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## Changes of the Kallikrein-Kinin System in Acute Phase of Hemorrhagic and Septic Shock

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### Introduction

Various protease inhibitors with anti-shock effects are used for treating various shock states. We evaluated the dynamics of the Kallikrein-kinin system, which is important as a site of action for these drugs as well as a factor associated with the formation of the shock cycle, and closely associated coagulation-fibrinolysis and complement systems (Fig. 1) in the acute stage of shock.

### Subjects and Methods

The subjects consisted of 17 patients with hemorrhagic shock and 5 with septic shock (mean age, 43 years) who were treated at 2nd Department of Surgery, Kinki University School of Medicine and at Critical and Emergency Center, Osaka Prefectural Hospital during the 2 years and 6 months between January, 1985 and June, 1987 (Table 1). Hemorrhagic shock was defined as bleeding with a blood pressure of 90 torr or less, and sepsis as arterial blood positive for bacilli with organ failure. Shock was considered to have developed when blood pressure fell to 90 torr or less. Shock improved in 12 of the 22 patients (55%), and 16 of the 22 patients (73%) died. Improvement of shock was defined as continuance of a systolic blood pressure of 100 torr or more for 6 hours within 48 hours of its onset.

The parameters measured were prekallikrein and high molecular weight kininogen (HMW-Kg), which are representative factors in the kallikrein-kinin system, AT-III, plasminogen (PLg), and  $\alpha$ 2-macroglobulin ( $\alpha$ 2-MG) in the coagulation-fibrinolysis system, C3 in the complement system, and lactic acid as a parameter of peripheral circulation. Blood was collected 0, 12, 24, 48, 72, and 96 hours after the development of shock, immediately centrifuged using a refrigerated

Key words: Kallikrein-kinin system, Coagulation-fibrinolysis system, Hemorrhagic shock, Septic shock, Prekallikrein, High molecular weight kininogen.

索引用語: カリクレイン・キニン系, 凝固・線溶系, 出血性ショック, 敗血症性ショック, プレカリクレイン, 高分子キノーゲン.

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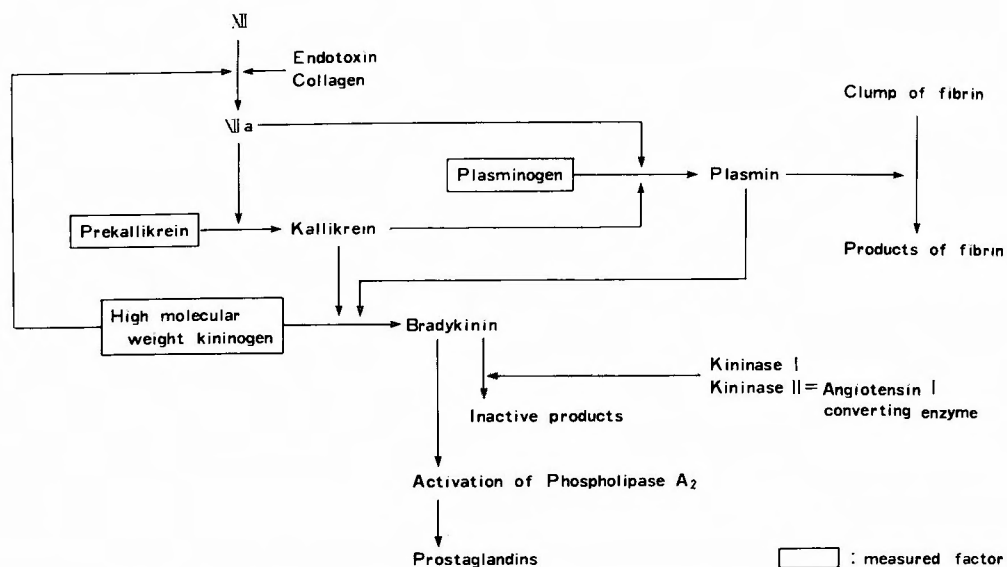


Fig. 1. Correlation between Kallikrein-Kinin system and other systems, matters

centrifuge, and the plasma was stored at  $-20^{\circ}\text{C}$ . Prekallikrein and HMW-Kg were measured by the SDA method, AT-III, PLg, and  $\alpha 2$ -MG by the chromogenic synthetic substrate method, C3 by the TIA method, and lactic acid by the enzymatic method using lactate oxidase.

