient}) / (V_{patient} + V_{prime}). \quad (1)$$

While Equation (1) does not provide a dose of albumin to use, it provides information about the degree of dilution occurring. It is also the first step in further determining how much albumin should be added in order to maintain a specific concentration.

3.3 Addition of Albumin to Maintain Concentration

Calculating the amount of added albumin necessary to maintain the patient's pre-bypass albumin concentration is done by replicating the patient's pre-bypass concentration ($A_{patient}$) in the prime volume (V_{prime}), and is calculated as shown in Equation (2). If the amount of albumin resulting from this equation is added to the cardiopulmonary bypass prime, there should be minimal physiological disturbance, as there is theoretically no change in the albumin concentration, and therefore, colloid osmotic pressure:

$$X = V_{prime} * A_{patient} * 0.01 \text{ dL/mL}. \quad (2)$$

3.4 Addition of Albumin to Correct for Hypoalbuminemia

Infants with pathologies such as sepsis, acute respiratory distress syndrome, hemorrhage, and renal failure, have a decrease in the plasma proteins (and consequently, colloid osmotic pressure) [16]. For patients with a low albumin count, Equation (2) is not appropriate, as it only calculates to keep the patient's concentration consistent. Therefore, a new equation was created to correct for a hypoalbuminemia. This was done by adding a calculated excess of albumin in order to achieve the desired albumin concentration.

Similar to Equation (1), the patient blood volume ($V_{patient}$) and the prime volume (V_{prime}) are used to determine the total volume. The amount of albumin needed to achieve the goal concentration was found by multiplying the goal concentration (A_{goal}) by the total volume. Finally, the amount of albumin already present from the patient is found by multiplying the pre-bypass albumin concentration ($A_{patient}$) by the patient's blood volume ($V_{patient}$). This amount is subtracted from the total albumin to be added, and the remaining albumin to add (X) is then found by using Equation (3):

$$X = ((A_{goal} * (V_{patient} + V_{prime})) - (V_{patient} * A_{patient})) * 0.01 \text{ dL/mL}. \quad (3)$$

Using Equation (3), early correction of hypoalbuminemia and a low colloid osmotic pressure can be made. This is important in preventing fluid shifts and edema during bypass. A low colloid osmotic pressure prior to bypass is a significant predictor for a low colloid osmotic pressure at the end of bypass [44].

3.5 Integration into Calculator

While these equations are undoubtedly useful, they are tedious to use individually, and subject to mathematical error. Because of this, a model was created to integrate these equations together, and provide for an easier, and error-proof utilization of these equations. This calculator incorporated all of the equations developed, allowing a perfusionist to see the dilutional albumin concentration, the albumin that should be added to maintain the concentration, and the albumin that should be added to achieve a goal concentration as entered by the perfusionist. This calculator was created in Google Docs, an online spreadsheet application, which was chosen to allow perfusionists to access this calculator from any device, and without need of logging into an account. Figures 3, Figure 4, and Figure 5 show the interface that the user sees when the calculator is opened, and when the four prompted values are inputted.

This calculator was designed with as many features integrated to make the use easy, and resistant to alteration or error. For the four cells that the perfusionist inputs values, there are rules created to highlight the cell in red, if a value entered outside the appropriate range is entered. This prevents the perfusionist from mistakenly entering the wrong units of a value. For example, the value for prime volume is to be entered in milliliters. If a value less than 100 is entered (such as “0.3”, as would be referencing a 0.3 liter prime), the cell will highlight in red, prompting the perfusionist to review their entry. This feature also alerts the user of any typing mistake that might be made. Each cell that is not one of the four inputtable cells is “protected” so that any formatting and equations are not accidentally typed over or altered. Finally, each cell with equations is

programmed to only display a value once all necessary variables are entered by the user, so as to prevent any incorrect dosage readings with partial equations.

4. Results

The calculator that was developed from the previously mentioned sections was implemented into practice to trial its efficacy. It was found that the suggested dosing of albumin found by the calculator was more than most perfusionists typically add to a cardiopulmonary bypass prime, especially in larger circuits due to the larger volume of prime. This demonstrates both the need for, as well as the effectiveness, of this calculator to preserve albumin concentration and colloid osmotic pressure. While it is always effective to use the calculator to find the diluted albumin concentration and subsequent dosing, it is especially useful to implement in patients with hypoalbuminemia or when a large circuit volume being used, as these are two factors that would most result in a lower dilutional albumin concentration and prompt a higher dose of albumin in the prime. The albumin calculator through the trial period is shown in Figure 3 through Figure 5.

