

Anticoagulation of Children Undergoing Cardiopulmonary Bypass Is Overestimated by Current Monitoring Techniques

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Hypothesis: Children who undergo cardiopulmonary bypass (CPB) are proportionally more hemodiluted than adults who undergo CPB. Current methods of monitoring high-dose heparin sulfate anticoagulation are dependent on fibrinogen level. Because of the decreased fibrinogen levels in children, current methods of monitoring heparin anticoagulation overestimate their level of anticoagulation.

Design: Prospective controlled trial.

Main Outcome Measure: Production of thrombin (adequacy of anticoagulation).

Methods: Children and adults undergoing cardiac surgery who received CPB were anticoagulated in the standard fashion as directed by activated clotting time (ACT) results. Each subject had blood sampled at baseline; heparinization; start of the CPB; CPB at 30, 60, and 90 minutes; and at termination of CPB. Samples were used to assess anticoagulation with the Heparin Management Test (less dependent on fibrinogen level than ACT). We also assessed 2 subclinical markers of thrombosis, thrombin-antithrombin complexes and prothrombin fragment F1.2; a marker of procoagulant

reserve, fibrinogen; the natural antithrombotic, anti-thrombin; and heparin concentration.

Results: Ten children and 10 adults completed the study. Children had lower fibrinogen levels than adults throughout CPB ($P < .05$). All adults had both therapeutic ACT and Heparin Management Test levels measured throughout CPB. Although children had therapeutic ACT levels, their Heparin Management Test levels were subtherapeutic while undergoing CPB. The children had significantly higher thrombin-antithrombin complexes and prothrombin fragment F1.2 than adults, indicating ongoing thrombin production ($P < .01$). The increases in thrombin-antithrombin complexes and prothrombin fragment F1.2 in children were inversely proportional to their weight.

Conclusions: Children undergoing CPB with heparin dosing adjusted to optimize the ACT manifest inadequate anticoagulation (ongoing thrombin formation). High-dose heparin anticoagulation therapy in children undergoing CPB should be directed by tests (like the Heparin Management Test) that are less dependent on fibrinogen level than ACT.

Arch Surg. 2000;135:1042-1047

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ONE OF the most important advances facilitating cardiopulmonary bypass (CPB) and thus cardiac surgery has been the ability to provide adequate anticoagulation. Early in the development of CPB it was recognized that failure to achieve adequate anticoagulation would result in both postoperative bleeding due to the consumption of procoagulant factors and end-organ dysfunction (eg, acute respiratory distress syndrome due to deposition of the consumed factors in the lungs).¹

During the early stages of CPB, large fixed doses of heparin sulfate were used in attempts to achieve adequate anticoagulation. In 1975 Bull et al^{2,3} demonstrated a wide patient response to hepa-

rin therapy. They found that patients' anticoagulant responses varied from 3-fold to 4-fold as a result of changes in body temperature and dosage-interval duration. Based on these findings, a method of heparin titration to individual patient effect was recommended rather than either fixed dose or titration to plasma heparin levels.

A critical factor in attaining the goal of adequate anticoagulation has been the ability to assess an individual patient's level of anticoagulation (heparin effect). In 1966 Hattersley,⁴ from our institution, introduced the whole blood activated clotting time (ACT) as a means of assessing anticoagulation or heparin effect. Bull et al^{2,3} incorporated the ACT as the primary tool used to assess the degree of heparin anticoagulation during CPB. The ACT was

PATIENTS AND METHODS

Our study was reviewed and approved by our institutional review board on human experimentation. The experiment was conducted for a 4-month period at the University of California–Davis Medical Center in Sacramento.

We studied 2 patient groups—10 children and 10 adults. Patients were enrolled in each group as a consecutive case series. The primary inclusion criterion for patients in both groups was that they were to undergo cardiac surgery requiring CPB. The single distinguishing inclusion criterion for children was that they were prepubescent. Patients receiving aprotinin therapy were excluded, as this drug is known to interfere with the ACT method used in this study.⁵

All patients were treated following our standard CPB protocol using unfractionated porcine heparin. Children and adults were treated with standard prepackaged roller pump (Sanrs, Ann Arbor, Mich) and membrane oxygenator circuit (Cobe, Arvada, Colo). The routine prime pump solution for adults was a 2-L albumin saline mixture; whereas, for children it ranged from 1.1 to 2 L. Therapy was started for both patient groups by hypothermic bypass using the membrane oxygenator and roller pump circuit. Ultrafiltration was not used during the pump runs. The recorded hypothermic temperature was measured by core body temperature. Just before bypass, heparin sulfate was given at a dose of 300 U/kg. The degree of anticoagulation was then monitored by ACT with a target of longer than 400 seconds. The ACT was routinely measured at 30-minute intervals during CPB. Additional heparin was given in cases where the ACT was shorter than 400 seconds.

