Inhibition of Kinin Formation by a Kallikrein Inhibitor during Extracorporeal Circulation in Open-heart Surgery

By Hideo Nagaoka, M.D., and Makoto Katori, M.D.

SUMMARY

Involvement of the kinin system was studied in 58 patients during extracorporeal circulation in open-heart surgery. At the onset of extracorporeal circulation, there was no increase of free kinin in blood and no reduction of plasma kininogen, when the latter was expressed as μg bradykinin/mg plasma protein. With the lapse of time, kinin in the blood increased significantly, and decrease of kininogen was also significant. The longer the circulation time, the greater the consumption of kininogen. The site of the kinin formation was presumed to be the heart-lung machine since the level of kinin increased slightly and kininogen decreased gradually in the blood leaving the machine, compared with those levels entering the machine.

The difference in kininogen was significantly different from zero at termination of extracorporeal circulation. Administration of a kallikrein-trypsin inhibitor, trasylo1 (A. G. Bayer), infused into the heart-lung machine, prevented the decrease of kininogen. Reduction of the total peripheral resistance during this circulation was also prevented. The hemoconcentration, presumably the result of vascular permeability increase caused by increased kinin, was prevented by trasylo1 in cases in which extracorporeal circulation lasted over 60 minutes. Trasylo1 applied thus appears to be an effective counteragent for circulatory disturbances which occur during extracorporeal circulation.

BRADYKININ, known as a potent pharmacological agent of vasodilatation and vascular permeability increase, disappears for the most part in a single passage through the pulmonary circulation.1 When pulmonary circulation is bypassed during extracorporeal circulation in open-heart surgery, it is plausible that bradykinin, once generated, might accumulate in the blood and cause hypotension, increase in vascular permeability, and reduction of the venous return, one of the most serious occurrences during extracorporeal circulation.

There are two short reports2,3 on the involvement of the kinin system during extracorporeal circulation. However, the conclusions were contradictory and the involvement of the kinin system remains an open question.

The present paper reports 1) the involvement of the kinin system during extracorporeal circulation, 2) the increased formation of kinin with prolongation of the circulation time, 3) the possible identification of the site of the activation at the heart-lung machine, 4) the usefulness of trasylo1 (A. G. Bayer, West Germany), a kallikrein inhibitor from bovine lung, in preventing a decrease of the total peripheral resistance during extracorporeal circulation and in maintaining a constant hematocrit in the prolonged cases (over 60 min).

Materials and Methods

Clinical subjects included 58 patients (23 males and 35 females) who underwent open-heart surgery at the Tokyo Medical and Dental University Hospital and affiliated hospitals, between October, 1971, and April, 1973. Heart diseases of the patients included 17 cases of congenital cardiac diseases and 41 of acquired diseases, as listed in table 1. Ages ranged from five to 54 years.

Perfusion Methods

The artificial heart-lung machine included a disposable sheet oxygenator or Temptrol (Bentley) disposable bubble oxygenator with a double-roller pump. Lactated Ringer's solution was used as the priming diluent of the oxygenator and the following agents were added to the solution: mannitol (1 g/kg), 7% sodium bicarbonate (40–60 ml), heparin (5000 units/1000 ml), chlorpromazine (0.5 mg/kg), 10% calcium chloride (5 ml/L ACD [anticoagulant citrate dextrose] blood), ACD blood, and antibiotics (2 g).

The blood dilution ratio (DR) was calculated by the following formula and was restricted within 14–33% (average, 21.4%):

$$DR = \frac{volume\ of\ diluent\ (ml)}{CBV\ (ml) + PFV\ (ml)} \times 100\ (%)$$

where CBV = circulating blood volume and PFV = priming fluid volume.

The circulating blood volume was calculated to be 80 ml/kg.
The returned venous blood was drawn back into the heart-lung machine by gravity. The perfusion was performed by a self-balancing method, so that blood loss during the perfusion was compensated for by transfusion of the same amount of blood. The perfusion flow rate was 2.3-2.4 L/m2/min for children and 2.0-2.2 L/m2/min for adults. Oxygenation of the blood was provided by bubbling of pure oxygen, and the rate of oxygenation was twice that of the perfusion rate. As a heat exchanger was not employed, body temperature was 33-36°C during the perfusion. The total time required for extracorporeal circulation was 22-165 min (average, 52.1 min). Perfusion time was less than 60 min in 40 cases and more than 60 min in 18. The arterial pressure was determined by a catheter inserted into the radial artery, and the central venous pressure at the superior vena cava by a catheter through the brachial vein or the superficial jugular vein.

