

# Functional Maturity of the Coagulation System in Children: An Evaluation Using Thrombelastography

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There are quantitative deficiencies in the coagulation system for at least the first 6 mo of life. Clinical experience, however, does not indicate an increased risk of excessive bleeding during surgical procedures. Thrombelastography, a test providing a functional evaluation of coagulation, was used to assess the hemostatic system of pediatric patients under 2 yr of age. Thrombelastographic data were obtained from 237 healthy pediatric patients less than 2 yr of age undergoing elective noncardiac surgery. Five groups were distinguished: under 30 days, 1–3 mo, 3–6 mo, 6–12 mo, and 12–24 mo. Thrombelastography revealed no defects in coagulation when these groups

were compared to each other or to adults, indicating a functionally intact hemostatic process even in neonates. Indeed, children less than 12 mo of age were found to initiate and develop clot faster than adults, with the coagulation process slowing to adult rates after 1 yr of age. In addition to defining functional integrity, our data represents a set of pediatric control thrombelastographic values that have not been previously reported and that may become important in understanding coagulation changes that accompany disease states and surgery in pediatric patients.

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**T**he coagulation system is quantitatively deficient at birth, with maturational improvement in factor levels occurring during the first six months of life (1,2). Even at six months of age, though, many factor levels have not reached values equivalent to those of adults. There does not, however, seem to be a propensity for newborns and infants to bleed excessively, indicating functional stability of this quantitatively immature system (3,4).

Thrombelastography provides an evaluation of the functional integrity of the coagulation system from initial clot formation to clot retraction or dissolution (5–7). The tracing produced by the thrombelastogram (TEG) gives information about the rapidity of clot formation, the strength of the formed clot, and the presence of any fibrinolysis (8–11). Thrombelastography is gaining wider clinical use in the evaluation and treatment of coagulopathies associated with liver transplantation (10,12) and cardiac surgery (8,9). In light of the quantitative coagulation deficiencies in young children, we have used thrombelastography as a clinical coagulation monitor to determine whether

there are also functional defects in this age group, and to determine a range of reference values for these children.

## Methods

After approval from our institutional review board, TEGs obtained from 237 healthy children less than 2 yr of age who presented for elective noncardiac surgery were evaluated. The TEGs were divided into five groups based on the age of the patients: Group I, younger than 30 days ( $n = 37$ ); Group II, 1–3 mo ( $n = 50$ ); Group III, 3–6 mo ( $n = 50$ ); Group IV, 6–12 mo ( $n = 50$ ); Group V, 12–24 mo ( $n = 50$ ). All patients in Groups II, III, IV, and V presented via our day surgery unit for elective surgery. During the study period only 37 patients could be enrolled in Group I, including both outpatients ( $n = 13$ ) and inpatients ( $n = 24$ ), due to the infrequent occurrence of elective surgery in this age group. No patient in any group exhibited signs of acute systemic illnesses; none had previously diagnosed congenital heart disease; and none was receiving any medication known to have an effect on coagulation. Additionally, none of the inpatients in Group I was premature, none had complicating pathology other than that for which the surgery was scheduled,

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none had received transfusions, and none was receiving heparin-containing intravenous fluids. TEGs were also performed on 50 healthy adult volunteers to allow comparisons between pediatric and adult values. None of these adult volunteers demonstrated signs of acute systemic illnesses and none was taking coumadin, nonsteroidal antiinflammatory drugs, aspirin, or any over-the-counter medications which could contain occult aspirin.

Pediatric TEGs were obtained during placement of an intravenous catheter after the induction of general anesthesia. Within 1-2 min of collection, 0.36 mL of the native whole blood sample with no additives was placed into a preheated plastic cup of a Haemoscope Thrombelastograph® Coagulation Analyzer (Haemoscope Corp., Skokie, IL). The machine's piston was then lowered into the cup, a layer of liquid paraffin was applied to the top of the blood in the cup to prevent evaporation, and the TEG tracing was begun. The tracing was allowed to run until at least 60 min after achieving maximum width (maximum amplitude). Subsequently, each tracing was analyzed by manual measurement.

Five values were measured from the TEG tracing and used to characterize clot formation and stability: R, K,  $\alpha$  angle, MA, and A-60. The R value (reaction time) was measured from the beginning of the TEG recording until an amplitude of 2 mm was reached and represents the time necessary for initial clot formation. This variable reflects the function of the intrinsic coagulation pathway and, therefore, may be prolonged by coagulation factor deficiencies or heparin administration and may be shortened by hypercoagulable states. The K value (coagulation time) is the time interval from the end of the R value (2 mm amplitude) until an amplitude of 20 mm is attained. This value appraises the rapidity of fibrin build-up and cross-linking as the clot forms. The  $\alpha$  angle value similarly assesses this rate of clot formation and is measured as the slope of the outside divergence of the TEG tracing from the point of the end of the R value. The function of both fibrinogen and platelets is reflected by this variable. The maximum amplitude (MA) of the tracing is a reflection of the maximum strength of the fibrin clot and is influenced most importantly by fibrinogen levels, platelet numbers, and platelet function as well as by factors VIII and XIII. Decreased levels of fibrinogen, thrombocytopenia, and platelet dysfunction all result in diminished MA values. The A-60 value is the amplitude of the TEG tracing 60 min after the MA value has been reached. This value is useful in measuring clot retraction or destruction by comparing it to the MA value. An A-60:MA ratio (whole blood clot lysis index) of less than 0.85 has been used to define fibrinolysis (8,9,10,11).

