

## Review Article

# Anticoagulation Strategies in Pediatric Cardiopulmonary Bypass, Weight-Based vs. Concentration-Based Approaches

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**Abstract:** Pediatric patients undergoing cardiopulmonary bypass (CPB) require adequate anticoagulation to combat hemostatic activation. Heparin is used to bind and catalyze antithrombin III (ATIII) that works to inhibit clot formation. To dose heparin, a weight-based (WB) or patient-specific concentration-based (PSCB) method can be used. The WB protocol calculates the dose based on the patients' weight and uses an activated clotting time (ACT) test to ensure anticoagulation. The ACT has limitations during CPB especially for pediatric patients who have immature hemostatic systems. The PSCB method predicts the patients' response to heparin by projecting a heparin dose–response (HDR) curve. Some investigators have found benefit to using the PSCB method but further investigation into how well the HDR predicts the heparin response is needed. A literature review was conducted for studies that looked at heparin management strategies in pediatric CPB

patients between 1992 and 2020. Articles that focused on pediatric physiology, heparin management strategies, and anticoagulation were included. Articles older than 1990 were excluded. The literature review highlights that utilizing the PSCB approach more adequately anticoagulated patients. The WB protocol was found to have several flaws due to its reliance on the ACT, especially in infants. The results show that further investigation is needed to understand why there is benefit to using the PSCB approach. Observing the association between the HDR curve and subsequent heparin concentrations could determine how accurately it predicts the patients' response to heparin and why there is benefit to using this method. **Keywords:** anticoagulation management, cardiopulmonary bypass, heparin, pediatric, hemostatic management system. *J Extra Corpor Technol. 2022;54:153–60*

Pediatric patients undergoing cardiopulmonary bypass (CPB) require accurate anticoagulation and effective anti-coagulant reversal to combat the activation of the hemostatic system. This is usually achieved by using heparin as an anticoagulant with protamine as its reversal. These pediatric patients are typically administered heparin following the weight-based (WB) heparin management protocol used in adult patients. Activated clotting time (ACT) measurement is the most widely used method to monitor anticoagulation during CPB (2). However, in pediatric patients, the use of a patient-specific heparin concentration-based (PSCB) protocol may be more effective in suppressing the generation of thrombin and conserving coagulation

products during CPB (2,3). This could lead to a decreased need for transfusions and reduce morbidity and mortality in these patients. This PSCB method can be executed using automated dose–response systems such as the Hepcon Hemostasis Management System (HMS). This type of machine uses whole blood to calculate a heparin dose–response (HDR) test, or HDR curve. The curve value will determine the concentration of heparin needed to reach a targeted ACT value (2). After this initial heparin dose is given, the heparin is measured using the protamine titration assay. This assay uses protamine to neutralize heparin in the patients' blood to determine the concentration of heparin. Additional heparin can be administered as needed. The administration of heparin is based on the patients' whole blood heparin concentration so it is specific to their anticoagulant needs. Studies have shown utilizing a patient-tailored approach increased the total heparin administered during bypass and allowed for more adequate anticoagulation in comparison to WB approaches (2,3,5). Despite these findings, current research efforts have failed to

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investigate the utilization of this technique and its impact on heparin administration. On PubMed, there is only three articles published from 2020 to 2022 that appear when searching “heparin,” “anticoagulation,” “pediatric,” and “cardiopulmonary bypass,” none of which investigate using the PSCB strategy for heparin management. The purpose of this review is to examine the association between the heparin concentration projected by the HDR test and the subsequent heparin concentrations measured by heparin protamine titration during CPB in pediatric patients.

## METHODS

A literature review was conducted from January 2021 to February 2022. PubMed was the search engine used to access articles that investigated pediatric physiology, heparin management strategies, and anticoagulation. Of the 106 articles that appeared in the original search (search words: “pediatric,” “heparin,” “anticoagulation,” “cardiopulmonary bypass”) only 7 were used. After the initial search, another 12 articles were added from “similar articles” to the seven articles that were included. Articles were excluded that were older than 1990. Ninety-nine studies were excluded from the original search that were not relevant to both pediatric CPB and anticoagulation management. Additional articles were included in this review to briefly discuss adult heparin management, protamine dosing, and transfusion requirements.