Heparin (300 units/kg) (Sigma, U.S.A.) was administered intravenously to the patients before cannulations for the perfusion. Protamine sulfate (6 mg/kg) was used for the neutralization of heparin at the termination of the perfusion.

The oxygenator and the connecting tubes of the heart-lung machine were mainly made of vinyl chloride, so that blood did not make contact with glass surface.

### Blood Collection

Blood samples were collected from the antecubital vein one day before, two hours after, and one week after the extracorporeal circulation. Blood taken immediately before the onset of this circulation was obtained from the right atrium. During this circulation, venous blood samples were drawn immediately before passing through the machine (V) from the tubing, which had been inserted into the inferior vena cava. Various indicators in V were also compared, if necessary, with those in the arterial blood leaving the machine (A), which was collected simultaneously. The blood (A) flowed back to the patients through the external iliac artery. Occasionally, the cannulae for monitoring central venous pressure or the arterial pressure were used for collection of blood two hours after the extracorporeal circulation.

### Bioassay of Kinin

The isolated rat uterus preparation was used for determination of free kinin, kininogen, and kininase activity. One horn of the eviscerated rat uterus was suspended at 28°C in 5 ml organ bath filled by aerated Munsick solution in the presence of 10⁻² g/ml of 2-bromosergic acid diethylamide (BOL, Sandoz). The contractions of the uterus were recorded using a frontal writing lever. Synthetic bradykinin (Peptide Center, Institute for Protein Research, Osaka University, Osaka) was used as the standard. The detailed method of bioassay has been described elsewhere.¹

### Extraction of Kinin

Five milliliters of the blood collected were ejected within 10 sec into 15 ml of chilled 80% (v/v) ethanol in a polyethylene tube in ice and kinin was extracted according to the method reported by Brocklehurst and Zeitlin.² The dried residues were stored at −20°C and dissolved in 0.5 ml of warm Munsick solution immediately before assay. Because of the small amount of kinin, the sensitivity of the uterus was increased by reducing the load on the uterus, so that 0.05 ng of bradykinin in the organ bath contracted the uterus by 1 mm deflection on the record.

Four recovery experiments were carried out with 1 μg of bradykinin. The rat uterus contracting substance was considered to be kinin, as it contracted the rat uterus and relaxed the rat duodenum, when applied to both preparations in series superfused with Krebs-Ringer solution (cascade superfusion).

### Kininogen Contents

The methods of Diniz and Carvalho³ were employed. Kinin-forming and kininase activities were destroyed by boiling plasma together with acetic acid as soon as possible. The substrate so denatured by this procedure formed bradykinin when reacted with trypsin (Nutritional Biochemical Corporation, U.S.A.). Bradykinin released was extracted with ethanol and the dried residues were stored at −20°C until assay. Kinin in 0.05 ml of sample dissolved in 4 ml of Munsick solution was assayed on rat uterus. As was recently reported⁴ and confirmed by us, this method also produced bradykinin potentiator(s). Therefore, the following special attentions were paid in the determination by the original method: The volume of Munsick solution required to dissolve the dried residues and the volume of the sample solution applied to the organ bath was restricted exactly to 4 ml and 0.05 ml, respectively. The level of plasma kininogen was expressed as the amount of bradykinin (μg) released by trypsin per ml plasma volume or mg plasma protein.