Table 1. Subjects (22 patients)

Patient	Age	Sex	Disease	Improvement of shock	Outcome
1	67	Male	traumatic aortic rupture	+	Death
2	43	Male	hemopneumothorax, pelvic fracture	+	Survival
3	43	Male	small intestine rupture, intraabdominal hemorrhage	-	Death
4	19	Male	traumatic liver rupture	+	Death
5	46	Male	brachial artery injury	+	Survival
6	54	Male	crushed thigh, pelvic fracture	+	Death
7	11	Male	liver and spleen rupture		Death
8	72	Male	depressed skull fracture		Death
9	19	Male	superior sagittal sinus fracture		Death
10	49	Male	brachiocephalic trunk injury	+	Death
11	49	Male	abdominal stab injury	+	Survival
12	18	Male	facial and femoral bone fracture	+	Survival
13	44	Male	crushed thigh, pelvic fracture		Death
14	54	Male	superior mesenteric artery and vein injuries		Death
15	35	Female	cervical duct injury	+	Survival
16	18	Male	subclavian artery laceration	+	Survival
17	49	Male	superior mesenteric artery injury	+	Death
18	47	Male	suture insufficiency (after operation for esophageal cancer)	-	Death
19	54	Male	large intestinal cancer rupture	-	Death
20	68	Male	mesenteric thrombosis	-	Death
21	39	Female	acute hemorrhagic pancreatitis	+	Death
22	39	Female	suture insufficiency (after operation for pancreatic cancer)	-	Death