Blood samples were drawn at baseline (after anesthetic induction and before heparin dosing), on heparin dosing, at the beginning of CPB, at 30, 60, and 90 minutes of CPB, and at the termination of CPB after protamine sulfate reversal. All samples were collected from an arterial line or circuit port using a double-syringe technique. The first syringe withdrew 10 mL of whole blood and was discarded. The second syringe was used to draw 10 mL of blood that was used for ACT and subsequent testing. All whole blood testing occurred within 10 seconds of acquisition. Because the HMT requires a citrated whole blood sample, residual blood not used for ACT testing was immediately anticoagulated using an evacuated tube containing 3.2% buffered sodium citrate (Becton Dickinson, Franklin Lakes, NJ). A portion of that citrated sample was then used to perform the HMT contemporaneously, though the operating team was blinded to the HMT results. Residual citrated whole blood not used for HMT testing was centrifuged at 1500g for 15 minutes and the plasma frozen at -70°C for future testing.

The ACT was performed using a commercially available near-care coagulation analyzer (HemoTec ACT;

Medtronics Inc, Minneapolis, Minn) that uses a kaolin activator. Whole blood sample is added to a double-test well inserted into the device. Once the blood is added, plungers move in an upward and downward motion mixing the reagent and blood. As the clot forms, the increase in resistance to plunger movement is optically detected and the resultant time displayed.

The HMT uses a celite activator. Citrated whole blood was added to the test cartridge and inserted into the thrombolytic assessment system analyzer. The sample moved by capillary action, mixing with reagent and paramagnetic iron oxide particles, simultaneously starting a pulsating magnetic field that caused the paramagnetic iron oxide particles to move. As the sample clotted, the decrease in paramagnetic iron oxide particle movement was detected and the resultant time displayed. In a previous study of patients undergoing CPB, we validated the therapeutic range for the HMT to be shorter than 350 seconds.⁶

Frozen plasma was tested for markers of thrombosis. Before analysis, the plasma was quick thawed in a 37°C water bath for 5 minutes and vortexed before use. Each plasma sample was tested for the following 6 assays: (1) heparin levels based on anti-Xa activity (Stago Asserachrome, Parsippany, NJ) on the medical laboratory automation results (MLA model 900C; Medical Laboratory Automation, Pleasantville, NY); (2) prothrombin fragment F1.2 using an enzyme immunoassay method (Dade-Behring Diagnostics Inc, Deerfield, Ill); (3) thrombin-antithrombin complexes (TAT) using enzyme-linked sandwich immunoassay (Dade-Behring Diagnostics Inc); (4) fibrinogen (FBG) using a modified Clauss technique (Dade International Inc, Miami, Fla) on the medical laboratory automation results (MLA model 1000C; Medical Laboratory Automation); (5) antithrombin levels using a chromogenic factor Xa inhibition method (Chromogenix AB, Molndal, Sweden); (6) tissue factor pathway inhibitor using an enzyme-linked immunoassay method (American Diagnostica Inc, Greenwich, Conn).

To determine the relation of age and hemodilution encountered during CPB to the adequacy of heparin anticoagulation, markers of coagulation in the pediatric group were compared with those of adults. Activated clotting times were compared with HMT values and each was correlated with subclinical markers of thrombosis (TAT complexes and F1.2). These correlations were done to (1) determine the correlation between ACT and HMT and (2) assess the accuracy of the ACT and HMT level in predicting ongoing coagulation (thrombin generation), and thereby the potential need for increased anticoagulation with heparin.

Linear variables were compared using the Pearson product moment correlation, repeated measures analysis of variance, and multivariate linear regression. Prior to data collection $P < .05$ was established as statistically significant.

used and remains the criterion standard for the assessment of heparin anticoagulation during CPB.