### Kininase Activity

Synthetic bradykinin (1 μg) was incubated with 0.2 ml of
Kinin Formation

On initiation of extracorporeal circulation, plasma kininogen, a precursor of kinin in plasma, suddenly decreased from 6.04 ± 0.17 (mean ± SE) before the circulation to 3.55 ± 0.16 one minute after the start of the circulation, when expressed in μg bradykinin/ml plasma volume (table 2). As the decrease was accompanied by systemic blood pressure fall at the onset of the circulation, it was assumed that kinin formation induced the hypotension. The decrease of kinogen concentration, however, was not the result of kinin formation, but rather hemodilution, since values of hematocrit as well as total plasma protein also decreased at the onset of the circulation (table 2). In fact, a recalculation of plasma kininogen in terms of mg plasma protein justified the interpretation, as shown in figure 1. Kininogen level (8.92 ± 0.20 × 10⁻² μg/mg plasma protein) after one minute of circulation was not significantly reduced from that before the circulation (9.54 ± 0.23 × 10⁻² μg/mg plasma protein). This was also confirmed by the fact that the amount of free kinin in blood after one minute of circulation (0.19 ± 0.04 ng/ml blood) did not differ from that before the circulation (0.17 ± 0.04 ng/ml blood) (fig. 2).

On the contrary, the amount of free kinin in the blood did increase significantly (P < 0.05) at 20 minutes (2.51 ± 0.46 ng/ml blood) and at termination (2.60 ± 0.90 ng/ml blood), when compared with the value before the circulation (fig. 2). The significance of differences were tested by Cochran’s method, as the variances were not homogeneous. Concomitant with the increased amounts of kinin, kininogen levels at 10, 20 minutes, and at termination of the circulation (fig. 1) were 7.99 ± 0.21, 7.57 ± 0.21, and 6.53 ± 0.24 × 10⁻² μg/mg plasma protein, all three being significantly reduced from the level before circulation (P < 0.001). These results demonstrated clearly that there was an increase in the formation of kinin during the period of extracorporeal circulation.

The longer the period of extracorporeal circulation,
Consumption of kininogen and its inhibition by trasylol during the extracorporeal circulation. Circles with solid line indicate the means ± standard errors of kininogen levels in the absence of trasylol treatment. The values in 10, 20 minutes, and at termination of extracorporeal circulation were significantly lower than that before the circulation (***P < 0.001). Circles with dotted line indicate those under treatment with trasylol. The values during extracorporeal circulation were significantly higher than those under no treatment at each time (△△△P < 0.001). Kininogen (KGN) is expressed as the amount of bradykinin released × 10^4 μg/mg plasma protein. Abbreviation and units of measure are the same for all figures. Numbers in parentheses indicate number of cases.

Free kinin in the blood before and during circulation on the heart-lung machine. (Mean ± se) The mean values in 20 min and at termination of the circulation were significantly higher than that before the circulation (* P < 0.05). Numbers in parentheses indicate number of cases.

Reduction of kininogen levels as a function of the duration of the extracorporeal circulation. All values at termination of the circulation were significantly lower than that before the circulation (P < 0.01). The kininogen level in 60-80 min of the circulation was significantly lower than that in 20-40 or 40-60 min (* P < 0.05).

The greater the amount of kininogen consumed (fig. 3). The mean kininogen level of five patients for whom the circulation time was 60-80 min was significantly lower than the level in circulation time of 20-40 or 40-60 min (P < 0.05). When the mean value of kininogen of seven cases in which circulation time was over 60 min was compared with that of 18 cases under 60 min, the former (5.21 ± 0.30 × 10^2 μg/mg protein) was significantly lower than the latter (7.01 ± 0.22 × 10^2 μg/mg protein) (P < 0.001). In three other cases, when over 60 min were required, free kinin showed the highest values at the termination of extracorporeal circulation in the blood leaving the machine (4.6, 5.0, and 18.0 ng/ml blood). Such data strongly suggest that when the extracorporeal circulation is extended beyond the 60 min period, cardiovascular disturbances may be induced. Two hours after termination of the extracorporeal circulation the kininogen level returned to the level present before the circulation.

Site of Kinin Formation

In order to determine the site of kinin formation, blood was collected simultaneously from the tubings entering (V) and leaving (A) the heart-lung machine. The differences of free kinin between A and V (A-V) were minor but always positive at 1 min (0.06 ± 0.03) (10 cases), at 20 min (0.25 ± 0.19) (3 cases), and at termination (0.96 ± 0.78 ng/ml blood) (10 cases) on extracorporeal circulation. The value at termination
was significantly higher than that at 1 min of the circulation \( (P < 0.05) \), when tested by Wilcoxon’s rank sum analysis. Coinciding well with the increased amounts of free kinin, the differences of kininogen between A and V (A-V) were changed to negative and were significantly lower at 20 min \( (P < 0.05 \) by the Cochran’s test) and at termination \( (P < 0.05 \) by t-test). Furthermore, the difference was significantly different from zero at termination of extracorporeal circulation (fig. 4). Thus, kininogen levels in blood leaving the machine were lower than the level entering the machine \( (P < 0.01 \) for A-V up to 60 min; \( P < 0.05 \) for A-V over 60 min). The differences in kininogen (A-V) at 1, 10, and 20 min decreased gradually but were not statistically different from zero.

