Aim: Stroke is well known to lead to hypertension; nevertheless, the role of vascular function in hypertension remains unclear. In this study, we aimed to clarify the mechanism underlying increased arterial stiffness following stroke.

Methods: The cardio-ankle vascular index (CAVI) was measured in five New Zealand White rabbits. Under general anesthesia, intracranial pressure (ICP) was increased by injecting saline (15 mL) into the cisterna magna. ICP was monitored using a catheter inserted into the subarachnoid space via right frontal bone craniotomy. Blood pressure (BP), CAVI, and common carotid flow (CCF) were evaluated, and the responses of these parameters to increased ICP were analyzed.

Results: Saline injection into the cisterna magna increased the ICP by over 20 mmHg. Both BP and CAVI increased from 63.2 ± 4.84 to 128.8 ± 14.68 mmHg and from 4.02 ± 0.28 to 4.9 ± 0.53, respectively. Similarly, BP and CCF increased. When hexamethonium was administered before the increase in ICP, the increase in BP (132.2 ± 9.41 mmHg with 10 mg/kg hexamethonium vs. 105.6 ± 11.01 mmHg with 100 mg/kg hexamethonium) and CAVI (5.02 ± 0.64 with 10 mg/kg hexamethonium vs. 4.82 ± 0.42 with 100 mg/kg hexamethonium) were suppressed in a dose-dependent manner.

Conclusion: Increased ICP causes an increase in BP and CAVI, suggesting that enhanced stiffness of the muscular arteries contributes to high BP. Blocking the autonomic nervous system with hexamethonium suppresses the increase in BP and CAVI, indicating that these increases are mediated by activation of the autonomic nervous system.

Key words: Blood pressure, Cardio-ankle vascular index, Carotid blood flow, Central venous pressure, Intracranial pressure

Abbreviations: ANOVA: one-way analysis of variance, BP: blood pressure, CAVI: cardio-ankle vascular index, HR: heart rate, CCF: common carotid flow, CVP: central venous pressure, ICP: intracranial pressure, ΔBP: the change of fluctuation with blood pressure, ΔCAVI: the change of fluctuation with CAVI, ΔHR: the change of fluctuation with HR, ΔCCF: the change of fluctuation with CCF, ΔCVP: the change of fluctuation with CVP.

Introduction

Severe hypertension is sometimes observed in stroke patients. Several mechanisms have been proposed for this increase in blood pressure (BP)1-5. In the early 1900s, Cushing performed experiments...
on dogs whereby the intracranial pressure (ICP) was increased and reported irregular breathing, bradycardia, and hypertension. The rostral ventrolateral medulla has been suggested to be a dominant region in the regulation of hypertension in the brainstem, and excitation of the autonomic nervous system has been reported to lead to hypertension. The occurrence of stroke may induce an increase in the ICP, and the resultant series of events may increase BP. BP is thought to be regulated by cardiac output and vascular resistance. The precise mechanism, including the role of arterial stiffness, that may contribute to vascular resistance has not yet been elucidated. Conventionally, pulse wave velocity is used as an indicator of arterial stiffness and is widely reported in investigations of vascular stiffness, including studies on cardiovascular disease. However, this parameter has the disadvantage of being dependent on BP at the time of measurement. Thus, it is impossible to analyze the role of arterial stiffness using pulse wave velocity under these conditions.

The cardio-ankle vascular index (CAVI) is an index reflecting arterial stiffness from the origin of the aorta to the ankle, which is independent from BP at the time of measurement. Previous studies have reported that the administration of an \( \alpha \)-blocker (doxazosin) decreases CAVI and BP. This indicates that CAVI reflects the contraction of the arterial smooth muscle and may also partly reflect peripheral resistance. The brain functionally controls blood vessels throughout the body to maintain a constant blood flow, and arterial stiffness is likely an important component of this regulation. Therefore, we hypothesized that when the brain has been comprised, for instance, by stroke, its ability to control and affect BP and vascular stiffness may likewise be compromised. To clarify the role of arterial stiffness in enhanced BP after subarachnoid hemorrhage, we increased the ICP by injecting saline into the cerebral cisterns of rabbits and subsequently measured vascular indices, including common carotid flow (CCF), BP, heart rate (HR), central venous pressure (CVP) and CAVI. Since blood vessels are dominated by the autonomic nervous system, we chose the ganglionic blocker hexamethonium to clarify the role of the autonomic nerves in enhanced ICP-induced hypertension, particularly related to changes in BP, HR, CCF, CVP and CAVI.