Recently it has become clear that the ACT has several limitations. Specifically, we have perceived clinically that the ACT tends to overestimate the heparin anticoagulant effect in hypothermic, hemodiluted pediatric patients undergoing CPB. To test our perception, we prospectively compared the adequacy of anticoagulation in children and adults undergoing CPB based on

accepted measurements of heparin anticoagulation and subclinical markers of coagulation. The adult population served as a control group who underwent hypothermic CPB with less hemodilution.

In addition to using subclinical markers of thrombosis to assess the effectiveness of anticoagulation, we also studied a new device, the thrombolytic assessment system (Thrombolytic Assessment System; PharmaNetics [formerly Cardiovascular Diagnostics Inc], Raleigh,

Patient Demographics*

	Pediatric Patients	Adult Patients	P
Age, y	3.05 (3.98)	59.4 (15.6)	<.05
Male, %	50	50	.99
Weight, kg	13.9 (14.0)	75.5 (12.9)	<.05
Heparin dose, U/kg	300	300	.99
Mean hypothermic temperature, °C	24 (3.6)	28 (1.5)	<.05
Pumping time, min	88 (20.8)	143 (32.7)	<.05

*Values in parentheses indicate SEM.

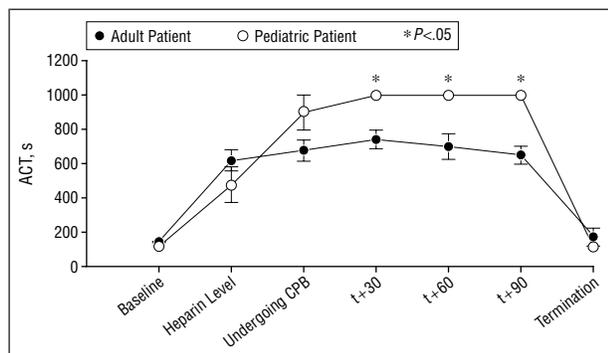


Figure 1. Activated clotting time (ACT) results in children and adults undergoing cardiopulmonary bypass (CPB) sampled at 30-minute intervals. t+30 indicates test result at 30 minutes; t+60, test result at 60 minutes; and t+90, test result at 90 minutes.

NC) for measuring the degree of heparin anticoagulation using the Heparin Management Test (HMT) cartridge. We compared the results of the HMT with the ACT proving the hypothesis that the HMT would identify pediatric patients as inadequately anticoagulated who were described as being adequately anticoagulated by the ACT.

RESULTS

A total of 10 consecutive children and 10 adults were enrolled in this study. Average demographic data are listed in the **Table**. As expected, significant differences were noted for all demographic data except for sex distribution and heparin dosing (based on a mass indexed dosing schedule). All patients were given heparin as previously described to maintain ACT for longer than 400 seconds.

For the adult group, the procedures included mitral valve replacement and atrial septal defect repair (1 patient), aortic valve replacement (1 patient), aortic valve replacement with coronary bypass grafts (1 patient), and multivessel coronary artery grafts (7 patients). The pediatric procedures consisted of arterial switch repair (2 patients), repair of tetralogy of Fallot (2 patients), arterioventricular canal (2 patients), repair of atrial septal defect (1 patient), Norwood procedure (1 patient), mitral valve repair (1 patient), and repair of an Epstein anomaly (1 patient).

All adult patients had ACTs longer than 400 seconds while undergoing CPB. Nine (90%) of the 10 children had ACT levels of longer than 999 seconds throughout CPB. The 1 pediatric patient whose ACT values were

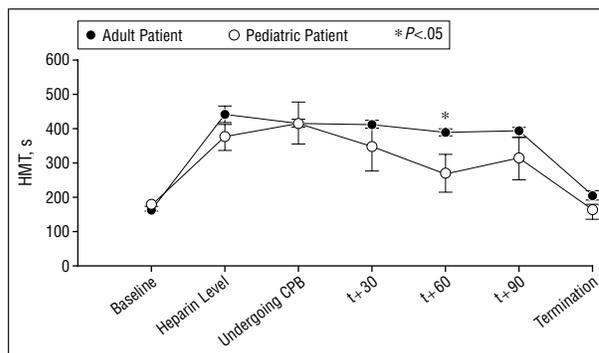


Figure 2. Heparin Management Test (HMT) results in children and adults undergoing cardiopulmonary bypass (CPB) sampled at 30-minute intervals. t+30 indicates test result at 30 minutes; t+60, test result at 60 minutes; and t+90, test result at 90 minutes.

