Maturation of the Hemostatic System During Childhood

By Maureen Andrew, Patsy Vegh, Marilyn Johnston, Janet Bowker, Frederick Ofosu, and Lesley Mitchell

The hemostatic system is assumed to be similar in children and adults and reference ranges established for adults are commonly used to evaluate children suspected of having congenital or acquired hemostatic problems. However, we know that the hemostatic system is not fully mature by 6 months of age and comprehensive studies of healthy older children have not been published. Therefore, we conducted a prospective cohort study of the hemostatic system in healthy children having minor, elective day surgery. After obtaining informed consent, a 3-mL blood sample was obtained at the time routine preoperative blood work was drawn. The plasma was fractioned and stored at -70°C for batch assaying. We know that the hemostatic system is not fully mature by 6 months of age and comprehensive studies of healthy older children aged 1 to 16 inclusive (a minimum of four subjects at each age). Eleven components of hemostasis (fibrinogen, prekallikrein, high-molecular weight kininogen, factors VIII and XIII, antithrombin III [ATIII], heparin cofactor II [HCII], α2-antitrypsin [α2AT], protein S, plasminogen, α2-antiplasmin [α2AP]) had mean values and ranges of normal that were similar to adults. Mean values of seven coagulants (II, V, VII, IX, X, XI, XII) were significantly lower than adult values and varied with age. Values for three inhibitors, α2-macroglobulin (α2M), protein C, and protein C1-inhibitor (C1-Inh) also differed from adults. α2M and C1-Inh inhibitor levels were elevated throughout childhood, whereas protein C levels were low, with a lower limit of normal of 0.40 U/mL until the age of 11. Finally, the upper limit of normal for the bleeding time was longer in children during the first 10 years of life, but decreased to adult values in the teenage years. In summary, there are important physiologic differences in the hemostatic system in children compared with adults. The decreased levels of several critical coagulants and increased levels of α2M may contribute in part to the lower risk of thrombotic events in childhood. Age-matched controls should be used for evaluation of the hemostatic system in children with suspected congenital or acquired defects.

THERE IS MINIMAL or no data available on plasma concentrations of many components of the hemostatic system during childhood because it has been assumed that normal ranges for adults also apply to children. Recent comprehensive studies of premature and fullterm infants during early postnatal life suggest that this may not be the case.1-3 Although plasma concentrations of many coagulation proteins reach adult ranges by 6 months of age, there remain significant differences from adults for both mean values and ranges of normal. Furthermore, there are isolated reports indicating that plasma concentrations of individual coagulation proteins or inhibitors may not reach adult levels until early or late childhood.4-10 Although slightly decreased mean plasma concentrations of certain coagulant proteins or inhibitors may not be of clinical significance, a lower limit of normal may well result in children being misclassified when investigated for an inherited or acquired defect.

For any given insult, whether it is inherited or acquired, children are at a significantly lower risk of developing thrombotic complications than adults.11 The physiologic mechanisms in place that are protecting children from thromboembolic complications have not been fully delineated. The purpose of the following study was to determine the normal plasma concentrations for the majority of known coagulation proteins during childhood, and gain insight into the lower risk of thromboembolic complications.

MATERIALS AND METHODS

Subjects. Healthy children aged 1 to 16 who were to be admitted to the short-stay unit at McMaster University Medical Centre in Hamilton, Ontario for elective day surgery between 1989 and 1991 were eligible for this study. These children were all clinically well and had no serious underlying illnesses nor history of bleeding problems in the family. Informed consent was obtained from the parents of all children and the study was approved by the Ethics Review Committee at McMaster University Medical Centre. In addition, 29 healthy adults receiving no medications were studied.

