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# Procoagulant Activity and Thrombelastography in Korean Hemorrhagic Fever*

Munho Lee, M.D., Seonyang Park, M.D., Jin Suk Han, M.D., Young Yiul Lee, M.D., Hyok Yop Lee, M.D., Kyung Chae Kye**, Byoung Kook Kim, M.D., and Jung Sang Lee, M.D.

*Department of Internal Medicine College of Medicine, Seoul National University*
***Cancer Research Institute College of Medicine, Seoul National University*

*Twenty male patients with Korean hemorrhagic fever were evaluated with thrombelastography (TEG) to assess the changes in coagulation system, and the results were compared with those of conventional coagulation tests. Procoagulant activity in the plasma was determined by comparing the reaction time "r" of the normal plasma and that of the mixture of equal parts of the normal plasma and the patient's plasma. The TEG was found to be a useful measure of the changes in the coagulation profile, and provided instant accurate assessment of the patient's hemostatic function. Presence of the procoagulant activity was demonstrated in the plasma of the patients and indicated occurrence of active intravascular coagulation during the early stage of the disease.*

Key Words: *Korean hemorrhagic fever, thrombelastography (TEG), procoagulant activity*

## INTRODUCTION

Korean hemorrhagic fever is an acute viral disease characterized by hemorrhagic manifestations and renal failure. Thrombocytopenia and disseminated intravascular coagulation appear to play the major role in bleeding diathesis of the patients (Furth, 1954; Lee et al., 1983). The changes of the coagulation profile, however, is so rapid, and the occurence of disseminated intravascular coagulation is transient and restored promptly as the disease progresses (Lee et al., 1983). This was the main reason why the occurrence of disseminated intravascular coagulation has not been demonstrated since the disease appeared three decades ago (Lee et al., 1983). Accordingly, a rapid and simple test that can reflect the changes of the whole hemostatic function will be very useful for accurate assessment of the coagulation system as well as for proper management of these patients with severe bleeding tendency.

The thrombelastograph (TEG) is a useful monitor of the process of blood coagulation and fibrinolysis (De Nicola, 1957; Hartert, 1952). Hasegawa (1983) also showed that the analysis of the TEG pattern using normal plasma mixed with the patient's plasma could indicate the presence of procoagulant activity in the patient's plasma.

The present study was designed to evaluate the clinical usefulness of TEG in the assessment of coagulation changes in Korean hemorrhagic fever, and to demonstrate the presence of procoagulant activity in plasma and provide a proof of the occurrence of disseminated intravascular coagulation during the early stage of this illness.

*Supported by the 1985 Clinical Research Grant of the Seoul National University Hospital.
Address for Correspondence: *Munho Lee, M.D., Dept. of Internal Medicine, College of Medicine, Seoul National University, 28 Yunkun-Dong, Chongno-Ku, Seoul, 110, Korea*

## MATERIALS AND METHODS

*Materials:*

Twenty male patients from 22 to 24 years of age from the 1984 epidemic in Korea were included in this study. The diagnosis of Korean hemorrhagic fever was established by clinical features and confirmed by the serological demonstration of Hantaan virus antibody. The patients were in the febrile/hypotensive or early oliguric phase of the illness. Day of illness was counted from the day of symptom onset.

Control values for TEG *measurements were obtained from 12 normal volunteers (11 males and one female) with the ages ranging from 17 to 38 years.

*Methods:*

Conventional coagulation parameters including the platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), finbrinogen, factor VIII procoagulant activity (VIIIC) and fibrinogen-fibrin degradation products (FDP), and the TEG changes and plasma procoagulant activity were evaluated serially during the early stage of the disease and in convalescence.

The conventional coagulation tests were performed using the following equipments/reagents or methods; platelet count-TOA Platelet Counter PL-100, prothrombin time—Quick's one stage method, activated partial thromboplastin time—kaolin, fibrinogen—Biuret's method, factor VIII procoagulant activity—deficient substrate plasma supplied by DADE Diagnostics Inc. Miami, FL, USA, and fibrinogen-fibrin degradation products—latex agglutination method.