**Aim**

In this study, we aimed to clarify the mechanism underlying increased arterial stiffness following stroke.

**Methods**

**Animals and Anesthesia**

All animal care and experimental procedures were approved by the Toho University Animal Care and User Committee (approval number: 19-53-360), and all efforts were made to minimize suffering. The rabbits were individually housed in stainless steel rabbit cages on a 12-h light (8:00–20:00 h)/12-h dark cycle at 23 ± 1°C with a relative humidity of 50–60%. Food and water were provided *ad libitum*.

Male New Zealand White rabbits (\( n = 5 \); age, 14–18 weeks; weight, 3–4 kg) obtained from Sankyo Labo Service (Tokyo, Japan) were used for this study. Ketamine (35 mg/kg) and xylazine (5 mg/kg) were administered intramuscularly into the thigh as anesthesia. The rabbits were initially placed in the supine position, and an intubation tube was inserted into the trachea. Respiration was managed using a ventilator with 100% oxygen and 1% isoflurane. The SN-480-7 (Shinano, Tokyo, Japan) ventilator was used at a setting of 6 mL/kg, 40 times/min. Temperature was maintained at 37.0°C using a body temperature mat. Isoflurane, adjusted to 0.5%, was used to maintain anesthesia and was administered through the ventilator.

**Installation of the Brain-Pressure-Monitoring Tube**

Under anesthesia, the rabbits were placed in the left lateral decubitus position and a skin incision was made linearly along the midline of the cranium extending from the same level of the tip of orbital to the external occipital ridge in the anteroposterior direction (Fig. 1). After reversing the skin, the right frontal bone was exposed and a perforation of approximately 3 mm was created inside the orbit using a high-speed drill (UC210; Urawa Minitorjet, Saitama, Japan). The dura matter that was exposed by the burr was cut with a pointed blade, and the outflow of cerebrospinal fluid was checked. Subsequently, a catheter tube (inside diameter: 0.58 mm; KN-392 SP-45; Natsume Seisakusho Co. Ltd., Tokyo, Japan) was inserted into the subarachnoid space toward the caudal side and indwelled at a depth of approximately 1 cm from the dura. Using this, the brain pressure was measured. The burr hole was closed using bone wax to adjust ICP, and it was strongly fixed with Aron Alpha (Aron Alpha for plastic; Konishi Co. Ltd., Osaka, Japan). Afterward, a 22-G surgical indwelling needle was inserted along the occipital bone from the distal part of the posterior side of the skin incision to the distal end of the later occipital ridge, and the dura between the occipital bone and the annulus was punctured. Once it was confirmed that cerebrospinal fluid flowed freely into the ventricle, the needle was removed, and the burr hole was closed with bone wax.
measuring probe was attached. Cerebral and peripheral blood flow rates were measured using an ultrasonic blood flow meter (MA 4 PSB 4 PSB 1277; Transic Systems, Japan).

CAVI was measured using a modified VaSera 1000 system (Fukuda Denshi Co. Ltd., Tokyo, Japan). To detect pulse wave velocity from the origin of the heart to the ankle, the starting wave was detected for humans. The pulse was detected at the ankle using a vasosensor inserted into the femoral artery.

CAVI was calculated using Equation 1:

\[ \text{CAVI} = \left( \frac{2p}{\Delta P} \right) \times \ln \left( \frac{P_s}{P_d} \right) \times \text{haPWV}^2 \]  

Where \( P_s \) is systolic BP (Pa), \( P_d \) is diastolic BP (Pa), \( \text{haPWV} \) is the heart-ankle pulse wave velocity (m/s), \( \Delta P \) is Ps minus Pd (Pa), and \( p \) is blood density (kg/m³).²²

**Drug Administration and Parameters of Interest**

The rabbits were repositioned from the left lateral decubitus position to the supine position, and drip lines were secured with 24-G surgical indwelling needles from the left and right auricular veins. Replacement fluid was introduced with Ringer’s solution from the left side and hexamethonium (hexamethonium bromide injection; FUJIFILM Wako Pure Chemical Co., Osaka, Japan) was administered.