Laboratory. Blood samples (3 mL) were obtained by venipuncture at the same time that routine preoperative complete blood work was obtained. The blood was directly placed into a premarked plastic tube containing 3.2% buffered sodium citrate (1 part citrate:9 parts blood). Blood was immediately centrifuged (1,700g) and platelet-poor plasma removed and frozen for further coagulation studies. All assays were performed using previously published microtechniques.2,12 Coagulation screening tests, consisting of a prothrombin time (PT) (Thromborel S Behring, Diagnostics, Montreal, Quebec, Canada, ISI of 1.2-1.14) and international normalized ratio (INR), were calculated. Activated thromboplastin time (APTT) (Dade Actin FS, Canlab, Ontario, Canada) and fibrinogen were measured on the ACL using 0.1 mL of plasma.

Factor XIII subunits A and S were measured by Laurell immunoelectrohoresis with antibodies obtained from Behring (Ontario, Canada). The plasma inhibitors antithrombin III (ATIII), C1-inhibitor (C1-Inh), α2-macroglobulin (α2M), α1-antitrypsin (α1AT), and heparin cofactor II (HCII) were all measured immunologically by radial immunodiffusion with commercially available antibody (Atlantic Antibodies, NCS, Ontario, Canada, and Behring Hoechst, Quebec, Canada). ATIII was mea-
sured functionally by chromogenic assay. Protein C was measured by a chromogenic assay (Behring, Canada) and by an enzyme-linked immunosorbent assay (ELISA; Diagnostica Stago, Wellmark Diagnostics, Guelph, Ontario). von Willebrand factor (vWF) was also measured by an ELISA using rabbit antihuman vWF (Diagnostica Stago). Protein S was measured as the total protein S and free protein S by quantitative ELISA using sheep antihuman protein S antibody from Affinity Biologicals (Yarker, Ontario). Free protein S was obtained by polyethylene glycol (PEG) precipitation according to the method of Comp et al. The unknown values for the free protein S were read from a standard curve made of dilutions of normal pooled adult plasma, where the level of the pool was arbitrarily set at 0.4 U/mL. Plasminogen was measured by chromogenic assay (Diagnostica Stago). TPA was measured using an ELISA assay (Diagnostica Stago) and PAI by functional chromogenic assay (Biopool).

A bleeding time was performed with an automated pediatric device (Surgicutt, International Technidyne, Edison, NJ). A pediatric blood pressure cuff was inflated to 40 mm Hg. A horizontal incision, 3.5 mm in length by 1 mm in depth, was made on the cleaned skin of the forearm. The pediatric automated device uses a retractable blade to cut the skin with a swiping action. Blood was absorbed from the incision every 15 seconds with filter paper until bleeding stopped. In adult volunteers only, the pediatric automated device was compared with the adult automated device (Surgicutt).

A one-way analysis of variance was performed on the data at each year of life. Significant differences over age were found in factors IX, V, vWF, and XI, and the inhibitors protein S and C1-esterase inhibitor. Therefore, the data on the children were divided into age groups by age: 1 to 5, 6 to 10, and 11 to 16 years. Children's values at each age were compared with adult values to determine when they were statistically indistinguishable using Dunnet's test. All P values less than .05 were considered significant.

**RESULTS**

*Subjects.* Of 278 mothers interviewed, 263 agreed to have their children join the study. Seventeen samples were not suitable for use for a variety of reasons (sample size, hemolysis). Of the remaining 246 children, 163 were studied for coagulation parameters and 83 for the bleeding time. A minimum of four and a maximum of seven children were studied at each age. The children were grouped in ages from 1 to 5, 6 to 10 and 11 to 16 years.

*Laboratory.* Mean values and upper and lower boundaries that encompass 95% of the population (±2 SD) for each of the tests performed are presented in Tables 1 through 3. Table 1 gives the reference values for screening and procoagulant proteins; Table 2, reference values for inhibitors of the coagulation system; and Table 3, reference values for the fibrinolytic system. Values that were skewed are identified in Tables 1 to 3 and the lower limit adjusted to exclude 2.5% of the population. Values that differed significantly from those of adults are shown in Tables 1 through 3.