1 - 17 : patients with hemorrhagic shock  
18 - 22 : patients with septic shock

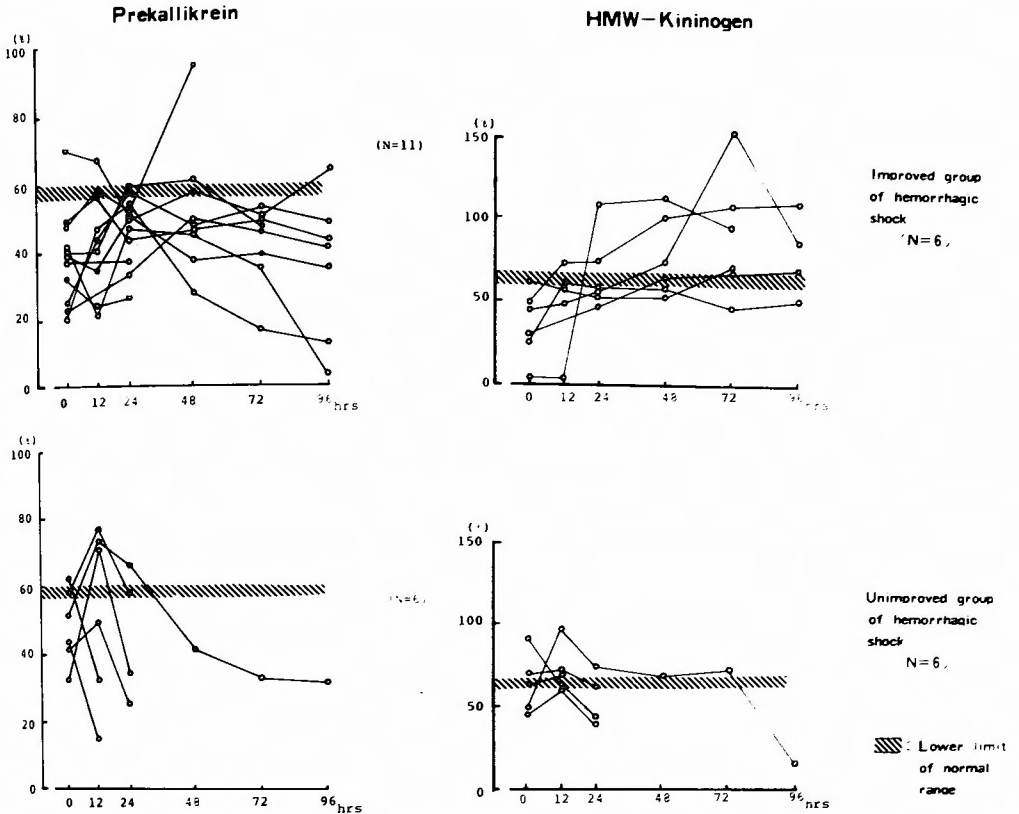


Fig. 2.

Results

1. Patients with hemorrhagic shock

The 17 patients with hemorrhagic shock were divided into a group in whom shock improved (improved group) and a group in whom shock did not improve (unimproved group). The time courses of prekallikrein and HMW-Kg values in the two groups are shown in Fig. 2. Prekallikrein and HMW-Kg were already decreased at the initial consultation, showing activation of the kallikrein-kinin system at the very early stage of shock. These parameters recovered in the improved group but not in the unimproved group. In the improved group, HMW-Kg recovered already after about 24 hours, while the recovery of prekallikrein was delayed. In the unimproved group, prekallikrein transiently increased after 12-24 hours and tended to decrease thereafter; the importance of these changes remains obscure.

As shown in Fig. 3, both AT-III and C3 were decreased at the initial consultation. They tended to increase in the improved group but decrease in the unimproved group.

PLg was also decreased at the initial consultation and tended to increase in the improved group. In the unimproved group, it tended to be consumed, showing further activation of the fibrinolysis system.  $\alpha$ 2-MG was nearly in the normal range in both groups but tended to be