The TEG samples were obtained at bed side, and the reaction time (r), clot formation time (k), and maximal amplitude (ma) were determined using the Thrombelastograph D* from Hellige GMBH, Freiburg im Breisgau, West Germany as described in the operation manual (Hellige, 1979). The "r" value was the time from the starting point to 1 mm deflection. It represents intrinsic clotting. The "k" value was the time measured from the end of "r" until the point at which an amplitude of a=20 mm was reached. It represents a gauge for the speed at which a thrombus of a certain solidity, given as shear modulus E=25, develops. The "ma" value was determined as the greatest transverse amplitude of the graph. It reflects the maximum dynamic properties of fibrin and platelets. The value "r+k" was also determined to assess both the first and the second phase of coagulation (Fig. 1).

Procoagulant activity of the patient's plasma was from the "r" value of the normal plasma and *Kindly donated by the Alexander von Humboldt Foundation (Bonn Godesberg), West Germany.

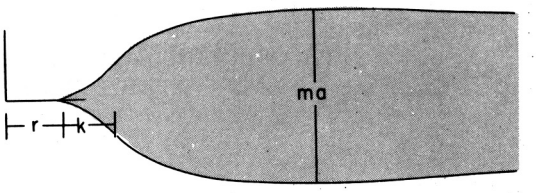



Fig. 1. Normal thrombelastograph
r=reaction time
k=clot formation time
ma=maximum amplitude

that of the mixture of equal parts of the normal plasma and the patient's plasma as described by Hasegawa (1983). It was determined as the ratio of the normal plasma "r"/"r" of the mixture of the normal plasma and the patient's plasma. The results were expressed as percentage and values greater than 130% were arbitrarily considered as abnormal.

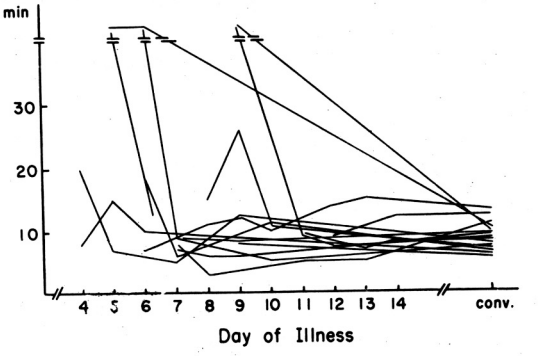



Fig. 2. Serial changes of reaction time (r) in 15 patients with Korean hemorrhagic fever

## RESULTS

*1. TEG values in normal controls*

The mean "r", "k", and "r+k" values in 12 normal volunteers were 11.2±2.4 min, 7.8±1.1 min, and 19.0±3.5 min, respectively. The mean "ma" value in normal controls was 103.8±4.1 mm.

*2. TEG patterns in Korean hemorrhagic fever*

The TEG patterns were evaluated in 15 patients. The "r" values were prolonged in the majority of the pa-

tients during the early stage of the disease. However, the "r" was restored promptly to normal levels as the disease progressed (Fig. 2). The "k" and "r+k" values revealed similar but more striking changes (Fig. 3, 4).

The "ma" values were significantly decreased in most patients during the early stage of the disease. The restoration of "ma" was much slower than that of "r", "k", or "r+k" (Fig. 5).

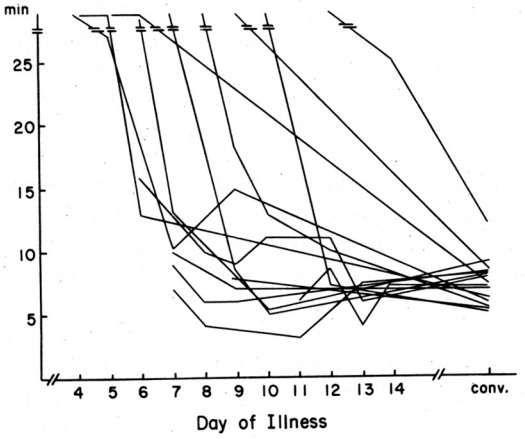



Fig. 3. Serial changes of clot formation time (k) in 15 patients with Korean hemorrhagic fever