Figures 1 through 5 show mean values for each test performed in children and adults, and from previously published data at birth and at 6 months of age. All standard errors of mean values were less than 5% and are not given in the figures for purposes of clarity. The line drawn between 1 and 16 years of life represents the regression analysis of the data at each year of life.

### Table 1. Reference Values for Coagulation Tests in Healthy Children Aged 1 to 16 Years Compared With Adults

<table>
<thead>
<tr>
<th>Coagulation Tests</th>
<th>1 to 5 yr</th>
<th>6 to 10 yr</th>
<th>11 to 16 yr</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (boundary)</td>
<td>Mean (boundary)</td>
<td>Mean (boundary)</td>
<td>Mean (boundary)</td>
</tr>
<tr>
<td>PT (s)</td>
<td>11 (10.6-11.4)</td>
<td>11.1 (10.1-12.1)</td>
<td>11.2 (10.2-12.0)</td>
<td>12 (11.0-14.0)</td>
</tr>
<tr>
<td>INR</td>
<td>1.0 (0.96-1.04)</td>
<td>1.01 (0.91-1.11)</td>
<td>1.02 (0.93-1.10)</td>
<td>1.10 (1.0-1.3)</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>30 (24-36)</td>
<td>31 (26-36)</td>
<td>32 (26-37)</td>
<td>33 (27-40)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.76 (1.70-4.05)</td>
<td>2.79 (1.57-4.0)</td>
<td>3.0 (1.54-4.48)</td>
<td>2.78 (1.56-4.0)</td>
</tr>
<tr>
<td>Bleeding time (min)</td>
<td>6 (2.5-10)*</td>
<td>7 (2.5-13)*</td>
<td>5 (3-8)*</td>
<td>4 (1-7)</td>
</tr>
<tr>
<td>II (U/mL)</td>
<td>0.94 (0.71-1.16)*</td>
<td>0.88 (0.67-1.07)*</td>
<td>0.83 (0.61-1.04)*</td>
<td>1.08 (0.70-1.46)</td>
</tr>
<tr>
<td>V (U/mL)</td>
<td>1.03 (0.79-1.27)</td>
<td>0.90 (0.63-1.16)*</td>
<td>0.77 (0.55-0.99)*</td>
<td>1.06 (0.62-1.50)</td>
</tr>
<tr>
<td>VII (U/mL)</td>
<td>0.82 (0.55-1.16)*</td>
<td>0.85 (0.52-1.20)*</td>
<td>0.83 (0.58-1.16)*</td>
<td>1.05 (0.67-1.43)</td>
</tr>
<tr>
<td>VIII (U/mL)</td>
<td>0.90 (0.59-1.42)</td>
<td>0.95 (0.58-1.32)</td>
<td>0.92 (0.53-1.31)</td>
<td>0.99 (0.50-1.49)</td>
</tr>
<tr>
<td>vWF (U/mL)</td>
<td>0.82 (0.60-1.20)</td>
<td>0.95 (0.44-1.44)</td>
<td>1.00 (0.46-1.53)</td>
<td>0.92 (0.50-1.58)</td>
</tr>
<tr>
<td>IX (U/mL)</td>
<td>0.73 (0.47-1.04)*</td>
<td>0.75 (0.63-0.89)*</td>
<td>0.82 (0.59-1.22)*</td>
<td>1.05 (0.55-1.63)</td>
</tr>
<tr>
<td>X (U/mL)</td>
<td>0.88 (0.58-1.16)*</td>
<td>0.75 (0.55-1.01)*</td>
<td>0.79 (0.50-1.17)*</td>
<td>1.06 (0.70-1.52)</td>
</tr>
<tr>
<td>XI (U/mL)</td>
<td>0.97 (0.56-1.50)</td>
<td>0.86 (0.52-1.20)</td>
<td>0.74 (0.50-0.97)*</td>
<td>0.97 (0.67-1.27)</td>
</tr>
<tr>
<td>XII (U/mL)</td>
<td>0.93 (0.64-1.29)</td>
<td>0.92 (0.60-1.40)</td>
<td>0.81 (0.34-1.37)*</td>
<td>1.08 (0.52-1.64)</td>
</tr>
<tr>
<td>PK (U/mL)</td>
<td>0.96 (0.65-1.30)</td>
<td>0.99 (0.66-1.31)</td>
<td>0.99 (0.53-1.45)</td>
<td>1.12 (0.62-1.62)</td>
</tr>
<tr>
<td>HMWK (U/mL)</td>
<td>0.98 (0.64-1.32)</td>
<td>0.93 (0.60-1.30)</td>
<td>0.91 (0.63-1.19)</td>
<td>0.92 (0.50-1.36)</td>
</tr>
<tr>
<td>Xllla (U/mL)</td>
<td>1.08 (0.72-1.43)*</td>
<td>1.09 (0.65-1.51)*</td>
<td>0.99 (0.57-1.40)</td>
<td>1.05 (0.56-1.55)</td>
</tr>
<tr>
<td>Xlllb (U/mL)</td>
<td>1.13 (0.69-1.56)*</td>
<td>1.16 (0.77-1.54)*</td>
<td>1.02 (0.60-1.43)</td>
<td>0.97 (0.57-1.37)</td>
</tr>
</tbody>
</table>