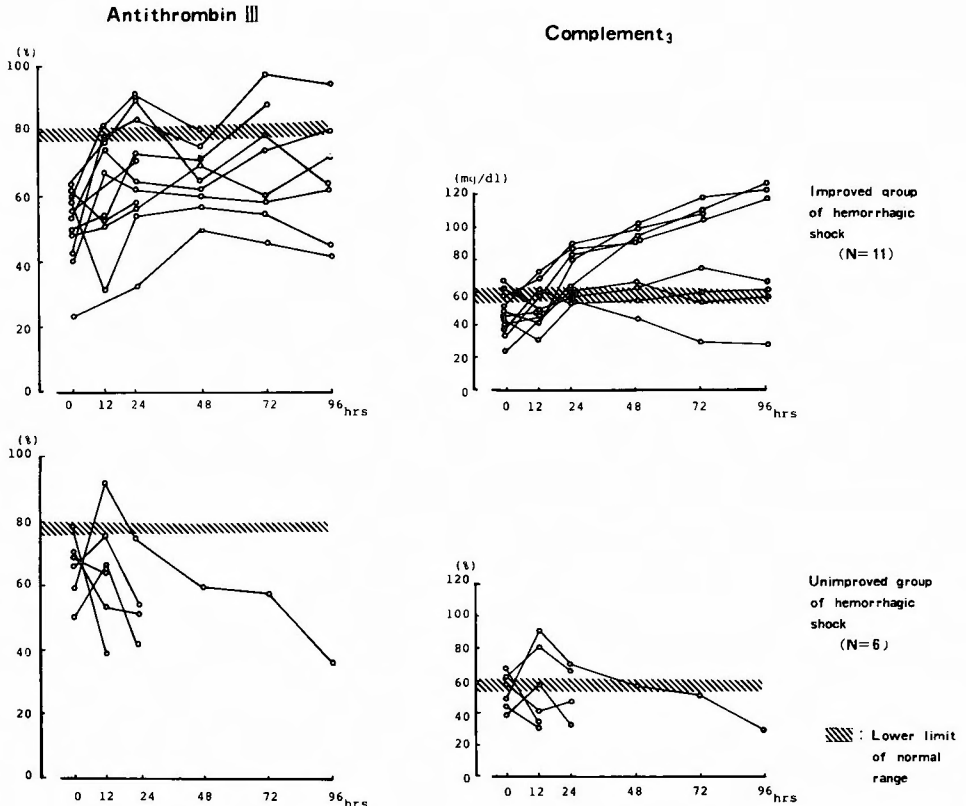


Fig. 3.

increased in the unimproved group (Fig. 4).

These results suggest rapid activation of the kallikrein-kinin, coagulation-fibrinolysis, and complement systems following the development of hemorrhagic shock. There were apparent differences in the reactions of these systems between the improved and unimproved groups.

Lactic acid markedly increased at the early stage, demonstrating peripheral circulatory failure. It decreased with time in the improved group (Fig. 5).

2. Patients with septic shock

All the 5 patients with septic shock died. Shock improved only in 1 patient, in whom, the parameters in each system tended to recover. However, in the other 4 patients in whom shock did not improve, values of these parameter were already abnormal at the initial consultation and did not improve with time (Figs. 6 and 7).

3. A patient with typical hemorrhagic shock who improved

Fig. 8 shows the recovery process of the parameters in the 3 systems in a 46-year-old male with simple typical hemorrhagic shock. He developed severe hemorrhagic shock due to rupture of the brachial artery resulting from stab injury to the brachium. Following cardiopulmonary resuscitation (CPR) and surgery and transfusion of 26 units of blood, the condition dramatically