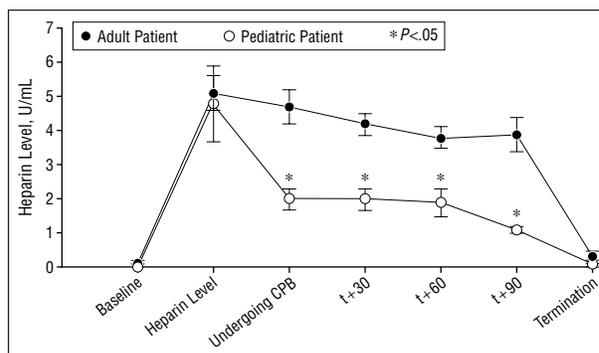


Figure 3. Heparin levels in children and adults undergoing cardiopulmonary bypass (CPB) sampled at 30-minute intervals. t+30 indicates test result at 30 minutes; t+60, test result at 60 minutes; and t+90, test result at 90 minutes.

not longer than 999 seconds throughout CPB was an 11-year-old girl who weighed 50 kg. The ACT values for the children were higher than those of the adults at the CPB intervals of 30, 60, and 90 minutes (**Figure 1**). All adults had HMT values considered therapeutic (<350 seconds) throughout CPB. Six (60%) of the 10 pediatric patients had HMT values considered subtherapeutic during CPB. Only the 60-minute interval indicated a significant difference between the pediatric and adult groups for HMT testing (**Figure 2**).

During CPB, heparin levels were significantly lower in the pediatric patients than in the adult patients despite having significantly more prolonged ACT (**Figure 3**). In the pediatric population, HMT values correlated more closely with heparin level than the ACT levels ($R=0.48$ and $R=0.28$, respectively, $P<.05$ for both). For the adult group, the HMT values and ACT levels correlated equally well with heparin levels.

Fibrinogen was the only plasma protein level studied that revealed a significant difference between children and adults at baseline. No differences were noted at baseline between the children's and adults' ACT level, HMT values, heparin levels, prothrombin fragment level, TAT complexes, D-dimer level, antithrombin level, or tissue factor pathway inhibitor level. During CPB, the children had significantly higher markers of thrombosis (TAT complexes, prothrombin fragment, **Figure 4** and **Figure 5**) and significantly lower natural anticoagu-

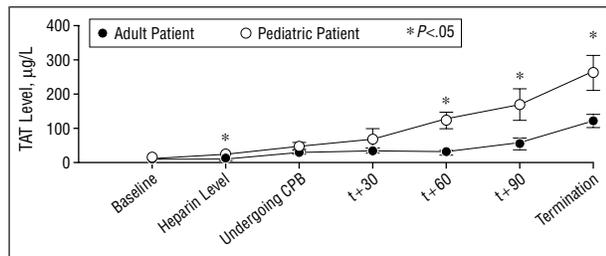


Figure 4. Thrombin-antithrombin (TAT) complex levels in children and adults undergoing cardiopulmonary bypass (CPB) sampled at 30-minute intervals. t+30 indicates test result at 30 minutes; t+60, test result at 60 minutes; and t+90, test result at 90 minutes.

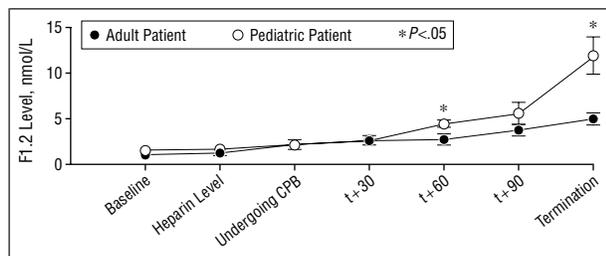


Figure 5. Prothrombin fragment F1.2 levels in children and adults undergoing cardiopulmonary bypass (CPB) sampled at 30-minute intervals. t+30 indicates test result at 30 minutes; t+60, test result at 60 minutes; and t+90, test result at 90 minutes.

lant activity (antithrombin level, **Figure 6**). Fibrinogen levels were significantly lower in the pediatric population at baseline and throughout CPB (**Figure 7**). Regression analysis of the markers of thrombosis at the end of CPB demonstrated strong inverse correlations with weight in the pediatric group ($P < .001$), but not in the adult group ($P > .05$). Intra-CPB TAT complex levels were inversely correlated with HMT ($P < .05$) (but not ACT) levels in both the pediatric and adult groups. No significant differences were noted in D-dimer levels throughout the course of CPB between the 2 groups.