## PHYSIOLOGIC DIFFERENCES IN THE PEDIATRIC POPULATION

### Antithrombin III Levels

Heparin is needed because CPB exposes the blood to artificial, unphysiological surfaces within the heart and lung machine. At a molecular level, these foreign surfaces activate a hemostatic mechanism in the blood, known as the intrinsic coagulation cascade. The activation of the clotting cascade leads to the conversion of prothrombin to thrombin.

Thrombin further activates hemostasis by cleaving fibrinogen to fibrin, activating platelets, and activating other coagulation factors. In addition, it activates fibrinolysis, and stimulates the release of proinflammatory mediators. Some of these mediators, which are released as a result of thrombin generation, have been associated with morbidity following cardiac surgery as a result of inadequate anticoagulation (5). Anticoagulants are used in hopes to prevent the generation of thrombin and subsequent clotting mechanisms from occurring. Heparin is the main anticoagulant used during CPB. Its primary mechanism of action is binding to antithrombin III (ATIII)

and catalyzing the inhibition of thrombin. In adult studies, the effects of heparin have been shown to be dependent on the level of ATIII in the blood (5). Newborns and infants have low ATIII levels, averaging between 60% and 80% of adult levels (6).

Guzzetta et al. found that the mean baseline ATIII level was significantly reduced in neonates when compared with older children (5). In their study, they categorized 20 children undergoing cardiac surgery into two groups. The neonatal group consisted of 10 patients who were less than 1 month old, while the older children’s group consisted of 10 patients who were greater than 10 years old. Both groups received an initial WB dose of heparin of 400 IU/kg. The neonate group was given 1,000 units of heparin in the prime whereas the children’s group was given between 3,000 and 6,000 units depending on their size. Additional heparin was given to both groups to maintain an ACT value of greater than 480 seconds during CPB. Blood samples were collected from the arterial catheter before surgical incision, 30 minutes after initiation of CPB, and at three different time intervals after the termination of CPB. They found that the neonate’s mean baseline ATIII levels ( $72\% \pm 13$ ,  $100\% \text{ ATIII} = 1 \text{ unit of ATIII in } 1 \text{ mL reference plasma}$ ) were significantly lower than the older children’s ( $94\% \pm 12$ ) using a two-sided student’s *t* test ( $p = .001$ ) (5).

In another study, Manlhiot et al. shared similar findings (7). They found the mean baseline ATIII levels were lower in neonates than in older infants ( $57\% \pm 15$  vs.  $77\% \pm 12$ ;  $p < .001$ ) (7). A study by Dietrich et al. also found similar results (8). In this study, they compared infants with patients older than 1 year, and also with adolescents and adults. They found that preoperative ATIII activity was significantly lower in the infant population than those older than 1 year ( $84\%$  (33) vs.  $97\%$  (17), median (interquartile range);  $p < .05$ ) (8).

A reduction of ATIII levels will lead to a degree of heparin resistance. Heparin works by binding to and catalyzing ATIII, when ATIII levels are low, heparin will be less likely to bind. More than the expected amount of heparin will be needed to reach the target ACT. A study by Jooste et al. observed the effects of administering exogenous ATIII ( $n = 20$ ) vs. a placebo ( $n = 19$ ) to infants with low ATIII levels ( $<70\%$  ATIII level) (9). They found that the patients who received ATIII had greater heparin sensitivity ( $.99 \text{ seconds/U/kg}$  [ $.84\text{--}1.53$ ] vs.  $.72 \text{ seconds/U/kg}$  [ $.65\text{--}1.04$ ]  $p = .004$ ), less chest tube drainage ( $17 \text{ mL/kg}$  (14–27) vs.  $31 \text{ mL/kg}$  (15–58),  $p = .04$ ), and required less blood products ( $.0 \text{ mL/kg}$  [ $.0\text{--}11.3$ ] vs.  $5.2 \text{ mL/kg}$  [ $.0\text{--}25.0$ ]  $p = .06$ ) (9). In a study by Hashimoto et al., they found that children’s ATIII levels were the most predictive ( $r = -.58$ ,  $p < .001$ ) for the production of fibrinopeptide A (FPA), a byproduct of thrombin activity (10). Alternatively, adult patients’ heparin levels were

more predictive ( $r = -.57, p < .03$ ) of FPA production (10). These results suggest the importance of ATIII levels in the use of heparin as an anticoagulant to prevent thrombin generation.