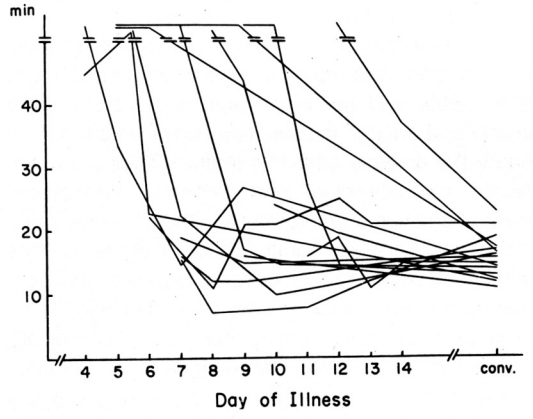



Fig. 4. Serial changes of reaction time plus clot formation time (r+k) in 15 patients with Korean hemorrhagic fever

*3. Conventional coagulation profiles in Korean hemorrhagic fever.*

The prothrombin time and activated partial thromboplastin time revealed marked prolongation in most patients during the early stage of the illness. The fibrinogen level was not significantly decreased during the early stage, but showed somewhat increasing tendency during the course of the disease. The factor VIII procoagulant activity was decreased in the majority of patients during the initial days (Fig. 6). Serum fibrinogen-fibrin degradation products were detected in all patients during the early stage of the disease.

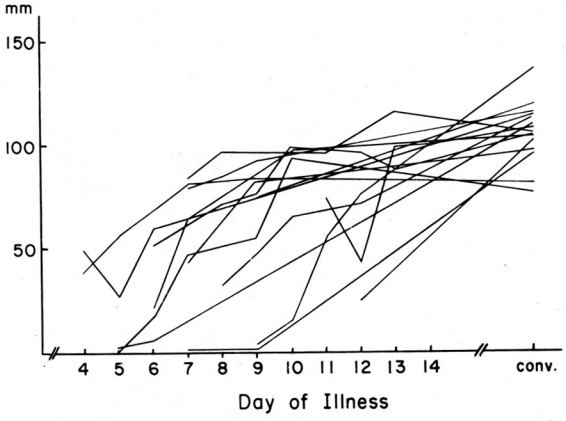



Fig. 5. Serial changes of maximum amplitude (ma) in 15 patients with Korean hemorrhagic fever

*4. Correlationship between the TEG measurements and the conventional coagulation parameters in Korean hemorrhagic fever*

No significant correlationship was found between the "r", "k", or "r+k" value and any of the conventional coagulation parameters.

*5. Procoagulant activity in Korean hemorrhagic fever*

Presence of the plasma procoagulant activity was observed during the early stage of the disease. Procoagulant activity greater than 130% was found in 16 of the 20 patients (80%) during the early stage of the illness. The procoagulant activity was restored to normal range in convalescence in the majority of the patients while two cases still showed mild to moderate elevations of the activity (Fig. 7).

*6. Case analysis*

Fig. 8 shows the serial changes of TEG and other coagulation parameters in a 22-year-old male patient with Korean hemorrhagic fever. The TEG revealed virtually no thrombin formation in day 5, when the platelet count was 20,000/ul, prothrombin time 12 sec, activated partial thromboplastin time 50 sec, serum

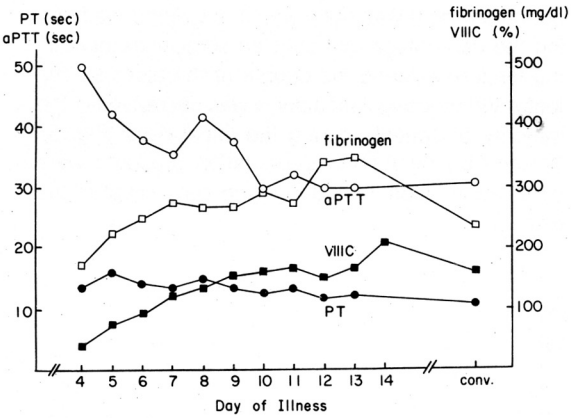



Fig. 6. Serial changes of the mean values of prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and factor VIII procoagulant activity (VIIIC) in 15 patients with Korean hemorrhagic fever