COMMENT

Inadequate heparin anticoagulation in the face of a clotting stimulus such as CPB leads to accelerated activation of procoagulant factors and fibrinogen. This process leads to 2 distinctly different consequences. First, the activated factors and platelets are deposited in the microcirculation as microemboli and cause end-organ dysfunction.¹ Second, as factors are consumed, a hypocoagulable state results and with it the potential of bleeding.⁷ The anticoagulant used in CPB, heparin, has its anticoagulant effect through the endogenous protein antithrombin (antithrombin III). Antithrombin once activated by heparin inactivates several coagulation factors including factor Xa and thrombin. The anticoagulant effect of high-dose heparin in the operating room has been measured traditionally with the ACT method (though other complex monitoring methods such as thromboelastography have also been used). The ACT method has been used rather than the activated partial thromboplastin time with CPB due to the instability of the activated partial thromboplastin time at high levels

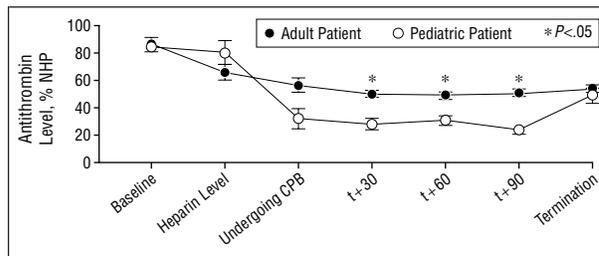


Figure 6. Antithrombin level in children and adults undergoing cardiopulmonary bypass (CPB) sampled at 30-minute intervals. t+30 indicates test result at 30 minutes; t+60, test result at 60 minutes; and t+90, test result at 90 minutes. NHP indicates normal human plasma.

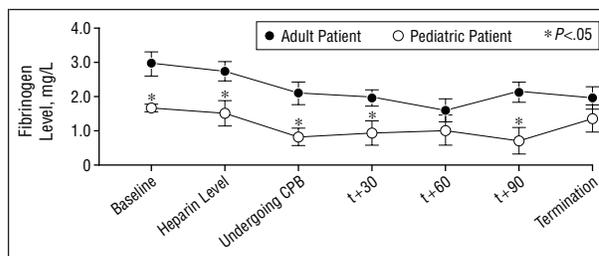


Figure 7. Fibrinogen levels in children and adults undergoing cardiopulmonary bypass (CPB) sampled at 30-minute intervals. t+30 indicates test result at 30 minutes; t+60, test result at 60 minutes; and t+90, test result at 90 minutes.

of heparin anticoagulation. Factors that contribute to this instability include the type and concentration of activator reagent used, the nonlinear response of the activated partial thromboplastin time to high heparin doses, and the limited endpoint (maximum 150 seconds) of most activated partial thromboplastin time measuring systems.

The HMT and ACT are both assays that provide a functional assessment of clotting in a patient on high-dose heparin therapy. The method of assessing clot formation, however, is different between these 2 assays. The HMT method uses the detection of reduced motion of microferric particles in an oscillating magnetic field to detect clot formation. Because the HMT method measures the change in movement on a microscopic rather than macroscopic scale, it seems less dependent on fibrinogen levels than traditional ACT methods.

Thrombin-antithrombin complexes are markers of active thrombosis in that their presence indicates that thrombin has been generated and then inactivated by antithrombin. Prothrombin fragment F1.2 also serves as an indicator of active thrombin production as it is a measure of the cleavage product formed when prothrombin is cleaved to form the active thrombin molecule. The presence of elevated levels of the TAT complex and F1.2, therefore, indicate ongoing thrombin generation. We found that even though the pediatric patients were more hemodiluted than the adults, they had significantly higher levels of TAT complex and F1.2. This suggests that the pediatric patients had dramatically more ongoing thrombosis than the adults did. In stark contrast to this observation, the ACT returned a result in the children suggesting that their anticoagulation levels were not only adequate but several times higher than those of the adult population.

The HMT method provided a more accurate assessment of anticoagulation than the ACT method. The HMT levels had a stronger direct correlation with the plasma heparin levels than did the ACT levels and showed a stronger inverse correlation with TAT complex and F1.2 than those of the ACT method. The decreased dependence on fibrinogen level by the HMT method may explain its more accurate assessment of heparin effect in our pediatric population who had relatively depleted fibrinogen levels.