### Thrombin Products

Thrombin formation and activity were measured in the Guzzetta et al. study by using an enzyme-linked immunosorbent assay (ELISA) (5). The ELISA was used to detect prothrombin fragment 1.2 (F1.2) for thrombin formation and FPA for thrombin activity. The F1.2 is released from prothrombin when it is converted to thrombin, it is a byproduct that occurs during coagulation. FPA is released when thrombin cleaves fibrinogen, it is also a byproduct of coagulation. Before CPB was initiated, Guzzetta et al. found that mean F1.2 levels were significantly increased at baseline in the neonatal group ( $n = 10, <1$  month old) than the older children's group ( $n = 10, >10$  years old) ( $1.9 \text{ nmol/L}$  vs.  $.6 \text{ nmol/L}$ ,  $p < .0001$ ) (5). The FPA levels also showed a significant increase at baseline in the neonatal group compared to the older children's group ( $18.5 \text{ ng/L}$  vs.  $3.1 \text{ ng/L}$ ,  $p < .0001$ ) (5). The combination of low ATIII levels with high baseline thrombin products before initiation of bypass puts neonates at greater risk of inadequate anticoagulation.

### Heparin Sensitivity

Adequate anticoagulation depends on the patient's sensitivity to heparin. The low ATIII levels seen in pediatric patients affect heparin sensitivity because heparin works primarily by binding to ATIII (11). D'Enrico et al. conducted a study to see if there is a difference between adults and children when it comes to heparin sensitivity and heparin/protamine interactions during CPB (11). The study consisted of four age groups: infants (<1 year), preschool (1–5 years), school age (5–14 years), and young adults (>14 years). D'Enrico et al. followed a PSCB method using the Hepcon HMS to determine the target heparin concentration needed to achieve a target ACT of at least 480 seconds. They used a protamine titration assay to determine the protamine dose. They found that the two younger groups (infants and preschool groups) required much lower protamine to heparin ratios (1.1:1 protamine/heparin ratio) than the two older groups (school age and young adult groups) (1.3:1 protamine/heparin ratio) ( $p = .04$ ) (11). The initial heparin dose was higher ( $p < .001$ ) for the infants ( $579 \pm 220 \text{ U/kg}$ ) and preschool ( $477 \pm 159 \text{ U/kg}$ ) groups compared to school age ( $327 \pm 57 \text{ U/kg}$ ) and adults ( $332 \pm 64 \text{ U/kg}$ ) groups (11). They found that the younger groups (infants and preschool groups) were less sensitive to heparin and may need as much as 500 U/kg of heparin while undergoing CPB (11). Pediatric patients have a wide range of variability of their sensitivity and response to heparin

(11,12). This wide range of variability could be attributed to interindividual drug responses and metabolism (12).

### Physiologic Differences

Pediatric patients have higher metabolic rates that can decrease the strength and duration of action of heparin (13). In addition to their heightened metabolisms, the anticoagulation of pediatric patients is also affected by hemodilution (13). Hemodilution is more significant in children than in adults (14). Pediatric patients have a higher circuit volume to blood volume ratio than adults, which could lead to greater effects of hemodilution and thus inadequate heparinization. Kern et al. found that levels of platelets ( $219 \pm 57 \times 10^9/\text{L}$  vs.  $64 \pm 26 \times 10^9/\text{L}$ ,  $p < .0001$ ), ATIII ( $50 \pm 17\%$  vs.  $29 \pm 100\%$ ,  $p < .0001$ ), and several factors (II:  $56 \pm 14\%$  vs.  $28 \pm 8\%$ ,  $p < .0001$ , V:  $70 \pm 21\%$  vs. not detected, VII:  $55 \pm 13\%$  vs.  $26 \pm 6\%$ ,  $p < .0001$ , VIII:  $58 \pm 26$  vs. not detected, IX:  $39 \pm 19\%$  vs.  $24 \pm 10$ ,  $p < .002$ , fibrinogen:  $210 \pm 52\%$  vs.  $91 \pm 15\%$ ,  $p < .0001$ ) were significantly reduced in pediatric patients from before vs. 1 minute after CPB initiation (15). The reduction in platelets and factors was due to the effects of hemodilution upon CPB initiation (15). Pediatric patients require higher heparin doses because of their high metabolism, their low ATIII levels, and their susceptibility to the effects of hemodilution (14).