All factors except fibrinogen are expressed as units per milliliter, where pooled plasma contains 1.0 U/mL. All data are expressed as the mean, followed by the upper and lower boundary encompassing 95% of the population. Between 20 and 50 samples were assayed for each value for each age group. Some measurements were skewed due to a disproportionate number of high values. The lower limit, which excludes the lower 2.5% of the population, is given.

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; VII, factor VIII procoagulant; vWF, von Willebrand factor; PK, prekallikrein; HMWK, high molecular weight kininogen.

*Values that are significantly different from adults.*
Table 2. Reference Values for the Inhibitors of Coagulation in Healthy Children Aged 1 to 16 Years Compared With Adults

<table>
<thead>
<tr>
<th>Coagulation Inhibitors</th>
<th>1 to 5 yr</th>
<th>6 to 16 yr</th>
<th>11 to 16 yr</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (boundary)</td>
<td>Mean (boundary)</td>
<td>Mean (boundary)</td>
<td>Mean (boundary)</td>
</tr>
<tr>
<td>ATIII (U/mL)</td>
<td>1.11 (0.82-1.39)</td>
<td>1.11 (0.90-1.31)</td>
<td>1.05 (0.77-1.32)</td>
<td>1.0 (0.75-1.26)</td>
</tr>
<tr>
<td>a2M (U/mL)</td>
<td>1.69 (1.14-2.23)*</td>
<td>1.69 (1.28-2.09)*</td>
<td>1.56 (0.98-2.12)*</td>
<td>0.86 (0.52-1.20)</td>
</tr>
<tr>
<td>C1-Inh (U/mL)</td>
<td>1.35 (0.85-1.83)*</td>
<td>1.14 (0.88-1.54)</td>
<td>1.03 (0.68-1.50)</td>
<td>1.0 (0.71-1.31)</td>
</tr>
<tr>
<td>α2AT (U/mL)</td>
<td>0.93 (0.39-1.47)</td>
<td>1.00 (0.69-1.30)</td>
<td>1.01 (0.65-1.37)</td>
<td>0.93 (0.55-1.30)</td>
</tr>
<tr>
<td>HCII (U/mL)</td>
<td>0.88 (0.48-1.28)*</td>
<td>0.86 (0.40-1.32)*</td>
<td>0.91 (0.53-1.29)*</td>
<td>1.08 (0.66-1.26)</td>
</tr>
<tr>
<td>Protein C (U/mL)</td>
<td>0.66 (0.40-0.92)*</td>
<td>0.69 (0.45-0.93)*</td>
<td>0.83 (0.55-1.11)*</td>
<td>0.96 (0.64-1.28)</td>
</tr>
<tr>
<td>Protein S</td>
<td>Total (U/mL)</td>
<td>0.96 (0.54-1.18)</td>
<td>0.78 (0.41-1.14)</td>
<td>0.72 (0.52-0.92)</td>
</tr>
<tr>
<td></td>
<td>Free (U/mL)</td>
<td>0.45 (0.21-0.69)</td>
<td>0.42 (0.22-0.62)</td>
<td>0.38 (0.26-0.55)</td>
</tr>
</tbody>
</table>