The presence of free kinin in the venous blood entering the machine, albeit in small amounts, is contradictory to the view that the main site of the kinin formation is the heart-lung machine. Its presence might suggest a simultaneous kinin formation in the intracorporeal circulation of the patients. However, this is irrelevant, since the kinin-destroying activity (kininase) in plasma was decreased by one half, as a prolongation of the half-life of bradykinin at the end of extracorporeal circulation (as indicated by the values obtained on and off the machine), probably due to hemodilution that occurred, as demonstrated by a fall in total plasma protein (table 3). The fact that there was practically no difference in the kininase activity between blood entering and leaving the heart-lung machine strengthens the argument that the heart-lung machine is the site of kinin formation, since the increased kinin concentrations in the blood leaving the machine was not accompanied by a decreased kininase activity in the arterial blood leaving the machine. Kininase activity was not markedly affected by the length of time on the machine. The kinin system in the blood is thus apparently activated gradually as the blood passes through the heart-lung machine, and becomes especially apparent as the period of exposure to the machine lengthens.

Inhibition of Kinin Formation by Trasylol

When \( 3 \times 10^5 \) KIU/person or \( 10^4 \) KIU/kg of trasylol, a kallikrein-trypsin inhibitor from bovine lung, was administered continuously during the extracorporeal circulation into the oxygenator of the heart-lung machine, the reduction of plasma kininogen (\( \mu g/\text{mg plasma protein} \)) was markedly prevented at 1 min \( (10.07 \pm 0.27), 10 \) min \( (9.86 \pm 0.23), 20 \) min \( (9.69 \pm 0.27), \) and at termination \( (9.18 \pm 0.34) \) of the circulation as shown in figure 1. The difference in each instance was highly significant \( (P < 0.001) \).

Dosages of \( 10^4 \) KIU/kg appeared to be slightly more effective than \( 3 \times 10^5 \) KIU/person in cases in which extracorporeal circulation lasted more than 60 minutes. Kininogen levels at termination were 7.60, 7.60, and 7.22 (average 7.50) \( \times 10^{-2} \) \( \mu g/\text{mg plasma protein} \) for three patients treated with \( 3 \times 10^4 \) KIU/person and 10.42, 9.27, and 9.00 (average 9.56) \( \times 10^{-3} \) \( \mu g/\text{mg plasma protein} \) for three patients treated with \( 10^4 \) KIU/kg. The latter was obviously greater than the former and the difference was significant, when calculated using Wilcoxon’s rank sum analysis \( (P < 0.05) \).

Effects of Trasylol

The administration of trasylol had other beneficial

**Table 3**

<table>
<thead>
<tr>
<th>Kininase Activity Total plasma</th>
<th>Total Protein in Plasma before and at Termination of Extracorporeal Circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
<td>Protein (mg/ml)</td>
</tr>
<tr>
<td>Before</td>
<td>4.8 ± 0.3</td>
</tr>
<tr>
<td>End</td>
<td>68.0 ± 3.2</td>
</tr>
<tr>
<td>entering machine</td>
<td>10.9 ± 1.3**</td>
</tr>
<tr>
<td>leaving machine</td>
<td>42.8 ± 2.2**</td>
</tr>
<tr>
<td><strong>P &lt; 0.01</strong></td>
<td></td>
</tr>
<tr>
<td>***P &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Kininase activity is expressed as the half-life of bradykinin. (Mean ± ss in six cases). 
**P < 0.01: values at the end were compared with those before the perfusion using Cochran’s formula. 
***P < 0.001: significantly different from that before the perfusion according to Student’s t-test.**
effects associated with preventing the reduction of kininogen. In 17 patients not treated by the inhibitor, the decrease of kininogen, which occurred between one minute and termination of the extracorporeal circulation, was accompanied by a decrease of the total peripheral resistance (fig. 5). The treatment of 11 patients with trasylol resulted in obvious prevention of decreases in both kininogen and total peripheral resistance in all. The mean value of the decrease of kininogen was suppressed from \(-2.92 \pm 0.40\) to \(-0.99 \pm 0.34 \times 10^{-2}\) \(\mu g/mg\) plasma protein under treatment, whereas the value for the reduction of total peripheral resistance became positive (from \(-0.18 \pm 0.05\) to \(0.12 \pm 0.08\) mm Hg/ml/sec) with administration of trasylol. The differences were highly significant for both indicators \((P < 0.01)\). These data strongly suggest that kinin formation in the blood causes a decrease in total peripheral resistance, and administration of trasylol prevents both such occurrences.