Hexamethonium was administered at an initial dose of 10 mg/kg, followed by a maximum dose of 100 mg/kg to completely block the ganglion. CVP was measured by inserting a heparinized catheter from the right external jugular vein and indwelling it in the superior vena cava. A heparinized catheter (inside diameter: 0.58 mm; KN-392 SP-45; Natsume Seisakusho Co. Ltd., Tokyo, Japan) was placed in the right radial and right femoral arteries, and BP and HR were recorded. The right common carotid artery and left femoral artery were exposed and a blood-flow-measuring probe was attached. Cerebral and peripheral blood flow rates were measured using an ultrasonic blood flow meter (MA 4 PSB 4 PSB 1277; Transic Systems, Japan).

CAVI was measured using a modified VaSera 1000 system (Fukuda Denshi Co. Ltd., Tokyo, Japan). To detect pulse wave velocity from the origin of the heart to the ankle, the starting wave was detected using the second heart-sound brachial pulse, as is used for humans. The pulse was detected at the ankle using a vasosensor inserted into the femoral artery.

Experimental Protocol

Experiments were initiated after all parameters became stable. To measure the control condition (increased ICP without any drug), saline was injected at 1 mL/min through a catheter placed in the cisterna magna to increase ICP (Fig. 2). A total of 15 mL of saline was injected within 15 min. When administering saline from the cisterna magna, the ICP was increased by over 20 mmHg. At 5 min after the completion of the injection, occluded saline and cerebral fluid were released to reduce intracranial pressure, and circulation was allowed to recover to the

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**Fig. 1. Schema of the measurement system of CAVI in the anesthetized rabbit**

Indicated is the positional relationship between each parameter and the catheter in the increased intracranial pressure model. To measure the intracranial pressure, the right frontal bone was drilled, and the catheter inserted into the subarachnoid space. A puncture was made into the cisterna magna using a 22-G needle, followed by saline injection.
Subsequently, changes in each parameter were compared between conditions of raised ICP, low-dose hexamethonium, and high-dose hexamethonium using two-way ANOVA and Bonferroni’s multiple tests. All statistical analyses were performed using GraphPad Prism 7 version 7.04 (GraphPad Software, Inc., La Jolla, CA, USA). The significance level was set at 5% ($p < 0.05$).

**Data Availability**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Results**

**Changes in Vascular Parameters Due to Increased ICP**

ICPs at each point are shown in Fig. 2. ICP increased to approximately 100 mmHg in all conditions. BP (systolic pressure), CAVI, HR, CCF, and CVP at each point are summarized in Table 1. In the control condition, the changes in each parameter were presented as the change in fluctuation from the basal level. As ICP increased, BP ($\Delta$BP; the change of fluctuation with blood pressure), CAVI ($\Delta$CAVI; the change of fluctuation with CAVI), HR ($\Delta$HR; the change of fluctuation with HR), CCF ($\Delta$CCF; the change of fluctuation with CCF), and CVP ($\Delta$CVP; the change of fluctuation with CVP) increased (Fig. 3).
Table 1. Changes to each parameter

|                     | No drug     | Control | 5 min     | 10 min    | 15 min    | p value |
|---------------------|-------------|---------|-----------|-----------|-----------|---------|
| ICP                 | 9.46 ± 0.82 | 84.26 ± 15.67 | 95.56 ± 20.06 | 97.78 ± 18.61 | p < 0.01 |
| BP                  | 63.20 ± 4.84/ | 104.00 ± 14.90/ | 127.40 ± 16.18/ | 128.80 ± 14.68/ | p < 0.05 |
| Systolic/Diastolic  | 41.00 ± 3.82 | 81.40 ± 12.08 | 103.4 ± 11.70 | 104.8 ± 12.53 |          |
| CAVI                | 4.02 ± 0.28 | 4.26 ± 0.12 | 4.94 ± 0.53 | 4.9 ± 0.53 | NS       |
| HR                  | 189.40 ± 11.83 | 227.20 ± 14.51 | 228.40 ± 14.85 | 229.60 ± 16.69 | NS       |
| CCF                 | 22.00 ± 1.98 | 37.00 ± 6.11 | 43.80 ± 8.08 | 42.40 ± 8.11 | NS       |
| CVP                 | 4.12 ± 0.70 | 6.36 ± 0.65 | 6.00 ± 0.82 | 6.04 ± 0.68 | NS       |