Hypothermia reduces the coagulation potential because the kinetic process of coagulation is optimized at 37°C. In CPB, hypothermia is induced to reduce metabolism and protect end organs. In our study the CPB was significantly cooler for the pediatric population than for the adults. However, the finding of increased thrombin production, as measured by prothrombotic markers TAT complexes and F1.2, in the pediatric population suggests inadequate heparin anticoagulation despite the cooler temperatures.

Children, due to their small blood volume, become significantly more hemodiluted than adults when undergoing CPB. Because of this hemodilution, the concentrations of fibrinogen, antithrombin, and other plasma proteins are reduced. The decreased antithrombin activity results in a relative heparin-resistant state. Although the children were initially given the same 300-U/kg dose as the adults, because of the ACT misinformation while undergoing CPB, their heparin levels fell significantly below those of the adults. The combination of decreased antithrombin activity with the lower heparin levels in the pediatric group provides a molecular explanation for their inadequate anticoagulation (increased thrombin production). Correction of the inadequate anticoagulation in children could be accomplished by increasing their heparin level, repleting their antithrombin activity, or both.

Tissue factor pathway inhibitor is another naturally occurring in vivo inhibitor of factors VIIa and Xa and tissue factor complex. Tissue factor pathway inhibitor levels are dramatically increased following heparin administration and then return to normal when protamine reversal is accomplished. In our study, the tissue factor pathway inhibitor levels did not rise to the same degree in the pediatric group as in the adult group. This is further evidence that the heparin levels were inadequate.

D-dimers are products of the breakdown of cross-linked fibrin. Thrombin cleaves fibrinogen to form fibrin. Thrombin will also activate factor XIII, which cross links polymerized fibrin to stabilize the clot. In the presence of plasmin, the cross-linked fibrin is broken down (fibrinolysis) resulting in the formation of D-dimer complexes. In our study no significant difference was noted in D-dimer levels between the pediatric and adult groups during any time frame. Therefore, since all patients receiving aprotinin or other antifibrinolytic drugs were excluded, these data suggest that both groups of patients have similar fibrinolytic capacities.

Our study has several limitations. The most important is that the end point we chose to use, subclinical evidence of thrombosis, though scientifically strong, may only represent a surrogate end point. The inci-

dence of adult respiratory distress syndrome or multiple organ dysfunction would be more clinically relevant. The size of our patient samples and the heterogeneity of their clinical processes made using these clinical parameters as end points impractical. Nevertheless, we believe the evidence of increased thrombin production in children relative to adults warrants further investigation. Two large groups of children undergoing operations while undergoing CPB, one anticoagulated with traditional dose heparin and the other with higher dose heparin anticoagulation or supplementation of anti-thrombin, should be compared for the incidence of adult respiratory distress syndrome and multiple organ dysfunction.

CONCLUSIONS

Pediatric patients undergoing hypothermic CPB with hemodilution continue to manifest ongoing thrombin generation reflective of inadequate heparin anticoagulation despite "therapeutic" ACTs. The HMT value is a better indicator of heparin level and is more sensitive to the presence of ongoing thrombin formation. The HMT method may be better at detecting inadequate heparin effect in the pediatric population. Alternative methods of anticoagulation monitoring, such as the HMT, should be used in pediatric patients to facilitate more effective heparin dosing and, thus, decrease thrombin production. If thrombin production can be decreased, potentially the incidence of 2 of the major complications of pediatric CPB (multiple organ dysfunction and bleeding) can be significantly reduced.

We acknowledge Cardiovascular Diagnostics Inc, Raleigh, NC, for providing us with free Heparin Management Test cartridges.

Presented at the 71st Annual Session of the Pacific Coast Surgical Association, San Francisco, Calif, February 20, 2000.

We acknowledge F. William Blaisdell, MD, as a leader in this field and a personal mentor to us. We also acknowledge James Sam, CCP, and Richard Yoshikawa, CCP, for their support of this study.

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DISCUSSION

Samuel E. Wilson, MD, Orange, Calif: For those West Coast surgeons who despair that the pressures of managed care practice put meaningful research beyond our reach, take heart. Read this manuscript carefully and realize that important basic and clinical research can still be accomplished. What is Dr Owings' and colleagues' secret? I attribute their continued success in critical care investigation to 3 factors illustrated by this article. First, they discern a problem important in their own clinical practice, in this case anticoagulation for CPB. Second, as the patients' surgeons, Dr Owings and colleagues take advantage of a unique and direct opportunity to measure disordered physiology in humans. Third, he has organized a multidisciplinary team—in this study, a surgeon, an anesthesiologist, and a clinical pathologist.