In the prolonged cases of the extracorporeal circulation (longer than 60 min), hematocrit increased at termination of the circulation. The development of hemoconcentration is presumably due to increased vascular permeability as a result of increased release of bradykinin (fig. 6). Trasylol prevented this hemoconcentration \((P < 0.05)\). Plasma protein concentration showed the same pattern at termination and trasylol suppressed the increase, but the difference was not significant, as the variations were great. A difference in hematocrit between patients treated with \(3 \times 10^6\) KIU/person and those with \(10^6\) KIU/kg was not observed.

Along with the beneficial effects mentioned above, maintenance of the venous return during extracorporeal circulation was facilitated under the treatment with trasylol; these data will be reported elsewhere.

**Discussion**

Wiegershausen et al.\(^2\) reported that plasma kininogen decreased gradually, but not significantly, during the extracorporeal circulation, and the decrease was maximal and significant two hours after the termination of the circulation. A kallikrein-trypsin inhibitor, contryskal, which is a polyvalent trypsin-kallikrein inhibitor of bovine organ and which appears to be the same type of inhibitor as trasylol, prevented the decrease of plasma kininogen, when \(2 \times 10^4\) antitrypsin units of the protease inhibitor were administered three times: before, during, and after the extracorporeal circulation.

Seidel et al.\(^3\) reported the decrease of plasma kininogen, expressed as \(\mu g/ml\) plasma volume, at the onset of the extracorporeal circulation. The decrease, however, was explained not as increased kinin formation but as hemodilution, because the decrease of kininogen was accompanied by a reduction of the plasma protein concentration \((g/100\ ml)\) as well as free bradykinin level \((ng/ml\ blood)\). The present work confirmed to some extent both reports. Kinin formation does not occur at the onset of the extracorporeal

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**Figure 5**

Effects of trasylol on the decrease of kininogen and the decrease of the total peripheral resistance during extracorporeal circulation. The decrease on kininogen (\(\Delta KGN\)) between 1 min and termination of the extracorporeal circulation was accompanied by a decrease of the total peripheral resistance (\(\Delta TPR\)) in the same period in the patients not given trasylol (unfilled circle with dotted lines). Under treatment with trasylol, the mean value of \(\Delta KGN\) was lowered and that of \(\Delta TPR\) changed to a positive value (black dot with solid lines). Horizontal lines indicate standard errors for \(\Delta KGN\), whereas vertical lines indicate those for \(\Delta TPR\). **\(P < 0.01\)**. Number of cases in parentheses.

**Figure 6**

Changes of hematocrit and plasma protein between 1 min and the end of the extracorporeal circulation. Unfilled circles with dotted lines indicate values in the cases without trasylol, whereas black dots with solid lines indicate those with trasylol. *\(P < 0.05\).
circulation, as there was no free kinin and no reduction of kininogen in plasma, when the latter was expressed in \( \mu g/mg \) plasma protein.

As for the concentration of kininogen in plasma, only when the kininogen level is expressed in terms of mg plasma protein instead of ml plasma volume is kinin release reflected by the reduction of kininogen in plasma. This reduction is interpreted as real consumption of kininogen, as previously reported.\(^4\),\(^1^\)

The claim made by Seidel et al.,\(^2\) however, that the kinin system was not involved, could not be supported by the present findings throughout the course of extracorporeal circulation. Plasma kininogen levels, when expressed in \( \mu g \) bradykinin/mg plasma protein, were reduced as the time on extracorporeal circulation increased (fig. 1). At the same time that plasma kininogen decreased, free kinin in blood increased \( (P < 0.05) \), as shown in figure 2. Thus, activation of the kinin system was clearly indicated.