|                     | 10 mg/kg hexamethonium | Control | 5 min | 10 min | 15 min | p value |
|---------------------|-------------------------|---------|-------|--------|--------|---------|
| ICP                 | 9.24 ± 0.90 | 108.36 ± 24.11 | 109.48 ± 22.40 | 115.80 ± 30.35 | p < 0.05 |
| BP                  | 68.20 ± 4.00/ | 116.00 ± 12.43/ | 128.00 ± 8.86/ | 132.20 ± 9.41/ | p < 0.001 |
| Systolic/Diastolic  | 48.40 ± 3.08 | 92.00 ± 11.83 | 103.00 ± 8.85 | 106.20 ± 8.09 |          |
| CAVI                | 4.60 ± 0.36 | 4.68 ± 0.52 | 4.9 ± 0.57 | 5.02 ± 0.64 | NS       |
| HR                  | 217.60 ± 15.34 | 222.20 ± 7.84 | 224.80 ± 8.83 | 227.00 ± 10.15 | NS       |
| CCF                 | 23.80 ± 2.82 | 45.80 ± 7.12 | 44.00 ± 6.57 | 45.20 ± 6.37 | NS       |
| CVP                 | 4.30 ± 0.85 | 5.90 ± 0.50 | 5.96 ± 0.71 | 6.16 ± 0.66 | NS       |

|                     | 100 mg/kg hexamethonium | Control | 5 min | 10 min | 15 min | p value |
|---------------------|-------------------------|---------|-------|--------|--------|---------|
| ICP                 | 10.64 ± 1.24 | 113.94 ± 23.70 | 97.08 ± 16.44 | 108.48 ± 23.59 | p < 0.01 |
| BP                  | 101.60 ± 4.94/ | 92.40 ± 7.95/ | 100.80 ± 11.02/ | 105.60 ± 11.01/ | NS       |
| Systolic/Diastolic  | 77.40 ± 6.67 | 74.20 ± 7.85 | 83.00 ± 9.19 | 86.80 ± 10.24 |          |
| CAVI                | 4.68 ± 0.42 | 4.58 ± 0.39 | 4.82 ± 0.37 | 4.82 ± 0.42 | NS       |
| HR                  | 229.00 ± 10.48 | 211.40 ± 5.57 | 211.00 ± 6.54 | 209.40 ± 8.88 | NS       |
| CCF                 | 35.40 ± 5.33 | 34.80 ± 6.32 | 28.80 ± 6.55 | 29.20 ± 5.96 | NS       |
| CVP                 | 5.50 ± 0.71 | 5.56 ± 0.67 | 5.40 ± 0.65 | 5.46 ± 0.73 | NS       |

All data indicate mean ± standard error. The data change in each parameter is shown. Intracranial pressure was significantly increased compared to the control condition. Blood pressure showed an upward tendency with statistical differences between no drug and 10 mg/kg hexamethonium, but without statistical differences between no drug and 100 mg/kg hexamethonium. Other parameters were not significantly increased in the control condition. BP, blood pressure; CAVI, cardio-ankle vascular index; HR, heart rate; CVP, central venous pressure; ICP, intracranial pressure; NS, not significant.

Fig. 3. Intracranial pressure and change of fluctuation with each parameter

Intracranial pressure was significantly increased compared to the control. Blood pressure and cardio-ankle vascular index presented significant upward tendency with increasing intracranial pressure. *p < 0.05 vs control on each time and parameter; **p < 0.01 vs control on each time and parameter. BP, blood pressure; CAVI, cardio-ankle vascular index; HR, heart rate; CCF, common carotid flow; CVP, central venous pressure. △BP, change of fluctuation with blood pressure; △CAVI, change of fluctuation with CAVI; △HR, change of fluctuation with HR; △CCF, change of fluctuation with CCF; △CVP, change of fluctuation with CVP.
Changes in Vascular Parameters Due to Increased ICP with Hexamethonium Pretreatment at Low and High Doses