Analysis of variance was used to ascertain whether differences existed in the TEGs between groups. Comparisons of groups were made using two-sided *t*-tests assuming unequal variances with Bonferroni correction for multiple comparisons.  $\chi^2$  analysis was used to determine differences between groups in the occurrence of fibrinolysis.

## Results

Results of our data collection are compiled in the following tables and are expressed as mean  $\pm$  SD. When the Group I outpatients ( $n = 13$ ) and inpatients ( $n = 24$ ) were compared, no significant differences were noted in the TEG values, so this data has been combined as a single Group I. As can be seen in Table 1, the coagulation variables of patients in Group I did not differ from those of older patients in Groups IV and V. While both Groups II and III had values that significantly differed from those of the other groups, Group II patients were more distinct in having values that suggested a more coagulable state. When compared to adult controls, almost all variables from the patients less than 12 mo of age (Groups I-IV) differed significantly from the adult values with the data from the pediatric patients demonstrating a faster initiation of clot formation (R value), a more rapid accumulation of clot (K and  $\alpha$  values), and increased clot strength (MA value). The oldest pediatric group's variables were the most similar to those of the adults but still exhibited increased clot strength.

Table 2 indicates the percentage of patients in each group in which the A-60 value was less than 85% of the MA value, a situation used to define fibrinolysis (11). No significant differences were found among groups by  $\chi^2$  analysis.

## Discussion

Although many coagulation factor levels in infants less than six months of age are significantly lower than those found in adults, functional maturity of the coagulation system of these children has been found using thrombelastography (Table 1). When compared to adults, children younger than one year demonstrate a seemingly more coagulable state as evidenced by a quicker onset of clot formation, a faster build-up of the clot, and an increased clot strength. Neonates do not differ from children over six months of age, and one- to three-month-old children possess the most coagulable system. The rates of clot initiation and build-up slow to adult rates after the age of 12 months. There is no difference in the occurrence of TEG-defined fibrinolysis in young children compared to adults.

The lack of a demonstrable functional coagulation defect by TEG in this study is remarkable in view of

**Table 1.** Thrombelastogram Values

Group	R (min)	K (min)	$\alpha$ angle ( $^{\circ}$ )	MA (mm)	A-60 (mm)
I (<30 days)	12.8 $\pm$ 3.7†	8.3 $\pm$ 2.5	35.5 $\pm$ 10.1†	58.6 $\pm$ 7.3†	52.9 $\pm$ 7.8†
II (1-3 mo)	13.0 $\pm$ 3.3†	6.2 $\pm$ 1.5*†	45.8 $\pm$ 7.4*†	65.4 $\pm$ 5.2*†	58.8 $\pm$ 6.1*†
III (3-6 mo)	12.0 $\pm$ 4.0†	6.6 $\pm$ 1.8*†	42.6 $\pm$ 8.9*†	61.3 $\pm$ 6.6†	55.0 $\pm$ 6.6†
IV (6-12 mo)	13.5 $\pm$ 3.1†	7.9 $\pm$ 1.7†	36.9 $\pm$ 6.7†	58.6 $\pm$ 4.9†	52.1 $\pm$ 5.6†
V (12-24 mo)	14.0 $\pm$ 3.4	8.5 $\pm$ 1.9	35.3 $\pm$ 7.6†	58.3 $\pm$ 4.5†	51.6 $\pm$ 5.3†
Adults	16.1 $\pm$ 3.3	9.2 $\pm$ 2.4	30.1 $\pm$ 6.7	51.6 $\pm$ 5.8	46.6 $\pm$ 6.7

R = reaction time; K = coagulation time;  $\alpha$  angle = assessment of rate of clot formation; MA = maximum amplitude; A-60 = amplitude of thrombelastogram tracing 60 min after MA has been reached.

\*  $P < 0.04$  versus Groups I, IV, and V.

†  $P < 0.025$  versus adults.