## ANTICOAGULATION MANAGEMENT IN PEDIATRIC PATIENTS

### WB Dosing

Heparin administration is required to achieve adequate anticoagulation for CPB. The heparin dose recommendation for pediatric patients undergoing CPB is a 400 (IU)/kg bolus dose of unfractionated heparin before initiation of CPB. It is also recommended to achieve a target ACT of over 400 seconds (16). The protocols used for children undergoing CPB have been extrapolated from adult protocols. These protocols are based on an empirical WB heparin and protamine dosing and using an automated whole blood ACT (17). However, these protocols may not work as well on infants undergoing CPB. The immaturity of their hemostatic system prevents adequate anticoagulation during CPB because of their inherent deficiencies in ATIII (17). This results in resistance to heparin and ineffective suppression in generating thrombin. Infants undergoing CPB are at higher risk for morbidity and mortality because of hemostatic derangements that result from increased hemodilution, activation of the coagulation system, and activation of the inflammatory system. This disturbance can lead to thrombotic issues and bleeding that result in a higher incidence of perioperative blood transfusions (2,4).

In addition to the physiologic obstacles of pediatric anticoagulation management, the ACT has several limitations for monitoring heparin on CPB. Neonates undergo a larger degree of hemodilution during CPB, this can lead to the dilution of clotting factors, platelet number, and function that can falsely prolong the ACT test (18). In addition to hemodilution, hypothermia is another variable that can prolong the ACT (18). In adults, the ACT has been found to be an inadequate representation of anticoagulation during bypass (19). Chen et al. demonstrated this finding in a study with 50 patients who were undergoing CPB by monitoring their anti-Xa levels in conjunction with ACT point-of-care instruments at multiple perioperative time points (19). The anti-Xa levels were used to determine the plasma heparin concentration. They found that there was a poor correlation between the ACT and anti-Xa levels after the initial bolus of heparin ( $r = .27$  and  $.15$  for the i-STAT and Hemochron) and the correlation was further reduced upon initiation of bypass ( $r = .11$  and  $.04$  for the i-STAT and Hemochron). These results indicate that normalizing the ACT value alone to maintain anticoagulation on bypass may be inadequate, leaving patients excessively or insufficiently heparinized. In another study by Shirota et al. in 2001, the ACT was compared with the Hepcon HMS and they found that the ACT poorly reflected the heparin level during moderate hypothermia although there was a correlation between the values ( $-50\%$  change at the lowest temperature,  $p < .01$ ) (20). The ACT was increased despite the drop in heparin concentration (20). They also looked at the correlation between heparin concentration and the ACT in deep circulatory arrest patients and found no correlation between the two values (150% difference in change at the lowest temperature,  $p < .01$ ). In both the moderately and deep hypothermic circulatory arrest patients, they found that the HMS group ( $200.5 \pm 18.5 \mu\text{g/L}$ ) showed lower thrombin-ATIII levels than the ACT group ( $1046.2 \pm 415.7 \mu\text{g/L}$ ,  $p < .01$ ). The low thrombin-ATIII levels seen in the HMS group are indicative of greater suppression of coagulation (20). Although the ACT correlated with heparin concentration before CPB in both the moderately hypothermic and deep circulatory arrest patients, the correlation dwindled after CPB initiation (20). The ACT was prolonged more with lower temperatures suggesting that temperature can affect the ACT's ability to accurately monitor the heparin concentration. The ACT's limitations on bypass coupled with neonates' immature physiology could lead to inadequate anticoagulation (1,18).

#### **Patient-Specific Heparin Concentration-Based Method**

Utilizing a PSCB approach, such as the Hepcon HMS, may improve pediatric patient outcomes. This method

generates a heparin dose–response curve by determining the patients' anticoagulation response to a known concentration of heparin. The test uses a cartridge that contains six channels. Each of the two channels contains an increasing concentration of heparin. The patient's whole blood is mixed with a clot-activating agent in each channel. Clot formation is detected to determine the clotting time for each channel. The HDR test generates a slope to predict the initial heparin dose needed to reach the target ACT value based on the patient's response to the different heparin concentrations (2). The steepness of the slope determines the patient's heparin sensitivity or resistance. Although HMS protocols are also derived from adult protocols, they are more patient tailored because the HDR curve varies from patient to patient, therefore, the initial heparin dose is specific for each patient. Once the initial dose of heparin is administered, the protamine titration assay can be used to determine the concentration of circulating heparin in the patients' whole blood. Protamine is used to neutralize the heparin and determine its concentration. The assay uses cartridges that consist of multiple channels that contain thromboplastin to activate the test and different amounts of protamine in each channel. A plunger within the cartridge is used to detect clot formation. The channel that clots first will be the sample that neutralizes the heparin without excess protamine (14). The amount of protamine in that channel can be used to determine the concentration of heparin.

