Possible Role of the Kidney as a Regulator of Circulating Plasminogen*

Masahiro Maki, Kazuma Nagasawa, Atsushi Urushihata, Yoshihiro Ogawa, Kazuhiko Seki and Tadayoshi Ishikawa

Department of Obstetrics and Gynecology (Prof. S. Shinagawa), Faculty of Medicine, Hirosaki University, Hirosaki

In 2 cases of postoperative acute renal failure, abnormally high level of plasminogen, low fibrinolytic activity of euglobulin fraction and decreased urokinase excretion into urine were observed.

These changes may be explained by the following mechanisms:
(1) Tissue activator of plasminogen from the kidney (urokinase) enters into the circulation and also is excreted into urine in normal condition.
(2) The production of urokinase might be suppressed markedly under such a condition as acute renal failure. This would be the cause of lowered urokinase level in both blood and urine. The lowered level of plasminogen activator in blood may cause an accumulation of plasminogen, because continuous conversion of plasminogen to plasmin is disturbed.

From the above consideration, we have reached the conclusion that the kidney may play an important role as a regulator of circulating plasminogen.

There has been no clear explanation as to how plasminogen is regulated in the blood. Clinical observations on 2 cases of acute renal failure suggested that the kidney might play an important role in plasminogen regulation. Our own clinical experiences are described and the mechanism of plasminogen regulation is discussed.

METHODS

Bleeding time by Duke, platelets count by Sahli-Fonio, prothrombin time by Quick's one stage method, fibrinogen by a modified method of Ratnoff and Menzie; plasminogen, caseinolytic activity of euglobulin fraction in the presence of streptokinase, spontaneous fibrinolytic activity of euglobulin fraction without any artificial activation procedure, split products derived from either fibrinogen or fibrin were determined by measuring thrombin clotting time and by simple radial immune assay of Mancini et al., urokinase by standard fibrin plate method of Astrup and Muellerz, and the electrolytes, non-protein-N and urea-N in blood were determined by routine laboratory methods.

CASE REPORTS

Case 1. A 19-year-old woman was admitted on July 22, 1967, complaining of abdominal mass. No contributory history was noted. Physical findings and

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hematologic examinations were almost normal except for hypertension (160–120 mm Hg). Gynecologic examination revealed that she had a cystic pelvic tumor sized approximately 6-month-pregnant uterus. On July 25, a pseudomucinous cystic ovarian tumor developing from the right-side ovary was removed uneventfully under spinal anesthesia. Her clinical course was illustrated in Fig. 1.

A transient fall in blood pressure was observed immediately after the spinal anesthesia. No blood transfusion was given during the entire course of her admission. After the operation, 500–1,000 ml of 5% glucose or Ringer’s solution were administered every day. However, her urine output was decreased day by day and anuria developed without definite etiology.

The laboratory tests presented in Table 1 showed marked elevation in urea-N and in plasminogen and lowered urokinase excretion.

As we had experienced effective diuresis by combined use of heparin and Hydergin (a mixed preparation of dihydroergocornin, dihydroergokryptin and...
dihydroergocristin from Sandoz) against obstetric oliguria, this therapy was indicated; it was, however, not effective. The peritoneal dialysis was started. Unfortunately she died from pulmonary edema 10 days after the operation without attaining effective diuresis.

**Case 2.** A 23-year-old nulliparous pregnant woman in the 19th week of gestation was admitted in order to interrupt the pregnancy because of toxemias. The interruption was performed at 4 p.m., June 5, 1968, by insertion of a catheter (No. 12) between the amniotic membrane and internal uterine wall, and 80 ml of 1% Rivanol was infused through the catheter. Approximately 1 hour after the procedure, she suddenly fell into severe shock with hypotension, tachycardia, elevation of temperature (40°C), dyspnea, and vomiting contaminated with blood. By use of 5% glucose, dexamethasone and other stimulants, blood pressure rose slowly. Meanwhile, her labor became stronger, and she was delivered of a female weighing 500 g without any abnormal postpartum hemorrhage. At 8 a.m., June 6, she fell again into shock and was given stimulants, dexamethasone and transfusion. However, low blood pressure (70-90 mm Hg max.) was not improved. Her urine output was markedly decreased and urea-N in blood was elevated to 45 mg/100 ml. Diuretics of various kinds were not effective. Therefore, peritoneal dialysis was started from June 7. Schottmüller's test for blood bacteria was negative. Her clinical course is presented in Fig. 2 and the laboratory tests in Table 2 and Fig. 3.