**Table 2.** Whole Blood Clot Lysis Index (Fibrinolysis)

Group	A-60/MA < 0.85 (% of patients)
I	13.5
II	6.0
III	10.0
IV	16.0
V	18.0
Adults	12.0

A-60 = amplitude of thrombelastogram 60 min after MA has been reached; MA = maximum amplitude.

the previously documented quantitative defects in children younger than six months. In both full-term and premature neonates, the contact factors (XII, XI, prekallikrein, and high molecular weight kininogen), the vitamin K dependent factors (II, VII, IX, and X), and many of the coagulation inhibitors (antithrombin III, heparin cofactor II, proteins C and S) are present in significantly smaller amounts than those found in adults with levels increasing into adult ranges by six months of age. Even at six months, though, mean levels for most of these factors remain significantly lower than those of adults (1,2). Experience gained while performing surgery on patients of this age does not indicate a tendency for these children to bleed excessively. Indeed, routine coagulation tests such as prothrombin time and thrombin clotting time demonstrate results similar to adult values even on the first day of life, implying adequate function of this quantitatively deficient system. By three to six months of age, the activated partial thromboplastin time has similarly achieved adult values after being initially prolonged due to low levels of the contact factors (1-3).

Several findings may help explain this discrepancy between numbers and function. First, it has been shown that coagulation remains intact with factor levels as low as 30% of normal in adults for all factors except V, which requires only 15% of normal levels (13). Levels above this are present in both full-term and premature babies even at birth (1,2). Secondly, investigations on infants' coagulation systems have focused mainly on plasma levels of factors and have not considered the kinetics involved. Accelerated metabolism and elimination of some factors (for example,

fibrinogen) have been demonstrated in infants; however, a continued increase in plasma levels during this time must indicate an even more accelerated synthesis of the factors (14). Therefore, quantitative deficiencies may simply result from a fast turnover rate of coagulation proteins and functional immaturity may not be present at all (15). Finally, several of the major participants in the clotting process, such as fibrinogen, factors VIII and XIII, and platelets, demonstrate no quantitative deficiencies at birth or within several days thereafter and thus may serve to anchor the coagulation system early in life (1,2,16,17).

When compared to adults, infants demonstrate a seemingly more coagulable state, as evidenced by a quicker onset of clot formation, a faster build-up of the clot, and an increased clot strength (Table 1). Similar results have been noted in other brief reports (4,16). It is known that during the period of hemostatic development in infancy, levels of some of the antithrombin proteins, the most important of which is AT-III (18), as well as the activities of these proteins are much lower than adult values (1,2,19). Quantitative maturation of AT-III occurs during the first six months of life, similar to the progression of the coagulation factors. However, plasma elimination of AT-III is greatly accelerated during at least the neonatal period (15). While the elimination rate of some coagulation factors has also been noted to be accelerated during this period (14). Elimination of AT-III is proportionately much faster when compared to adult rates than is that of the coagulation factors. One could speculate that an imbalance could result between factors promoting blood clotting and proteins inhibiting clotting and that this may explain the faster rate of clot initiation in younger children.

We found no differences in the occurrence of TEG-defined fibrinolysis among any of our groups (Table 2). While our observed incidence may be somewhat high, one must consider that this is a laboratory, not clinical, definition. Fibrinolysis is a normal physiologic event that accompanies any clot formation. None of our pediatric patients or adult controls bled excessively during surgery or after venipuncture. Our results

demonstrate functional maturity of this aspect of coagulation in young children as well. There is no previous report of the incidence of TEG-defined fibrinolysis in either children or adults.

We have not attempted to relate our TEG data to that of routine clotting tests since previous attempts to do so have shown poor correlations. In the normal population, fibrinogen levels and TEG MA values provide the only significant correlation between these two types of tests (6). The rationale behind this observation lies in the ability of the TEG to measure the hemostatic process in whole blood from the initiation of clot formation to the final stages of clot retraction or lysis. Routine clotting tests terminate with the formation of the initial fibrin strands. TEG variables, therefore, provide significantly more information about coagulation than do the isolated routine clotting tests performed on plasma samples (5,6). Consequently, it has been demonstrated that TEG data better predicts clinically significant coagulopathies after cardiopulmonary bypass, liver transplantation, and other major surgical procedures than do conventional clotting tests and that guidance of factor replacement therapy based on TEG data reduces the number of donor exposures needed to regain hemostatic balance (8,9,11,12,20). Our aim with this investigation was to provide evidence by thrombelastography of the functional status of the coagulation system in young children.

When comparing TEG values to published controls, one must be aware not only of age-related differences but also of discrepancies resulting from the addition of coagulation activators (celite) or pharmacologic therapies ( $\epsilon$ -aminocaproic acid, protamine, heparinase) to the native blood sample prior to its testing. Additionally, differences can also be introduced during the measurement of the TEG values. We have found significant discrepancies between values obtained by manual measurement of TEG tracings and those generated by computer evaluation. One must be aware of these potential variations when comparing their TEG values to reported "normals."

In summary, we have used thrombelastography to demonstrate functional maturity of the coagulation system in young children despite quantitative deficiencies in coagulation factors that persist until at least the age of six months. This data may help explain the lack of propensity for young children to bleed excessively during surgery or other invasive procedures, despite their quantitatively deficient coagulation systems. We have also defined a set of "normal" values for native TEGs measured manually in various subsets of children less than two years old. Care must be taken

to compare future TEG data to similarly tested and measured control values.

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