The maximal and significant reduction of kininogen \( (\mu g/ml) \) two hours after termination of the extracorporeal circulation, which was reported by Wiegshauser et al.,\(^2\) could not be confirmed by the present work.

The gradual activation of the kinin system, particularly in passage through the heart-lung machine, allows us to assume that small amounts of kinin, a potent mediator of vasodilation and vascular permeability increase, will flow into the arterial circulation of the patients during the period of extracorporeal circulation and cause a disturbance in the circulatory system of the patients. The amounts of kinin found in the blood leaving the machine \( (0.56-18.0 \text{ ng/ml blood}) \) were sufficient to decrease arterial blood pressure and to increase vascular permeability. Threshold levels of bradykinin have been reported to be 0.06 \( \mu g/min \) (i.a.) for hypotension in dogs,\(^1^2\) 2-5 ng/kg (i.a.) for vasodilatation in dogs,\(^1^3\) 0.05 \( \mu g/min \) (i.a. infusion) for vasodilatation in man,\(^1^4\) and 5-10 ng/ml (intradermal) for vascular permeability increase in the guinea pig.\(^1^5\),\(^1^6\)

Evidence from this study that released kinin actually does induce the cardiovascular disturbances includes the reduction of the total peripheral resistance during this circulation and the increase of hematocrit in cases of prolonged exposure to the heart-lung machine. The fact that the decrease of the total peripheral resistance was accompanied by a reduction of kininogen does not preclude the existence of other factors influencing this effect. However, treatment with trasyrol clarifies that kinin formation shown by a decrease of kininogen level caused a reduction of the total peripheral resistance during the extracorporeal circulation.

Prolongation of the extracorporeal circulation beyond 60 min causes a greater production of free kinin with further consumption of plasma kininogen (figs. 3, 4). The continuous and more marked activation of the kinin system in the prolonged time of the circulation results in an increase of hematocrit and plasma protein concentration (fig. 6). This means that a hemoconcentration occurred, probably due to the vascular permeability increase caused by the presence of more bradykinin, and thus explains the reduced venous return which always occurs during extracorporeal circulation and which is difficult to overcome. The effect of circulation time on kinin levels may provide a partial explanation for cardiovascular disturbances which appear during extracorporeal circulation and postoperatively, when the heart-lung machine has been used for a long period.

Infusion of trasyrol into the heart-lung machine during extracorporeal circulation prevented the decrease of the total peripheral resistance during the circulation and the increase of hematocrit in the cases of prolonged use, together with the reduction of plasma kininogen. These facts clearly indicate that trasyrol is a beneficial agent during the use of extracorporeal circulation.

The mechanism of activation of the kinin system remains to be elucidated. Heparin, which is always administered before the onset of the extracorporeal circulation, did not cause the activation, because the values of kininogen as well as total plasma protein and hematocrit were not altered significantly before and after this administration, as shown in table 4. Hemo- dilution and contact with a negative surface are known to activate the kinin system. Recent work on PF/dil (permeability factor/dilution) have shown that the action of the increased vascular permeability occurs through the activation of prekallikrein and is suggested to be a 30,000 molecular weight fragment of the active Hageman factor.\(^1^7\) On the other hand, it was reported that kinin was formed gradually after simple dilution of human plasma and synovial fluid even in plastic tubes.\(^1^8\) Thus, the kinin system in

| Table 4 |
|---|---|---|
| **Effects of Heparin on Kininogen, Hematocrit and Total Plasma Protein** | **Before** | **After** |
| Kininogen \( (\times 10^{-2} \text{ mg/mg protein}) \) | 5.65 ± 0.90 | 5.83 ± 1.44 |
| Hct (%), | 39.0 ± 5.2 | 36.9 ± 3.3 |
| Total plasma protein \( \text{(mg/ml)} \) | 62.1 ± 7.0 | 63.1 ± 8.7 |
| Mean ± se in eight cases, | | |
plasma may be activated not only in solid phase, but also in fluid phase.18, 20 The real mechanism of the activation during extracorporeal circulation will have to be clarified by further investigations.

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