ALBUMIN CALCULATOR

Fill in only the red values.

Patient Weight:		kg	*Blood Volume: mL/kg*
Albumin Concentration:		g/dL	*This value will fill automatically.*
Prime volume:		mL	
Goal Concentration:		g/dL	

Estimated Blood volume:	L
Total Circulation Volume:	L
Native patient albumin concentration:	g/dL
Total albumin in the patient:	g

Diluted Albumin Concentration: The concentration of albumin that the patient will see, if there is none given in the prime.	**g/dL**
To maintain pre-bypass concentration:	
Albumin to add to prime:	g
Volume of 25%:	mL
Units of 25%:	
To achieve specified goal concentration:	
Albumin to add to prime:	g
Volume of 25%:	mL
Units of 25%:	

Figure 3: The Calculator without Values Inputted.

ALBUMIN CALCULATOR

Fill in only the red values.

Patient Weight:	7	kg	*Blood Volume: 85 mL/kg*
Albumin Concentration:	3.7	g/dL	*This value will fill automatically.*
Prime volume:	300	mL	
Goal Concentration:	4.1	g/dL	

Estimated Blood volume:	0.60	L
Total Circulation Volume:	0.90	L
Native patient albumin concentration:	3.7	g/dL
Total albumin in the patient:	22.015	g

Diluted Albumin Concentration: The concentration of albumin that the patient will see, if there is none given in the prime.	**2.5**	**g/dL**
To maintain pre-bypass concentration:		
Albumin to add to prime:	1.11	g
Volume of 25%:	44.4	mL
Units of 25%:	0.888	
To achieve specified goal concentration:		
Albumin to add to prime:	14.68	g
Volume of 25%:	58.72	mL
Units of 25%:	1.17	

Figure 4: The Calculator with Example Values Inputted.

ALBUMIN CALCULATOR

Fill in only the red values.

Patient Weight:	6	kg	*Blood Volume: 85 mL/kg*
Albumin Concentration:	4.5	g/dL	*This value will fill automatically.*
Prime volume:	0.3	mL	
Goal Concentration:	4.7	g/dL	

Estimated Blood volume:	0.51	L
Total Circulation Volume:	0.51	L
Native patient albumin concentration:	4.5	g/dL
Total albumin in the patient:	22.95	g

Diluted Albumin Concentration: The concentration of albumin that the patient will see, if there is none given in the prime.	**4.5**	**g/dL**
To maintain pre-bypass concentration:		
Albumin to add to prime:	0.00135	g
Volume of 25%:	0.054	mL
Units of 25%:	0.00108	
To achieve specified goal concentration:		
Albumin to add to prime:	1.03	g
Volume of 25%:	4.1364	mL
Units of 25%:	0.08	

Figure 5: The Calculator Reacting to an Out-of-Range Value.

5. Discussion

This model and resulting calculator were developed to address and attenuate the issues of hypoalbuminemia in pediatric patients caused by dilution of albumin, that results in fluid shifts and postoperative edema. Because this model is user-friendly and resistant to errors, it can be utilized with ease into the practice of any perfusionist. The dilutional albumin concentration has remained in the calculator for the purpose of encouraging the perfusionist to consider the dilution of albumin, should they choose not to add any to the prime, and the suggested doses that are calculated allow perfusionists to make more knowledgeable clinical decisions regarding their practice of adding albumin to the cardiopulmonary bypass prime. The use of this calculator may also be extended into the practice of adult perfusion, should the weight and prime volume be entered as such.

While this calculator may serve as a useful tool for perfusionists, it is not without its limitations. The calculator provides the dose of albumin in both grams and milliliters, as well as the correlating number of units of 25% albumin, to the tenth of a unit. This may be a barrier to implementation, as it is impractical and imprecise to divide a unit of 25% albumin to achieve the exact aliquots desired. When this occurs, perfusionists are encouraged to use their discretion to round to the nearest number of units, or administer half of a unit, if half a dose is called for.