Although the Protamine titration assay are useful to estimate the whole blood heparin concentration, anti-Xa assays are the most sensitive tests to measure the plasma heparin concentration (21). Guzzetta et al. used the anti-Xa assay to compare the heparin concentrations when using a PSCB vs. a WB method (21). Forty-four pediatric patients younger than 6 months old were included in the study. Their blood was drawn after initial heparin bolus and before termination of CPB. They used the Hepcon HMS, Hemochron, and i-STAT to perform ACTs. They used the protamine titration assay to determine the heparin concentration. They used the anti-Xa level to measure the plasma heparin concentration and correlated the ACT and protamine titration assay to the plasma heparin concentration. They found that the Hepcon HMS had a weak positive correlation ( $r = .3$ ,  $p = .05$ ), the i-STAT had a moderate positive correlation ( $r = .53$ ,  $p < .001$ ), and the Hemochron had no correlation ( $r = .28$ ,  $p = .08$ ) with the plasma heparin level (21). They found that the protamine titration and anti-Xa heparin levels correlated (concordance correlation coefficient =  $.3$  [after heparin initiation] and =  $.67$  [before termination]), but the anti-Xa level was significantly higher ( $p \leq .01$ ). They concluded that relying on the ACT alone in pediatric patients younger than 6 is not advisable because of its poor correlation with plasma

**Table 1.** Thrombin generation and activity.

Study	F1.2	FPA
Guzzetta et al. (2005)	Baseline F1.2 levels greater in neonates: <ul style="list-style-type: none"> <li>• Neonates (1.9 nmol/L) vs. older children (.6 nmol/L) (<math>p &lt; .0001</math>)</li> </ul> During and after CPB both groups had increased levels but neonatal group was higher and remained elevated longer: <ul style="list-style-type: none"> <li>• (2.6 nmol/L at 3 hours after CPB, and 1.9 nmol/L 24 hours after CPB, <math>p = .0004</math>)</li> </ul>	Baseline FPA levels greater in neonates: <ul style="list-style-type: none"> <li>• Neonates (18.5 ng/L) vs. older children (3.1 ng/L) (<math>p &lt; .0001</math>)</li> </ul> Decreased FPA levels 3 hours post-CPB compared to baseline: <ul style="list-style-type: none"> <li>• Neonates (8.5 ng/L, <math>p &lt; .0001</math>) and the older children (2.5 ng/L, <math>p = .0002</math>)</li> </ul>
Codispoti et al. (2001)	Increase in F1.2 levels from pre to post-CPB in both groups but less with the PSCB group: <ul style="list-style-type: none"> <li>• PSCB (1.21 ± .11–1.4 ± .34 nmol/L) (<math>p = .02</math>)</li> <li>• WB (1.09 ± .16–3.5 ± .68 nmol/L) (<math>p &lt; .001</math>)</li> </ul>	
Guzzetta et al. (2008)	Statistically significant increase in F1.2 production from pre- to post-CPB in the WB group but not the PSCB group: <ul style="list-style-type: none"> <li>• PSCB (.36 ± .11) to (.54 ± .18 nmol/L)</li> <li>• WB (.53 ± .37) to (.64 ± .37) (<math>p &lt; .05</math>)</li> </ul>	Statistically significant decrease in FPA production from pre- to post-CPB in both groups: <ul style="list-style-type: none"> <li>• PSCB (4.89 ± 3.30) to (2.39 ± 1.32) (<math>p &lt; .05</math>)</li> <li>• WB (6.20 ± 2.98) to (3.33 ± 2.01) (<math>p &lt; .05</math>)</li> </ul>

CPB, cardiopulmonary bypass; F1.2, prothrombin fragment 1.2; FPA, fibrinopeptide A; PSCB, patient-specific concentration-based; WB, weight-based.

heparin levels. They supported the use of the Hepcon HMS for determining heparin concentrations bedside because of its correlation with anti-Xa (21).

In contrast to these findings, Gruenwald et al. found that there was no correlation in heparin concentration between the protamine titration assay and the anti-Xa activity (14). They looked at 51 patients under 1 year of age undergoing CPB. They retrieved blood samples 5 minutes into CPB and at the end of CPB. They did not find a significant association between the two variables ( $r = .133$ ,  $p = .429$  at 5 minutes into CPB, and  $r = -.247$ ,  $p = .080$  at the end of CPB), however, they contributed their findings to the amount of hemodilution that occurs in pediatric patients during CPB (14). Despite these findings, several studies found that using a PSCB approach increased the total heparin dose (2,3,5,22).