Owings et al recognized that the wide individual variance in heparin requirements, which, as no doubt you recall from previous meetings of this society, Dr Blaisdell had overcome by giving early large, fixed doses of heparin, eg, greater than 10 000 U of IV heparin as a bolus for pulmonary embolus. The wide variations in therapeutic dose heparin could be explained by such differences as the degree of hypothermia, time undergoing CPB, and the parameter the investigators chose here, hemodilution. Dr Owings' goal was important—more accurate and safer use of heparin in surgery.

In this case-controlled study, they have demonstrated convincingly that small children undergoing CPB have lower than optimal heparin dosage, largely due to surgeon's reliance on the ACT, which is a misleading characterization of the coagulation status in the hemodiluted patient. Inadequate anticoagulation, as the University of California–Davis Group has previously shown, leads to consumption of procoagulant factors and the consequences of fibrin and platelet deposition in the microcirculation.

I have several questions for Dr Owings and colleagues. (1) Hemodilution reduces blood viscosity, as well as fibrinogen levels. Could rheologic and dilutional changes other than decreased fibrinogen levels account for some of the change you noted in the ACT? Was there a significant difference in the hematocrit that would allow us to grasp the extent of hemodilution in your 2 patient groups? (2) Planned hemodilution is not unusual in adult surgery today to avoid blood transfusions. Should your measurements be extended to the adult patient undergoing deliberate hemodilution? (3) Did you observe any adverse clinical effects of the heparin underdosing? (4) Time undergoing CPB was 1½ times longer in the adults. How did platelet destruction and the other consequences of the blood materials' interface affect your results? (5) Last, should cardiovascular surgeons replace the ACT method with more precise measurements such as heparin levels intraoperatively?

William B. Long, MD, Portland, Ore: This paper raises a question of whether the surface area of the oxygenator and the pump circuit in general being larger proportionally for children than it is for adults causes any absorption of heparin onto the circuit? Consequently, did the authors tear down any of the circuits to see whether or not this had taken place?

Dr Owings: First, regarding the question of hemodilution reducing the viscosity, could there have been other factors at play here other than simply hemodilution? Certainly, that is a possibility, but with decreased viscosity one would expect actually decreased rather than increased coagulation.

What about the hematocrit? That is an excellent question and in looking back at these data, what we find is that the adults, indeed, had higher hematocrits. However, smoking causes an increase in the hematocrit and several other things that adults tend to do that children either are not allowed to do or should not do cause an increase in the hematocrit. Although hematocrit was significantly higher in adults, we chose to use the fibrinogen level to evaluate hemodilution because of its inherent importance in the clotting system.

What about hemodilution in the adults? I do believe that enough hemodilution in the adults would have the same consequences as what we saw here in the children. Yes, when we looked at our multivariate logistic progression model; however, what we did not find was a correlation between adult size, specifically in kilograms and this effect. So with either a hematocrit as a marker or the fibrinogen level as a marker of dilution once these markers are within a reasonably normal range, the ACT level appeared to correlate with heparin effect.

What about clinical outcomes? In this study where we had 10 children and 10 adults, our end points were laboratory-based rather than clinically based. We did have one mortality in the children's group, but that was far from statistically significant which led me to my final conclusion that a larger study with clinical end points would be warranted. I think that Dr Wilson's point on this is one that is well taken.

What about the time on the pump? A piece of data that was in the paper but not shown on the slides, was significantly longer pump runs for the adults than for the children. There again, that would tend to lead one to believe that the adults should have had a greater degree of thrombin formation rather than a lesser degree which was not the case.

Regarding Dr Wilson's final question, what about replacing the ACT method with the HMT, I do not think I can really come out with that recommendation at this point. The ACT does appear to be of value in adults, so all the adult cardiac surgeons need not throw away the machine they have, but the pediatric cardiac surgeon should really reconsider the use of the same machine that the adult surgeons are using when they are working on children.

Dr Long, certainly the children face a much larger proportional surface area in the pump than the adults do relative to their size. We did not, unfortunately, break apart any of these pumps and subject them to microscopic analysis, although that is an excellent idea. In part it has something to do with the degree of increased consumption that occurs in the children.