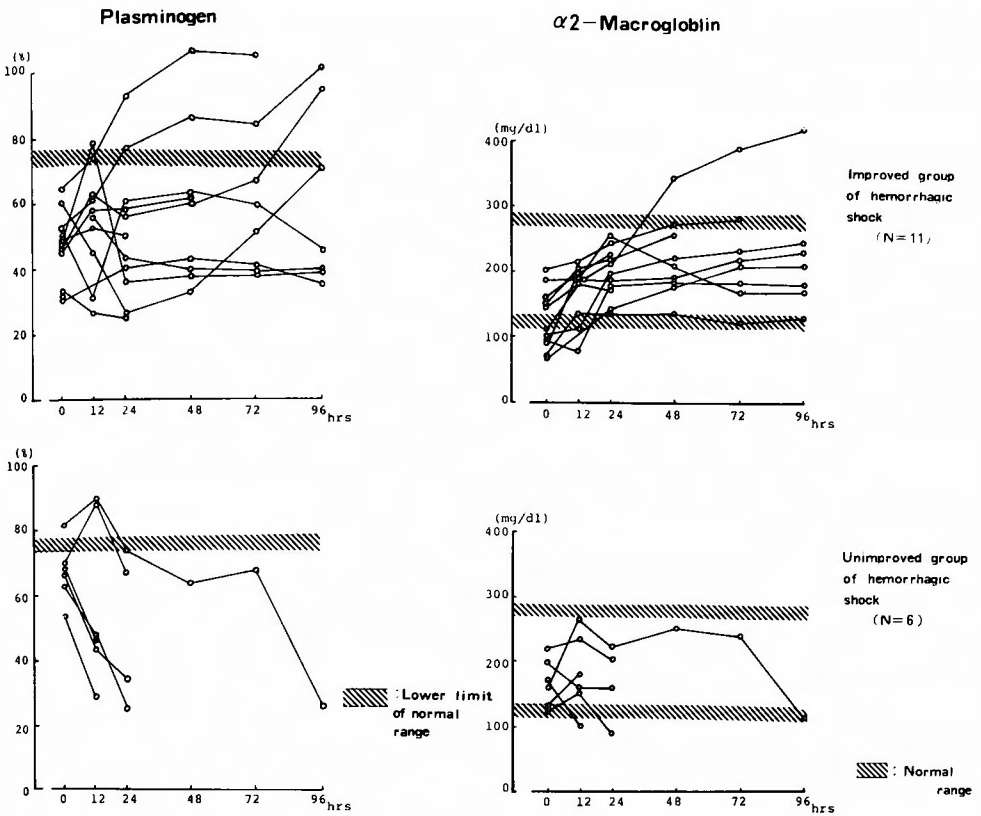


Fig. 4.

improved.

In this patient, as suggested above in the patient who improved, despite continuously decreased prekallikrein, HMW-Kg recovered after about 24 hours, and AT-III and C3 also improved. These findings suggest the importance of inhibitors at the stage of HMW-Kg activation by kallikrein rather than prekallikrein depletion in resuscitating patients from shock.

### Discussion

Shock induces, unless its cause is removed, and appropriate treatment is done, destruction of kinetic equilibrium in each biologic system, resulting in an irreversible state of disseminated intravascular coagulation (DIC) with a very poor prognosis for life<sup>3)</sup>. Therefore, for treating shock it is necessary to evaluate changes in parameters in the kallikrein-kinin, coagulation-fibrinolysis, and complement systems. Recently the importance of chemical mediators has been recognized, and especially, hydrolases that escape from lysosomes, which are minute granules in the cell, have attracted attention. These proteases are considered to cause extensive cell injuries in vital organs, aggravating shock<sup>6)</sup>. In this study, the dynamics of the 3 systems was evaluated from the ultra-acute stage.

### Lactic acid

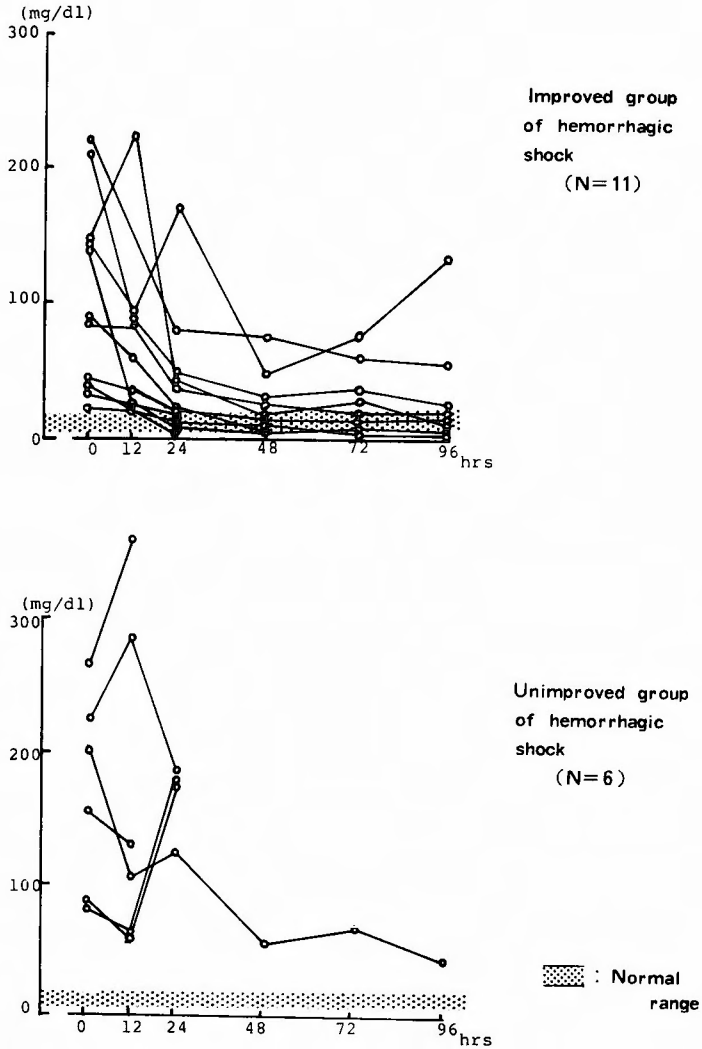


Fig. 5.