## HEPARIN LEVELS FOLLOWING WB VS. PATIENT SPECIFIC PROTOCOLS

In both the adult and pediatric populations, heparin doses tend to be greater when using a PSCB approach in comparison to a WB protocol (2,3,5,22). In adult cardiac patients, Slight et al. found that using the Hepcon HMS system resulted in greater heparin administration (633 ± 32 IU/kg) when compared with the ACT (510 ± 15;  $p = .001$ ) (22). In the pediatric population, a similar occurrence was noted, neonates had a greater need for heparin to achieve the targeted ACT resulting in higher total heparin administration (2,3,5). Guzzetta et al. used the mean heparin anti-Xa activity level to determine that there was significantly more heparin administered to neonates (841 ± 112 U/kg) than older children (561 ± 93 U/kg,  $p = .001$ ) (5).

Some studies compared the amount of heparin administered using WB protocols (control group) vs. PSCB heparin management strategies (intervention group) (2,3). Codispoti et al. found that the intervention group had a significantly higher total amount of heparin (891 ± 108 U/kg) administered compared to the control group (311 ± 5 U/kg) after analysis using a two-tailed student *t* test ( $p < .001$ ) (2). Guzzetta et al. found that their intervention group received a significantly larger mean total heparin dose (1,080 ± 392 U/kg) than the control group (597 ± 22 U/kg) (3). Utilizing PSCB methods for pediatric patients is beneficial because it increases total heparin administration to meet their heightened anticoagulant needs.

Although greater heparin dosing can be beneficial, it can also lead to poor outcomes. Gruenwald et al. began a study in August 2006 that was temporarily suspended in June 2007 by the safety committee because the original protocol was causing adverse effects such as greater chest tube drainage (PSCB group 28.1 [8.0–162.7] mL/kg vs. WB group 18.1 [9.6–129.0] mL/kg, [ $p < .001$ ]), transfusion requirements (PSCB group mean 112 [SD 46–465] mL/kg vs. WB 97 [37–205] mL/kg [ $p < .001$ ]), and longer hospital stays (PSCB group 307 [117–3,480] hours vs. WB 196 [114–916] hours [ $p < .001$ ]) (17). The original protocol resulted in high initial (mean of 451 U/kg) and total heparin doses (mean 1,448 U/kg) for the PSCB group. They revised their protocol to limit the heparin dose recommended by the HMS system and resumed their study in October 2007 (original study had an initial heparin dose limit of 6.1 U/mL that was changed to 4.0 U/mL for <1 month and 3.5 U/mL for 1 month to 1 year old in the new protocol) (17). Greater total heparin dosing with the PSCB methods is likely due to the different functional methodology in comparison to WB protocols. The

PSCB method uses the HDR tests, PTAs, and ACTs to determine how much heparin is needed to maintain anticoagulation while the WB protocol relies solely on the ACT. Owings et al. discussed that the ACT may rely more heavily on fibrinogen levels than the HMS system (23). Owings et al. found that fibrinogen levels in pediatric patients (1.7 mg/L) were lower in comparison with adults (3.0 mg/L;  $p < .05$ ) (23). The low fibrinogen levels seen in pediatric patients could suggest further limitations the ACT as the main measure of adequate hemostatic management. They found that the HMS required higher doses of heparin and had less generation of thrombin than the ACT and concluded that the PCSB more accurately assessed pediatric anticoagulation (23).