Changes in vascular parameters during pretreatment with hexamethonium, administration of low- and high-dose hexamethonium, and enhanced ICP by saline injection are shown in Fig. 4.

a) BP: BP increased significantly after increasing ICP in the control experiment without hexamethonium and also following the administration of low-dose hexamethonium. ΔBP after increasing ICP was suppressed by pretreatment with high-dose hexamethonium (Fig. 4-A).

b) CAVI: CAVI increased significantly after increasing ICP in the control experiment without hexamethonium but not with pre-administration of either low- or high-dose hexamethonium (Fig. 4-B). Thus, ΔCAVI was reduced at all time points following hexamethonium administration as compared with the control; however, the difference between ΔCAVI in response to increased ICP without hexamethonium and low- and high-dose hexamethonium remained statistically significant at each timepoint: 10 min (no drug vs. high dose), 11 min (no drug vs. low or high dose), and 14 min (no drug vs. high dose).

c) HR: HR increased after increasing ICP in the control experiment without hexamethonium. Pre-administration of low-dose and high-dose hexamethonium suppressed ΔHR after increasing ICP (Fig. 4-C).

d) CCF: CCF increased significantly after increasing ICP in the control experiment without hexamethonium and also following the administration of low-dose hexamethonium. ΔCCF after increasing ICP was suppressed by pretreatment with high-dose hexamethonium (Fig. 4-D).

e) CVP: CVP increased significantly after increasing ICP in the control experiment without hexamethonium and also following the administration of low-dose hexamethonium. ΔCVP after increasing ICP was suppressed by pretreatment with high-dose hexamethonium (Fig. 4-E).

When no drug and low concentration hexamethonium were compared, no statistical difference was observed in CVP, but each reaction was suppressed in an almost dose-dependent manner.

When no drug and low concentration hexamethonium were compared, no statistical difference was observed in CVP, but each reaction was suppressed in an almost dose-dependent manner.  
*<p<0.05, **<p<0.01, ***<p<0.001; no drug vs low dose hexamethonium at the same timepoint for each condition. 
*p<0.05, **<p<0.01, ***<p<0.001; no drug vs high dose hexamethonium at the same timepoint for each condition.

BP: blood pressure; CAVI: cardio-ankle vascular index; HR: heart rate; CCF: common carotid flow; CVP: central venous pressure.

ΔBP: the change of fluctuation with blood pressure, ΔCAVI: the change of fluctuation with CAVI, ΔHR: the change of fluctuation with HR, ΔCCF: the change of fluctuation with CCF, ΔCVP: the change of fluctuation with CVP.
Correlations of ICP with Various Vascular Parameters

Correlations of ICPs with various vascular parameters with or without hexamethonium are shown in Table 2. Each parameter, BP, HR, CAVI, CCF, and CVP, correlated positively with ICP without hexamethonium and low-dose hexamethonium. However, correlations between ICP and HR, CAVI, CCF, and CVP were non-existent following the administration of high-dose hexamethonium.

Discussion

When ICP was increased by saline injection into the cerebral cisterns of rabbits, BP also increased, accompanied by enhancement of CAVI, HR, CCF, and CVP. Each response was highly correlated and statistically significant (Table 2).

The CAVI reflects functional stiffness due to arterial smooth muscle contraction as well as organic stiffness. Enhanced CAVI that occurred as a result of increasing ICP indicated that the arterial smooth muscle was contracting, thereby increasing vascular stiffness. Therefore, it suggests that the increase in vascular resistance as indicated by CAVI, caused an enhancement in BP and CCF. CVP increased due to enhancement of the autonomic nervous system with increased ICP. As cardiac output could not be measured, the problem of volume overload or the mechanism behind these results could not be investigated. Stroke is sometimes associated with abnormal cardiac function named Takotsubo cardiomyopathy. This cardiac disfunction might have decreased the cardiac output in this experimental model, but this assumption requires further verification. In addition, in the sympathetic nerve enhancement state due to increased ICP, pulmonary vascular hyperpermeability with increased pulmonary vascular resistance has been reported, as has the onset of neurogenic pulmonary edema. These conditions could be due to increased CVP with volume overload. As illustrated in Fig. 5, we suggest a model in which raised ICP might induce brain tissue ischemia by compressing brain tissue. Ischemic brain tissue might then release a signal to induce arterial smooth muscle contraction, leading to an enhanced CAVI accompanied by an increase in vasoconstriction. As a result, BP increases and CCF is enhanced. A ΔCCF might compensate for brain ischemia.