Prekallikrein, HMW-Kg, AT-III, PLg, and C3 were already decreased in the patients with hemorrhagic or septic shock at the development of shock, suggesting activation of the 3 systems from the ultra-acute stage. In the patients with hemorrhagic shock, these parameters improved as the shock state improved, showing a correlation with clinical condition. Retrospective comparison of the mean volume of blood transfusion showed no statistical difference between the improved group (41 units) and the unimproved group (53 units). This finding excludes the possibility of the contribution of blood transfusion to the difference between the improved and unimproved groups.

## Septic shock

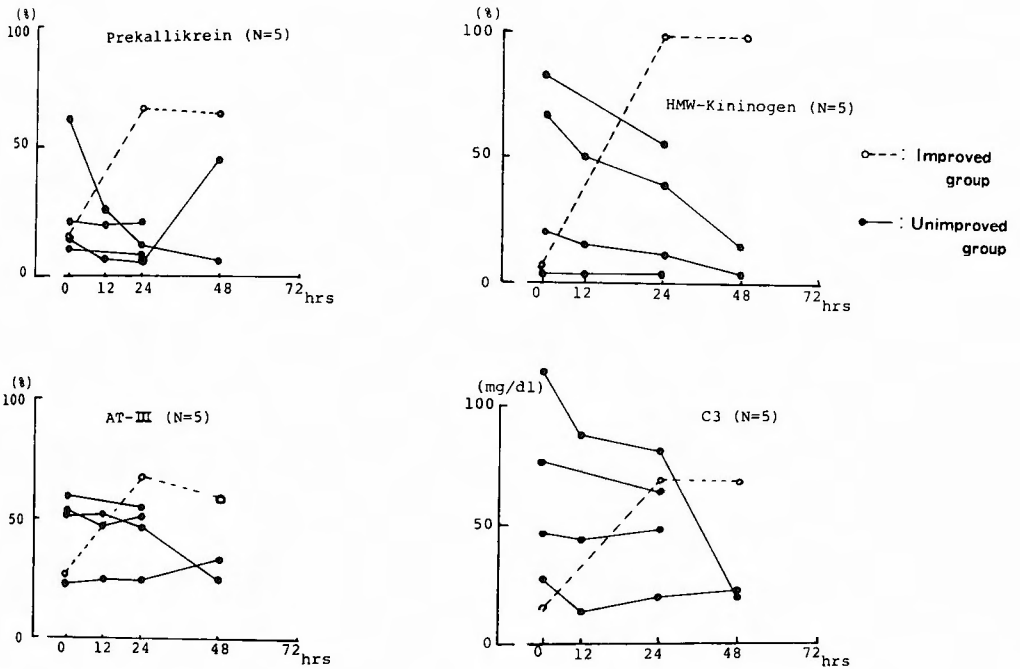


Fig. 6.

Of the patients with septic shock, only 1 showed improvements in shock, demonstrating the seriousness of this pathologic condition. Attention should be also paid to the underlying diseases that induced sepsis. Septic shock in these patients was the terminal condition of highly lethal diseases such as esophageal cancer, suture insufficiency after radical operation for pancreatic cancer, rupture of large intestinal cancer, and acute thrombosis of the superior mesenteric artery. The underlying disease was not successfully treated, and there is high possibility that shock was already irreversible when its diagnosis was made. This may be a cause of the no improvement. In the 1 patient who improved, intensive treatment was initiated at a relatively early stage under a diagnosis of acute hemorrhagic pancreatitis, and weaning from a respirator and discontinuation of hypertensors were successful. However, she died of necrosis of the entire stomach of unknown cause<sup>9)</sup>. In acute pancreatitis, UEHARA<sup>7)</sup> reported decreased plasma prekallikrein, a negative correlation between kallikrein-like activity and prekallikrein activity, and decreased high molecular and low molecular kininogen. In our study, the patient with acute pancreatitis also showed decreases in plasma prekallikrein and HMW-Kg at the early stage but their increases as shock improved.