## HEMOSTATIC ACTIVATION AS A RESULT OF INADEQUATE HEPARINIZATION

### Thrombin Generation and Activity

As discussed earlier, heparin binds to ATIII and catalyzes the inhibition of thrombin. Thrombin generation produces byproducts such as F1.2 during CPB can occur when there is inadequate heparinization. Guzzetta et al. used a repeated measures analysis of variance to compare the means for F1.2 and FPA levels between neonates and children (5). Immediately after initiation of CPB, they found that F1.2 and FPA levels decreased in both groups, likely due to hemodilution. During and after CPB, the F1.2 levels rose in both groups, but the neonatal group levels trended higher and remained significantly increased at the 24-hour post-CPB interval (2.6 nmol/L at 3 hours after CPB, and 1.9 nmol/L 24 hours after CPB,  $p = .0004$ ) (5). The FPA levels decreased in both groups after CPB initiation and remained decreased 3 hours post-CPB in the neonate group (18.5 ng/L at baseline to 8.5 ng/L 3 hours after CPB in neonatal group,  $p < .0001$  and 3.1 ng/L at baseline to 2.5 ng/L in the older group,  $p = .0002$ ) (5). The decreased FPA levels seen in children could be the result of hemodilution or qualitatively defective fibrinogen seen in neonates (3). Despite the decrease in FPA levels, F1.2 levels did rise. The rise in this thrombin generation byproduct could indicate that the neonates were inadequately heparinized. It can be inferred that the neonates may have a greater need than older children for alternative heparin management strategies.

Another study, by Codispoti et al., investigated how heparin management strategies can impact the activation of the coagulation cascade in children (2). In their study, the control group consisted of 10 children that received 300 IU/kg of heparin while the intervention group consisted of 11 children that were given an individualized heparin dose to maintain an ACT of at least 480 seconds indicated by the Hepcon system. The F1.2 level was measured in this study with an enzyme immunoassay. It was increased in

both groups ( $1.09 \pm .16$ – $3.5 \pm 0.68$  nmol/L pre- to post-CPB in the control group, and  $1.21 \pm .11$ – $1.4 \pm .34$  nmol/L in the intervention group,  $p < .001$ ) but it was significantly less pronounced in the intervention group ( $1.21 \pm .11$ – $1.4 \pm .34$  nmol/L pre- to post-CPB,  $p = .02$ ) (2).

Guzzetta et al. shared similar findings (3). They randomly assigned infants less than 6 months old into two groups. The control group consisted of 12 children that were administered 400 U/kg of heparin while the intervention group consisted of 13 children who were administered a PSCB on the Hepcon HMS result to achieve an ACT value of 480 seconds or more. An ELISA test was used to measure F1.2 levels in both groups and the means were compared using a student *t* test. They found that infants who received the intervention had lower thrombin generation ( $.36 \pm .11$  nmol/L to  $.54 \pm .18$  nmol/L) than the control group ( $.53 \pm .37$ – $.64 \pm .37$  nmol/L) based on their pre-CPB to post-CPB F1.2 levels ( $p < .05$ ). All three of the previously described studies demonstrated increased thrombin generation products in infants undergoing CPB (see Table 1). The second two studies demonstrated that utilizing a PSCB heparin dose may decrease these byproducts (2,3). Less generation of byproducts is indicative of greater suppression of thrombin and thus superior anticoagulation on bypass.

## IMPACTS OF INCREASED HEPARIN ADMINISTRATION IN PEDIATRIC PATIENTS

Increased heparin dosing seen with PSCB methods has been found to decrease the generation of thrombin (2,3). The increased amount of total heparin requires adequate reversal.

### Effects on Protamine Dose

Protamine is used to reverse the effects of heparin. During CPB, adequate anticoagulation is essential as is a proper reversal after CPB. However, excess protamine can promote coagulopathy and increase bleeding through platelet and serine protease inhibition. Protamine has also been found to induce anaphylactoid and anaphylactic reactions as well as pulmonary hypertension (11). According to Nybo and Madsen, the incidence of anaphylactic reaction to protamine is between .06% and 10.6% (24). A study by Seifert et al. determined that the incidence of systemic hypotension after protamine administration on infants and children following CPB was between 1.76% and 2.88% (25). Protamine dosing is generally determined either by a WB formula or based on the heparin concentration using the HMS (26). Codispoti et al. found that utilizing the heparin concentration method in their intervention group resulted in significantly lower protamine administration ( $2.9 \pm .2$  mg/kg) than the control group

( $8.6 \pm 1.4$  mg/kg,  $p < .001$ ) (2). The intervention group received a 1 mg/1 mg ratio for the residual heparin while the control group received a 1 mg/1 mg ratio of the total administered heparin. A lower protamine dose could result in less consumption of coagulation factors.