All values are expressed in units per milliliter, where for all factors pooled plasma contains 1.0 U/mL, with the exception of free protein S, which contains a mean of 0.4 U/mL. All values are given as a mean, followed by the lower and upper boundary encompassing 95% of the population. Between 20 and 30 samples were assayed for each value for each age group. Some measurements were skewed due to a disproportionate number of high values. The lower limits, which exclude the lower 2.5% of the population, are given.

*Values that are significantly different from adults.

The screening tests consisting of the PT, APTT, and fibrinogen were similar throughout childhood compared with adults (Table 1). For purposes of comparison of PT values measured with different reagents, the INR is also reported. In contrast to the latter tests, the bleeding time was significantly prolonged during childhood compared with adults using the pediatric device. The upper limit of normal was up to 13 minutes until the age of 10, compared with an adult upper limit of 7 minutes with the pediatric device. Twenty-seven percent of children had bleeding time values above the adult normal range determined using pediatric device. None of these children had any bleeding history nor bleeding during their surgical procedure. The pediatric bleeding time device was compared with the adult device in adults and gave consistently shorter values for both factors VI11 and vWF were similar to adults. Elevated in early childhood and decreased over age (Table 1). Mean plasma concentrations of the vitamin K-dependent coagulant factors (II, VII, IX, X) were among those that significantly differed during childhood from adults (Table 1 and Fig 1). Levels of all four factors remained comparable with those of adults until ages 11 to 16, when they decreased slightly. In contrast, the values for pre-kallikrein (PK) and high molecular weight kininogen (HMWK) were similar to adults at all ages (Table 1 and Fig 2).

Factor V showed a decreasing mean plasma concentration during childhood, with significantly lower levels during the teen years compared with adults (Table 1 and Fig 3). In contrast to the vitamin K-dependent factors and contact factors, the plasma concentrations of fibrinogen, VIII, and vWF, were similar to adults throughout childhood (Table 1 and Fig 4). Factors VIII and vWF showed a slightly skewed distribution, with some very elevated values. The lower limit of normal was adjusted to reflect the true limit excluding 2.5% of the population. The mean lower boundary for both factors VIII and vWF were similar to adults. Finally, plasma concentrations of factor XIIIa were the same as for adults, whereas factor XIIIb levels were elevated in early childhood and decreased over age (Table 1).

Plasma concentrations of many coagulation inhibitors showed striking differences from adults (Table 2 and Fig 4). Mean values and lower boundaries of normal for protein C and protein S were significantly decreased in children compared with adults. Indeed, 25% of children had protein C values less than 0.64 U/mL, the lower boundary of normal for adults. Although mean values for total and free protein S were similar, the lower boundaries were again

Table 3. Reference Values for the Fibrinolytic System in Healthy Children Aged 1 to 16 Years Compared With Adults