As dynamics of the kinin system in septic shock, WERLE et al<sup>8)</sup> showed in patients or animals in septic shock, a correlation between decreases in blood pressure during shock and decreases in blood kininogen associated with release of kinin. KADOKURA<sup>2)</sup> produced strangulation ileus in the upper small intestine in dogs and observed that blood plasma kinin gradually increased as



## Septic shock

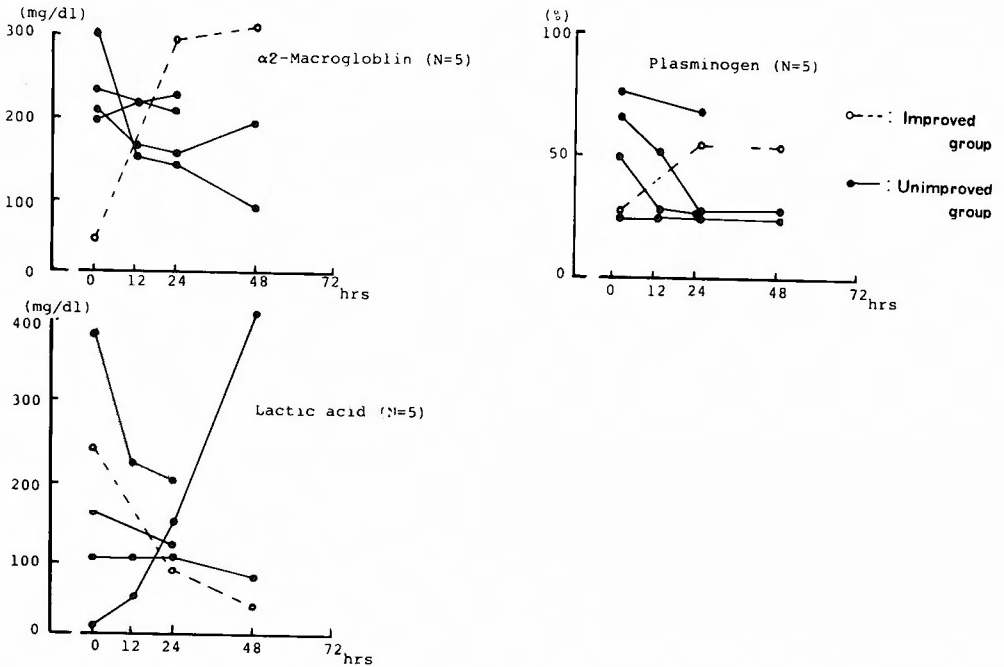


Fig. 7.

the ileus progressed, reaching markedly high values at the time of death. In association with these observations, SHIBA<sup>5)</sup> and HENMI<sup>1)</sup> reported that blood kinogen tended to decrease while kallikrein and plasmin activity increased with the progression of ileus. O'DONNELL et al.<sup>4)</sup> measured kinin and prekallikrein in 21 patients with sepsis and observed a decrease in blood prekallikrein in all patients and an especially marked decrease in those with hypotension. The decreases in these parameters seem to be consumption associated with enhanced activity of the kinin system, and inhibition of kinin activity may be important for resuscitation from the shock cycle. Our findings may provide rationale for the effectiveness of aprotinin, which inhibits the kinin system at the stage of the action of kallikrein on HMW-Kg, and urinastatin with multivalent effects.