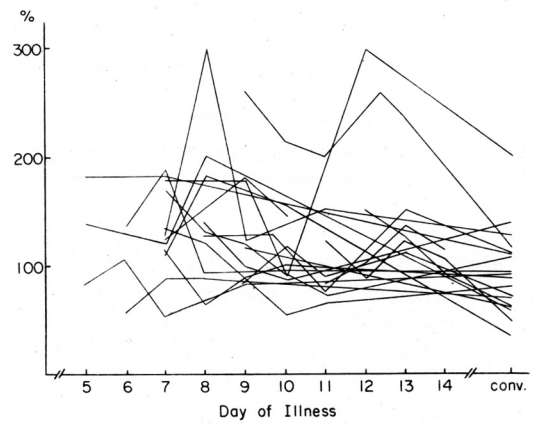



Fig. 7. Serial changes of procoagulant activity in the plasma of 20 patients with Korean hemorrhagic fever

fibrinogen 175 mg/dl, and factor VIII procoagulant activity 40% of normal. The prothrombin time was in normal range during the course of the disease, and activated partial thromboplastin time and serum fibrinogen levels were rapidly normalized while the factor VIII procoagulant activity was increased to even above the normal range. The "r" and "k" values were restored to normal range on day 7, but the amplitude curve revealed characteristic disaggregatory patterns even after the "ma" values began to increase and most of the conventional coagulation parameters were normalized.

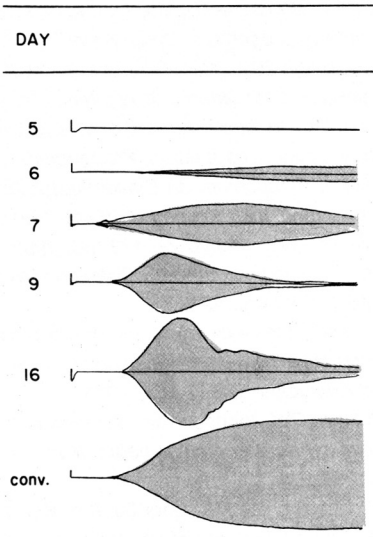
## DISCUSSION

Korean hemorrhagic fever is an acute febrile disease caused by Hantaan virus (Lee et al., 1978). The clinical course of the disease is characterized by fulminating hemorrhagic tendency and renal failure. The pathogenetic mechanisms of hemorrhagic tendency may generally be framed in terms of thrombocytopenia, disseminated intravascular coagulation, abnormal platelet function, capillary damage, and uremia (Park et al., 1985). Although the most likely explanation appears to be a combination of the factors listed, thrombocytopenia and disseminated intravascular coagulation undoubtly play the major role for the hemorrhagic tendency in the early stage of Korean hemorrhagic fever (Furth, 1954; Lee et al., 1953; Park et al., 1985).

Shortened platelet survival and increased megakaryopoiesis was demonstrated in the early stage of this disease when the thrombocytopenia reached its maximum (Park et al., 1985). Disseminated intravascular coagulation has been suggested as a cause of bleeding since Dennis and Conrad (1968) reported a patient with accelerated intravascular coagulation. Although questions have been raised concerning the occurence of disseminated intravascular coagulation in Korean hemorrhagic fever, well-designed studies from our laboratory (Lee et al., 1983) and elsewhere (Bunin and Abdurashitov, 1976; Sirotin et al., 1977) revealed that it is encountered rather frequently during the initial days of the disease.

In Korean hemorrhagic fever, the changes in coagulation system is abrupt in onset and progression (Lee et al., 1983), and the hemorrhagic manifestations are impressive enough to have lead early investigators to name the disease after this feature. They are manifested by petechiae, hematemesis, hemoptysis, melena and hematuria (Lee et al., 1980, Sheedy et al., 1954). Accordingly, accurate evaluation of the changes in hemostatic function is essential for proper management of these patients. Conventional coagulation tests, however, are time-consuming and numerous items are required to comprehensively understand the changes.