In addition to using the provided equations to appropriately dose albumin in the cardiopulmonary bypass circuit, there are also other practices that would promote a normal colloid osmotic pressure during cardiopulmonary bypass. One technique would be to utilize a tool to monitor colloid osmotic pressure periodically during bypass, through means of a colloid osmometer. This would allow real-time analysis of colloid osmotic pressure, and together with albumin concentration, would provide information as to the state of the patient. Golab *et al.* [41] and Eising *et al.* [1] implemented the Osmomat 050 with a 20-kDA (kilodalton) membrane in order to monitor colloid osmotic pressure. Loeffelbein *et al.* [5] implemented a BMT 921 oncometer with a 20-kDa membrane to monitor COP during bypass.

Another consideration to help prevent edema formation would be to utilize pulsatile flow during bypass. Pulsatile flow is a potential setting available on some cardiopulmonary bypass machines that allows for regular, intermittent periods of high-flow and low-flow that attempt to mimic the systolic and diastolic pressure waveform. While the benefits of pulsatile flow remain debatable, some studies indicate that edema formation is decreased when pulsatility is utilized. [45, 46, 47]. Shen *et al.* found that pulsatile flow significantly decreased edema and better preserved renal function in cases utilizing deep-hypothermia and low-flow perfusion [48]. Several studies support the theory that in low-flow perfusion, pulsatility is especially useful in preventing edema [18]. One proposed mechanism for this is that pulsatility increases lymphatic drainage, which helps to attenuate any positive fluid balance in the interstitial space [18].

Lastly, hemoconcentration is a significant strategy to maintain albumin concentration. Hemoconcentration, also known as ultrafiltration, is a technique that is

common in the practice of cardiopulmonary bypass. When utilized, a hemoconcentrator (or ultrafiltrator) is incorporated into the cardiopulmonary bypass circuit and blood is allowed to flow through it. The hemoconcentrator consists of hundreds of hollow fibers, and each has a semipermeable, microporous membrane in which the pores range from 10 to 35 Ångström [27]. These pores only allow for molecules up to 20 kDa to pass through and be removed through filtration [27]. Molecules such as sodium, potassium, chloride, urea, creatinine, and glucose all have a molecular weight under 10 kDa, allowing for them to be removed easily [27]. Albumin (which is around 66 kDa) and other blood components are too large to be removed through the pores [27]. Therefore, through hydrostatic pressure and concentration gradients, a significant amount of plasma water and electrolytes may be removed, while retaining albumin [27]. As a result, albumin levels are measured at a higher concentration, as the circulating volume has been reduced by hemoconcentration [27].

5.1 Summary

This project explored the development of a model to properly dose albumin in pediatric cardiopulmonary bypass circuit primes. This model was based on the fact that a large dilution of albumin by the circuit prime results in a reduction in colloid osmotic pressure, and results in edema and negative clinical outcomes. The developed model was incorporated into a calculator that would provide perfusionists with the ability to input any patient information, and be given dosing information. The cost of albumin and potential risk of transfusion reaction were also explored, and did not warrant any reason to not fully utilize the proposed model for albumin priming. If implemented, this model

would help improve overall patient outcomes in pediatric patients by most appropriately dosing albumin in the cardiopulmonary bypass prime.

5.2 Future Research

It has been presented that edema is the pathophysiology that is responsible for adverse outcomes in pediatrics with hypo-oncotic primes. While decreased colloid osmotic pressure resulting from a hypo-oncotic prime was the focus for this research, inflammatory response and the subsequent increase in vascular permeability through capillary leak syndrome also play a role in edema formation. This suggests that it may be worthwhile to explore the potential of dosing steroids in the cardiopulmonary bypass prime in addition to albumin, to even further prevent edema formation and potential protein extravasation during cardiopulmonary bypass.

Finally, this research may be extended to focus on the adult patient population. The focus of this research was on the pediatric population due to the many specific factors that make them more susceptible to the adverse effects of a hypo-oncotic prime. While not to the same degree, adult patients are also susceptible to the same effects. Certain factors make adults more prone to these adverse outcomes, such as advanced age, diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal failure [18].

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Perfusion

Thesis Approval Form

Master of Science in Perfusion – MSP

Milwaukee School of Engineering

This thesis, entitled “Albumin Priming in Pediatric Extracorporeal Circuits,” submitted by the student Julie Fenske, has been approved by the following committee:

Faculty Chairperson: _____ Date: _____

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