## Conclusion

We serially measured representative parameters in the 1) Kallikrein-kinin system, 2) coagulation-fibrinolysis system, and 3) complement system in 17 patients with hemorrhagic shock and 5 patients with septic shock from the acute stage of shock and obtained the following results.

1. In the patients with hemorrhagic shock, these 3 systems were simultaneously activated from the very early stage of shock but tended to improve as shock improved.
2. In the patients with septic shock, the 3 systems were difficult to improve.

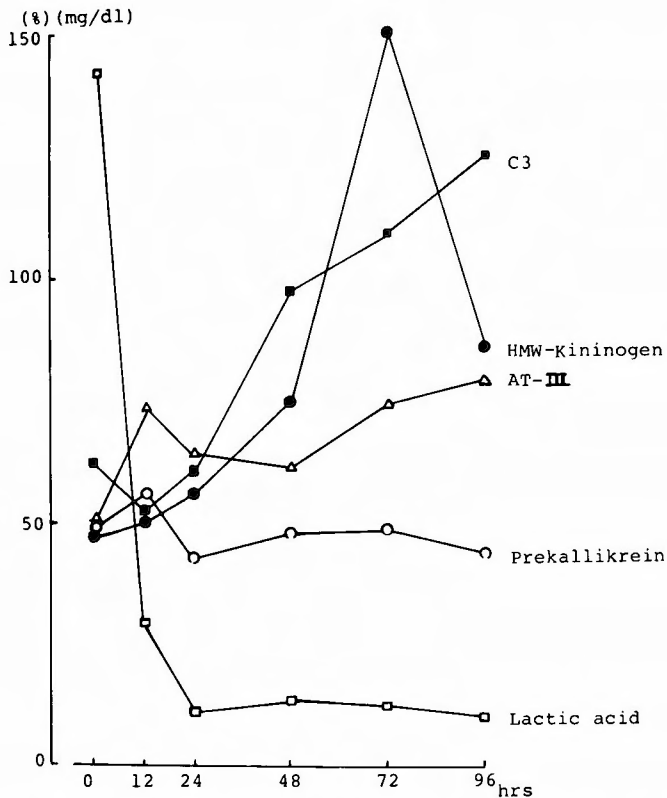


Fig. 8. A improved case of hemorrhagic shock 46 years old, male, brachial artery injury, dead on arrival (DOA), base excess (B.E.) -12.

- The decreases in prekallikrein and HMW-Kg seem to be consumption associated with enhanced activity of the kallikrein-kinin system, suggesting the involvement of a certain factor that inhibits activation of HMW-Kg by kallikrein in improvement of shock.

#### Acknowledgments

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## 和文抄録

# 出血性・敗血症性ショックにおける急性期 カリクレイン・キニン系動態について

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久山 健, 角谷 富男

現在, 各種ショックに対しその抗ショック作用に着目されて様々な protease inhibitor が用いられているが, これら薬物の作用点として, また, ショックサイクルを形成する一因として重要な位置を占めるカリクレイン・キニン系, 及びこれと密接に関連する凝固・線溶系, 補体系のショック超急性期よりの動態についての知見は意外と少ない。本研究は, 出血性ショック症例17例, 敗血症性ショック症例5例について, 1) カリクレイン・キニン系, 2) 凝固・線溶系, 3) 補体系の各代表的因子をショック超急性期より経時的に測定し, 以下の結果を得た。

1. 出血性ショック症例においては, ショック発生と共に極めて早期よりこれら3系は一斉に活性化が始まり, ショックの改善に伴い, これら因子の明らかな改善傾向が認められた。
2. 敗血症性ショック症例においては, 上記3系とも改善しにくい傾向がみられた。
3. プレカリクレイン, HMW-Kg の減少は, カリクレイン・キニン系の活性亢進に伴う消費と考えられ, カリクレインによる HMW-Kg の活性化を抑制する何らかの因子がショックの改善に寄与する可能性が示唆された。