From the laboratory tests, acute renal failure in this case was thought to be a result from disseminated intravascular coagulation. Therefore, she was given drip infusion of 10,000 units of heparin, which was, however, not effective in inducing diuresis and caused about 700 ml of bleeding from the uterus. The peritoneal dialysis was continued for 11 days until diuresis was obtained. We did not have an opportunity to examine the coagulation-fibrinolysis system before and 1 day
TABLE 2. Laboratory tests in Case 2

<table>
<thead>
<tr>
<th>Tests</th>
<th>Date</th>
<th>K (IU/L)</th>
<th>Na (mEq/L)</th>
<th>Prothrombin time (sec)</th>
<th>bleeding time (min)</th>
<th>Fibrinogen (mg%)</th>
<th>Plasminogen (IU/L)</th>
<th>Fibrinolytic activity of euglobulin fraction (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7/V</td>
<td>128</td>
<td>98</td>
<td>13.7</td>
<td>4.5</td>
<td>63.0</td>
<td>68.0</td>
<td>128</td>
</tr>
<tr>
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<td>8/V</td>
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<td>68.0</td>
<td>128</td>
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<tr>
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<td>9/V</td>
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<td>68.0</td>
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<tr>
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<td>15/V</td>
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<tr>
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<tr>
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<td>68.0</td>
<td>128</td>
</tr>
</tbody>
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Fig. 3. Changes in plasminogen (--; --) and fibrinogen (--; --) after the interruption. The results on June 7 revealed slight decreases in platelets, fibrinogen and plasminogen. The thrombin clotting time of the patient's plasma, a mixture of non-heated patient's plasma and normal plasma, and a mixture of patient's plasma heated at 56°C for 15 minutes and normal plasma were prolonged. In addition, heat-stable split products, which might have been derived from fibrin, not from fibrinogen, were detected in an amount of approximately 40 mg% by a simple radial immune diffusion technique of Mancini.
et al. The results obtained might suggest that there was disseminated intravascular coagulation with secondary fibrinolysis. These findings seemed to have been marked in the stage of shock. A marked elevation of plasminogen and very low fibrinolytic activity of euglobulin fraction were noted in the stage of anuria. These changes, however, returned to the normal range with improving diuresis.

**DISCUSSION**

No clear evidence has been demonstrated as to how blood plasminogen is regulated. In Case 1, we noted incidentally a high concentration of plasminogen which reached almost 2 times the normal level. This led us to examine very carefully the coagulation-fibrinolysis system through the entire course of hospitalization of Case 2.

The laboratory tests in these 2 cases of postoperative anuria seemed to suggest a possible role of the kidney as a regulating organ of plasminogen. It is quite obvious from the comparative study of fibrinolytic activity between arterial and venous blood samples of the kidney\(^9\) as well as the uterus\(^10,11\) that plasminogen activator of tissue origin can enter into the circulation. The tissue activator entering into the circulation, therefore, may be one of the blood activators. This blood activator of tissue origin may convert slightly but steadily plasminogen to plasmin, which is finally inactivated by naturally occurring antiplasmin in plasma. Therefore, when the plasminogen activator in the blood is lowered, this normally occurring latent activation of plasminogen to plasmin may be suppressed, with a result of an accumulation of plasminogen in the blood (Fig. 4). A high level in plasminogen found in the patients reported in this paper did not seem to be a result of the surgical procedure or the interruption of pregnancy, because the plasminogen level did not change significantly before and after the surgical

![Fig. 4. Fibrinolysis system in normal and impaired renal function.](image-url)
procedure or the delivery which were utterly uncomplicated.\textsuperscript{12,13} The very low fibrinolytic activity of the euglobulin fraction obtained from the patients with acute renal failure might be due to the lowered activator level in the blood resulting from the failure in producing urokinase in the kidney. The decrease in urokinase excretion into urine also indicated the failure in renal function as described by Vreeken \textit{et al.}\textsuperscript{14}

Recent work by Goldschmidt and Marosvari\textsuperscript{15} showed that in children with acute glomerulonephritis plasminogen, proactivator and spontaneous fibrinolysis were diminished. The discrepancy might be due to the difference of location and extent of damage between acute renal failure and glomerulonephritis.

References