<table>
<thead>
<tr>
<th>Age</th>
<th>1 to 5 yr</th>
<th>6 to 10 yr</th>
<th>11 to 16 yr</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (boundary)</td>
<td>Mean (boundary)</td>
<td>Mean (boundary)</td>
<td>Mean (boundary)</td>
</tr>
<tr>
<td>Plasminogen (U/mL)</td>
<td>0.98 (0.78-1.18)</td>
<td>0.92 (0.76-1.08)</td>
<td>0.86 (0.68-1.03)*</td>
<td>0.99 (0.77-1.22)</td>
</tr>
<tr>
<td>TPA (ng/mL)</td>
<td>2.16 (1.0-4.5)*</td>
<td>2.42 (1.0-5.0)*</td>
<td>2.16 (1.0-4.0)*</td>
<td>4.90 (1.40-8.40)</td>
</tr>
<tr>
<td>α2AP (U/mL)</td>
<td>1.05 (0.93-1.17)</td>
<td>0.99 (0.89-1.10)</td>
<td>0.98 (0.78-1.18)</td>
<td>1.02 (0.68-1.36)</td>
</tr>
<tr>
<td>PAI (U/mL)</td>
<td>5.42 (1.0-10.0)</td>
<td>6.79 (2.0-12.0)*</td>
<td>6.07 (2.0-10.0)*</td>
<td>3.60 (1.0-11.0)</td>
</tr>
</tbody>
</table>

For α2AP, values are expressed as units per milliliter, where pooled plasma contains 1.0 U/mL. Values for TPA are given as nanograms per milliliter. Values for PAI are given as U/mL, where 1 U of PAI that inhibits 1 IU of human single-chain TPA. All values are given as the mean, followed by the lower and upper boundary encompassing 95% of the population (boundary).

*Values that are significantly different from adults.
THE HEMOSTATIC SYSTEM DURING CHILDHOOD

1.61

Fig 1. Mean values for vitamin K-dependent factors (II, VII, IX, X) in healthy term infants (F, n = 118) on day 1 and at 6 months of life; in healthy premature infants (P, n = 137) on day 1 of life; during childhood; and in adults. The line drawn between 1 and 16 years of age represents a best fit (regression analysis) of all the mean points at each year of life. SEMs were all less than 5%.

decreased compared with adults, and 15% of children had total protein S levels less than 0.60 U/mL. Mean HCII levels also remained lower throughout childhood. In contrast to low plasma concentrations for protein C and S, levels of α2M and C1-Inh were elevated in early childhood, and α2M levels remained elevated throughout childhood. There was no significant difference between immunologic and functional measurements of protein C and ATIII (data not shown).

Plasma concentrations of components of the fibrinolytic system are shown in Table 3 and Fig 5. Levels of plasminogen and α2-antiplasmin (α2AP) were similar to adults, whereas levels of tissue plasminogen activator (TPA) were low, and levels of plasminogen activator inhibitor (PAI) were increased.

DISCUSSION

The hemostatic system has been studied extensively during fetal life and immediately following birth. Studies of the early development of hemostasis during the first months of life were limited until recently. A comprehensive study of infants from day 1 of life until 6 months of age clearly showed that, although the hemostatic system continued to mature postnatally, it was still significantly different from adults at 6 months of age. For this reason, we proceeded to evaluate, in a similar systematic fashion, the hemostatic system throughout childhood.

A Medline search from 1980 to 1991 (blood/coagulation/children) failed to provide any references focused on normal values for components of the hemostatic system during childhood. Some studies that reported normal values for infants also evaluated plasma concentrations of...
selected coagulation proteins (prothrombin, factor IX, protein C, α2M, HCII, TPA, PAI) during early childhood alone. Our results for these proteins were similar to these previous publications. We extended these reports by studying children of all ages for most known coagulation proteins in plasma. The coagulation screening tests were similar in children compared with adults. However, plasma concentrations of certain procoagulants (II, V, VII, IX, X, XI, XII) were significantly lower at some time during childhood, while others were similar to adults (Table 1 and Figs 1 and 2). Plasma concentrations for two inhibitors (α2M, C1-Inh) were increased in early childhood (Table 2 and Fig 4). Indeed, plasma concentrations of α2M were twice adult values in early childhood and remained elevated throughout childhood. In contrast, mean plasma concentrations of protein C and HCII were significantly lower than for adults until early teenage years. Although plasma concentrations of plasminogen and α2AP were similar to adults, levels of TPA were lower and levels of PAI were higher than for adults (Table 3 and Fig 5). Finally, the bleeding time was significantly longer for children until approximately 10 years of age, compared with adults.