There are several candidates for the signal released from ischemic brain tissue. We hypothesized that the autonomic nervous system is involved in the mechanism underlying arterial smooth muscle contraction induced by intracranial ischemia. Herein, we tested this hypothesis by investigating the effects of hexamethonium, a ganglionic blocker.

These results indicate that arterial vascular elasticity is clearly influenced by the autonomic nervous system and that the brain functionally controls blood vessels. After observing the change in each parameter in response to an increase in ICP, the effects of pre-administration of hexamethonium were investigated. Arterial stiffness decreased due to the effect of complete postganglionic nerve blockade on arterial smooth muscle tone, despite an increase in ICP. In addition, low doses of hexamethonium caused significant suppression of HR, whereas high doses caused changes in BP, CAVI, CCF, and CVP to near complete suppression (Fig. 4). These results indicate that the autonomic nervous system might be involved in this series of events, especially in CAVI.

Table 2. Correlations of intra cranial pressure with each parameter

|                  | No drug | 10 mg/kg hexamethonium | 100 mg/kg hexamethonium |
|------------------|---------|------------------------|-------------------------|
|                  | r       | p value                | r                       | p value                |
| Systolic BP      | 0.940   | p < 0.001              | 0.936                   | p < 0.001              | 0.509                   | p < 0.05 |
| Diastolic BP     | 0.943   | p < 0.001              | 0.936                   | p < 0.001              | 0.584                   | p < 0.05 |
| CAVI             | 0.782   | p < 0.001              | 0.643                   | p < 0.01               | 0.126                   | NS        |
| HR               | 0.969   | p < 0.001              | 0.801                   | p < 0.001              | -0.484                  | NS        |
| CCF              | 0.958   | p < 0.001              | 0.939                   | p < 0.001              | 0.200                   | NS        |
| CVP              | 0.936   | p < 0.001              | 0.895                   | p < 0.001              | 0.387                   | NS        |

All data indicate Pearson correlation and p value on each parameter compared with ICP. Intracranial pressure was significantly increased compared with ICP. However, when high dose hexamethonium was used to completely block the autonomic nervous system, the above relationship was broken. ICP and BP, HR and CCF, CCF and CVP remained positively correlated, but ICP and CVP, CAVI and HR, CAVI and CCF, CAVI and CVP changed to negative correlation. In particular, CAVI and CCF showed a negative correlation with a significant difference.
There are some limitations to the present study. First, saline injection into the subarachnoid space increased pressure across the entire brain. Thompson and Malina7, and other researchers8, 9) have confirmed the dominant region of BP control in the brain by identifying the rostral ventrolateral medulla as a cause of hypertension; nevertheless, it is difficult to confirm the dominant region in terms of vascular stiffness by infusing the entire brain. Second, CAVI was measured across a wide range that spanned the origin of the aorta to the femoral artery. The pathology of blood vessels greatly varies between that of the aorta and muscular blood vessels to the capillaries. As Horinaka et al.30) reported, blood vessels in different tissues might play different roles. Therefore, it may be necessary to examine segmental CAVI in terms of blood vessel function. Third, when using high-dose hexamethonium, BP and CCF did not return to the same levels as the no drug and low-dose hexamethonium controls. From the viewpoint of animal protection, the reactions to no drug and low- and high-dose hexamethonium were measured in the same animal to reduce the number of sacrificed rabbits. The results might have been different if individual animals were employed for each condition.

Conclusion

Increased ICP causes BP and CAVI to increase, suggesting that enhanced stiffness of muscular arteries might contribute to high BP. Blocking the autonomic nervous system with hexamethonium suppresses the increase in BP and CAVI, indicating that these increases are mediated by autonomic nervous system activation. Further studies on the function of blood vessels are required. As this research focused on the effects of cardiovascular diseases associated with acute brain disease, we reckon that it can be useful for future applications, such as drug selection or clinical testing.

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Conflict of Interest

Tomoyuki Yamamoto is employees of Fukuda Denshi Co., Ltd. and were involved in the development of CAVI.

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