The TEG is a useful monitor of the process of blood coagulation including fibrinolysis (De Nicola, 1957; Hartert, 1952). It provides instant accurate measurements of the clinically useful indices of clotting and lysis by recording the speed of coagulation, the shear elasticity and clot retraction (Hellige, 1979). It may be particularly useful in clinical conditions when abrupt changes in coagulation system produce profuse bleeding and rapid assessment of the whole coagulation profile is essential for proper management of the patient.



| DAY | PLATELET (/μl) | PT (sec) | aPTT (sec) | FIBRINOGEN (mg/dl) | VIIIC (%) | FDP |
|---|---|---|---|---|---|---|
| 5 | 20000 | 12.0 | 50 | 175 | 40 | + |
| 6 | | 12.0 | 30 | 300 | 220 | + |
| 7 | | 13.5 | 32 | | 220 | + |
| 9 | 70000 | 12.0 | 32 | 360 | 150 | − |
| 16 | | | | | | |
| conv. | | 12.0 | 33 | 275 | 150 | − |

Fig. 8. Serial changes of the thrombelastograph and conventional coagulation tests in a 22-year-old male patient with Korean hemorrhagic fever

The reaction time (r) reflects intrinsic clotting and is very sensitive to changes in thromboplastin plasma procoagulants (Howland et al., 1974). The latter characteristic can be utilized to detect procoagulant activity through demonstration of the shortening of the "r" value of normal plasma when mixed with the test plasma (Hasegawa, 1983). The clot formation time (k) represents a gauge for the speed at which a thrombus of a certain solidity develops (Hellige, 1979). The value "r+k" includes both the first and the second phase of coagulation and indicates any shortening or lengthening of the coagulation time to a much finer degree than "r" alone. Determination of the value "r+k" has proved particularly beneficial in the prophylaxis of thromboembolisms (Hellige, 1979). The maximum amplitude (ma) is a direct function of the maximum dynamic properties of fibrin and platelets. The slightest platelet abnormality, whether qualitative or quantitative, substantially disturbes "ma". A value less than 40 mm indicates inadequte platelet function and/or a deficiency of fibrinogen (Howland, 1974).

In this study, the TEG was found to be a useful and relatively accurate measure of the coagulation system in patients with Korean hemorrhagic fever. The "r" value and, more strikingly, "k" and "r+k" values were prolonged and indicated decreased levels of coagulation factors. The "ma" value was markedly decreased in the early stage of the disease. With the restoration of the platelet counts, the "ma" value began to increase while the distored shape and disaggregatory pattern indicated an increase of the fibrinolytic activity. The overall assessment of the changes in the coagulation profile could be promptly made at bed side, and the conspicuous and characteristic changes of the graph were impressive enough to denote even minor changes in the coagulation as well as fibrinolytic systems although the individual TEG values did not show any significant correlationship with the results of conventional coagulation tests.

The clinical diagnosis of disseminated intravascular coagulation depends on the demonstration of decreases of the platelet count and clotting factors, and the detection of fibrinolytic products (Colman et al., 1972). All these findings, however, reflect the secondary changes following the initial intravascular coagulation event by a certain cause with procoagulant activity. Theoretically, it may be more reasonable to demonstrate the procoagulant activity in blood to diagnose accurately disseminated intravascular coagulation. Hasegawa (1983) suggested that the TEG measurement of the procoagulant activity in plasma might be the most useful and rapid diagnostic test in disseminated intravascular coagulation. In the present study, the upper limit of normal procoagulant activity was arbitrarily determined for statistical analysis at 130%, the usual cut-off value for the most coagula-

tion tests in common use, for we did not have sufficient data in our laboratory nor in the literatures for its determination.

In Korean hemorrhagic fever, 80% of the patients showed evidence of the presence of procoagulant activity in plasma during the early stage of the disease. The procoagulant activity was still demonstrated in convalescence in two cases indicating persistence of the intravascular coagulation process in some patients up to this late stage of the illness. This is in accordance with our previous finding that some fibrinolytic products were detected in serum of the most patients in the early recovery phase of this disease (Lee et al., 1983) and a Russian report that evidence of ongoing fibrinolysis was demonstrated by six months after recovery from hemorrhagic fever with renal syndrome (Sirotin et al., 1977). To our knowledge, the present study appears to be the first direct demonstration of the procoagulant activity in Korean hemorrhagic fever, and undoubtedly supports the occurrence of disseminated intravascular coagulation during the course of this illness.

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