Although the hemostatic system is different in children compared with adults, it should be considered physiologic. There is no evidence that children are at greater risk for hemorrhagic problems than adults for any given insult. In addition, the risk for thrombotic complications is considerably less than for adults, suggesting that the hemostatic system in the young may have at least one significant advantage over the adult. For example, first thromboembolic events due to inherited deficiencies of protein C, protein S, or ATIII rarely occur in childhood. Thrombotic complications secondary to the nephrotic syndrome occur in only 2% of children compared with approximately 20% of adults. Children routinely undergo major abdominal and lower limb orthopedic surgery and do not require anticoagulant prophylaxis because thromboembolic complications are so rare. In contrast, adults undergoing similar procedures have a high risk of thromboembolic events and benefit from prophylactic anticoagulant therapy. The specific physiologic mechanisms that protect children are uncertain; however, there are several possibilities. The generation of thrombin is of central importance to the development of thrombotic complications. Plasma con-
centrations of prothrombin are directly related to the total amount of thrombin that can be generated in vitro in cord plasma and in plasma from patients on coumadin. Plasma prothrombin concentrations during childhood are 10% to 20% lower than for adults. Whether the latter influences the risk of thrombotic complications in children is unknown, but is a reasonable hypothesis to be explored. Prospective studies in adults have shown a significant positive relationship between plasma concentrations for factor VII and ischemic cardiovascular events in adults. Factor VII levels are significantly lower in children than young adults.

The effective inhibition of thrombin is also necessary for prevention of thrombolic complications. In adult plasma, ATIII is the major inhibitor of thrombin, with a2M and HCII fulfilling less important roles. We have reported that a2M inhibits more thrombin in plasma from children than from adults, likely reflecting the increased plasma concentration of a2M in childhood. One can hypothesize that high plasma concentrations of a2M provide additional protection from thrombotic events in healthy children. We also know that increased plasma concentrations of a2M complex with more thrombin in healthy infants who all have physiologic low levels of ATIII and in children with congenital heterozygote ATIII deficiency.

One potential mechanism for prevention of thromboembolic events is an enhanced fibrinolytic system. However, our data and another study of teenage girls both suggest that, under basal conditions, fibrinolysis is suppressed as evidenced by lower plasma concentrations of TPA and higher concentrations of PAI. When the same teenage girls were studied after venous occlusion to assess their fibrinolytic capacity, their response was again significantly less than similarly studied older women. In our study, the TPA and PAI ratio is significantly decreased during childhood (0.37) compared with adults (1.36). This information suggests that the fibrinolytic response increases with age.

In addition to fluid phase of hemostasis, the vessel wall provides an important antithrombotic surface under physiologic circumstances in adults. Although not well studied, it is apparent that the vessel wall undergoes an aging process that likely begins in early life. For example, concentrations of vessel wall glycosaminoglycans vary with age. The bleeding time measurement is the only currently available test of platelet vessel interaction in vivo. The long bleeding times reported here are similar to those of another report of children referred for a hemostatic evaluation.

In summary, the coagulation system in children is distinctly different from that in adults, and this difference must be considered physiologic. Based on the strikingly low rate of thrombotic complications during childhood, it seems apparent that the hemostatic system in children has at least one distinct advantage over the adult system. This study has established normal ranges for most known components of the hemostatic system throughout childhood and provided some insight into age-dependent features of both the coagulation and fibrinolytic systems.

ACKNOWLEDGMENT

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Maturation of the hemostatic system during childhood

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