Studies have shown there are benefits in achieving a lower protamine dose such as reducing platelet aggregation, complement activation, decreasing blood loss, and subsequent need for transfusion (2). A study by Meesters et al. found that postoperative blood loss was decreased in patients who received a low protamine dose (470 mL; 95% confidence interval [CI] 420–530 mL) in comparison to a high dose (615 mL; 95% CI 500–830 mL,  $p = .021$ ) (27). The high-dose group received greater amounts of transfusions in comparison with the low-dose group (fresh frozen plasma 11% vs. 0%,  $p = .02$ , platelet concentrates 21% vs. 6%,  $p = .04$ ). They concluded that lower protamine doses were associated with a decreased amount of blood loss and the requirement for transfusions (27). A study by DeLaria et al. had similar results (28). In this study, less protamine resulted in fewer transfusions of: RBCs ( $p < .001$ ), platelets ( $p < .01$ ), and FFP ( $p < .03$ ).

### Risk of Bleeding

Patients undergoing CPB are often exposed to blood transfusions. Pediatric patients may experience more blood loss compared to older patients and therefore require more transfusions. According to Caneo et al. hemodilution causes hematocrit levels to decline, along with other blood components, resulting in the need for transfusions (26). A study by Williams et al. had similar findings, they concluded that neonates ( $\leq 1$  month) are subjected to more transfusions than any other age group (median of 8 units [range 1–19 units] differed significantly compared to other age groups  $p < .001$ ) and have higher mortality than any other group (66% mortality) (29). This is a result of neonates undergoing more complex surgeries with longer CPB and having a higher degree of hemodilution.

Administering blood products is associated with the risk of complications such as transfusion reactions and transmission of blood-borne diseases (6). Giving older blood has been found to pose further risks in the pediatric population (15,30,31). Some strategies that are used to reduce the need for transfusions are to use low-prime volume circuits with and without vacuum-assisted venous drainage, ultrafiltration, and cell salvage for all pediatric patients (26).

Using a PSCB could decrease the need for transfusion as well (2,4). In a study performed by Codispoti et al., they found that their intervention group, who received a PSCB heparin dose protocol, required less postoperative transfusions ( $3.1 \pm 1.3$  mL/kg) than the control group ( $11.4 \pm 3.6$  mL/kg,  $p = .05$ ) (2). In another study,

Despotis et al. compared the need for transfusions using a PSCB approach vs. a WB protocol in adults (4). They found that the PSCB protocol resulted in significantly fewer units of platelets ( $1.7 \pm 3.6$  vs.  $3.7 \pm 6.7$  units,  $p = .003$ ), frozen plasma ( $.4 \pm 1.3$  vs.  $1.4 \pm 2.5$  units,  $p = .0001$ ), and cryoprecipitates ( $.0 \pm 0.0$  vs.  $.2 \pm 1.2$  units,  $p = .04$ ) in comparison to the group that used a WB protocol. A decreased requirement for transfusions reduces associated complications and is a potential benefit of utilizing a PSCB heparin management strategy.

### SUMMARY

As discussed, pediatric patients have a different physiology than adults. In addition to the difference in size compared with adults, they also have immature hemostatic systems (1,18). They have lower ATIII levels and higher thrombin levels causing them to respond differently to heparin compared to adults. Despite the differences in pediatric physiology, adult protocols for WB approaches are still being used for heparin management strategies in pediatric patients. The WB protocol has several limitations due to the effects of CPB on the ACT test. The PSCB approach eliminates some of these limitations by using the whole blood heparin concentration to monitor anticoagulation status, using a PSCB protocol has been shown to increase the heparin administered and more adequately anticoagulated these patients. The result of using this management strategy is improved pediatric outcomes such as less blood loss and postoperative transfusions. Despite these findings, few studies are looking at the association between the heparin concentration projected by the HDR test and the subsequent heparin concentration measured by the heparin protamine titration assay during CPB in pediatric patients. A study by Nakamura et al. looked at the HDR's ability to predict heparin responsiveness in children (32). They found that it did not reliably predict the heparin responsiveness in a large cohort of 1,281 children ( $< 17$  years of age). In their study, 60% of the children were less than 12 months old. They found that the heparin responsiveness was overestimated in 65% of the children leading to inadequate heparin boluses. They also found the younger population ( $< 12$  months) had further heparin resistance, likely due to their low ATIII levels (32). A recently published article by Min-Ho Lee and William Riley discussed the HDR's ability to predict the heparin concentration in adult patients (33). They found that the HDR estimates individual heparin doses with significant error. Upon their findings, they conclude with the recommendation to use a flow chart for individualized heparin management (33). Perhaps, the PSCB should be implemented as a gold standard for pediatric anticoagulation management but

further investigation is needed into creating a refined protocol that is designed specifically for neonates.

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