

## Ammonia Determination as an Early Indicator in Experimental Superior Mesenteric Artery Occlusion

Masanobu WATARI<sup>1)</sup>, Hironobu MURAKAMI<sup>1)</sup>, Kazumasa ORIHASHI<sup>1)</sup>,  
Taijiro SUEDA<sup>1)</sup>, Yuichiro MATSUURA<sup>1)</sup> and Hiroki KAJIHARA<sup>2)</sup>

1) First Department of Surgery, 2) Institute of Health Sciences, Hiroshima University School of Medicine, Hiroshima, Japan

### ABSTRACT

Superior mesenteric artery occlusion (SMAO) is often fatal. An indicator which enables the early diagnosis of SMAO is needed. As we think putrefaction products must appear and increase in the blood and ascites in SMAO, changes in the concentrations of ammonia, one of the putrefaction products, were measured in this study.

Thirteen adult mongrel dogs were used for the *in vitro* experiment. The jejunum, ileum, and ascending colon were resected and incubated in saline. Changes in ammonia concentrations in the saline were examined at various incubation times.

In the *in vivo* experiment, 11 mongrel dogs comprised the SMAO group and another 10 mongrel dogs comprised the control group. Changes in ammonia concentrations in the blood and ascites were examined in both groups.

In the *in vitro* experiment, ammonia concentrations in the saline bath increased in all samples. It was highest in the sample from around the ascending colon, and lowest from around the jejunum. However, at the end of experiment, this difference became insignificant.

In the *in vivo* experiment, ammonia concentrations in samples of the blood increased early and significantly in the SMAO group, compared with the control group. Ammonia concentrations in samples of the ascites also increased significantly.

The *in vitro* experiment showed that ammonia leaked from the ischemic intestines, and secondarily, a large amount of ammonia was produced from intestinal putrefaction. The *in vivo* experiment revealed that the ammonia level in the blood could be used as a good early indicator of acute mesenteric ischemia.

**Key words:** Ammonia, Putrefaction, Mesenteric ischemia, Superior mesenteric artery occlusion

Superior mesenteric artery occlusion (SMAO) is typical of acute mesenteric ischemia. The early diagnosis of SMAO remains difficult and the condition is associated with a high mortality<sup>1,6,9,10</sup>. Since it is impossible to predict the occurrence of SMAO, early diagnosis is of primary importance. Although a number of indicators for making early diagnosis have been reported<sup>2,3,5,7,8,11,13-18</sup>, the mortality of SMAO has not been reduced. Thus a new indicator is needed.

We have hypothesized that putrefaction products must appear and increase in the blood or ascites of the patient with SMAO. The putrefaction products, ammonia, hydrogen sulfide, thiols, indole, and skatole are generated by the decomposition of protein by bacteria. In this study, ammonia was especially researched because it has already been measured on clinical emergency.

The purpose of this study was to examine the leakage of ammonia from the intestine and the production of new ammonia from progressive intestinal putrefaction in an *in vitro* model. In addition, we studied increases in the ammonia concentration in the blood and ascites in an *in vivo* experiment, focusing on the early diagnosis of SMAO.

### MATERIALS AND METHODS

The experimental protocol described below was approved by the Research Facilities for Laboratory Animal Science, Hiroshima University School of Medicine, and met the standards outlined by the American Physiological Society and the National Institutes of Health in the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-23, revised 1985).

## ***in vitro* experiment**

### **Procedures**

Thirteen adult mongrel dogs weighing 10 to 20 kg were fed standard laboratory food containing 27.9 g of protein, 8.6 g of fat, and 46.0 g of carbohydrate per 100 g. The animals were not fasted. Each dog was induced with ketamine (10 mg/kg) given intramuscularly and anesthetized with a bolus injection of thiamylal sodium (6 mg/kg) intravenously. Thiamylal sodium was subsequently administered as needed until the dog was killed with a potassium chloride injection. The dog underwent laparotomy, and the jejunum, ileum, and ascending colon were resected in segments of approximately 10 g with both ends closed. The skeletal muscle was also resected in a piece of approximately 10 g from the rectus abdominis muscle. Each segment and each piece of muscle were weighed precisely and placed in a flask filled with 10 times its weight of saline. All of the flasks were incubated at 37°C. Four sets of flasks were similarly prepared for pathologic analysis of the sequential changes.

In addition, the contents of the intestines were collected from the residual jejunum, ileum, and ascending colon for determination of their own ammonia concentrations.

### **Determination of ammonia concentration**

The ammonia concentration in the saline in each flask was measured at 4, 8, 12, 16, and 32 hours, using the FUJI DRI CHEM 5500 (Fuji Medical System Co., Tokyo, Japan)<sup>4,12</sup>. A small amount of saline (10 µl) from each flask was spotted on a multilayer-film slide for plasma (NH<sub>3</sub>-P II)<sup>12</sup>. If the concentration was beyond the measurable range, it was determined after the sample was appropriately diluted with saline.

The contents of the intestines were diluted with saline for determination of their own ammonia concentrations.

### **Pathologic study**

Specimens were removed from the flasks at 4, 8, 12, 16, and 32 hours and fixed in 10% buffered formalin. Small tissues of the specimens were subsequently embedded in paraffin, and processed in the routine manner. Sections (3 µm) were stained with hematoxylin and eosin, and with Gram's method for light microscopic examination.

## ***In vivo* experiment**

### **Procedures**

Twenty-one adult mongrel dogs weighing 8 to 17 kg were used after they were pretreated and anesthetized in the same manner as in the *in vitro* experiment. After intubation, ventilation was assisted mechanically using a pressure limited respirator (MARK 7 respirator, 3M Bird Co.,

Palm Springs, CA, USA) and room air. Saline was infused continuously during the experiment unless hemoconcentration and hemodilution developed. The femoral artery was cannulated for sampling the blood and monitoring blood pressure. The dogs were warmed by lighting so that their rectal temperature was maintained at 36° to 38°C.

Eleven dogs were assigned to the SMAO group of which the anterior mesenteric artery (corresponding to superior mesenteric artery in the human) was ligated at its trunk. The communicating arteries from the posterior pancreatic and posterior mesenteric arteries were also ligated in order to reduce their collateral blood flow. When the mean blood pressure dropped below 40 mmHg, the dog was killed with an injection of potassium chloride. Ten dogs were assigned to the control group which underwent a sham operation and were observed for 24 hours. In both groups, the abdominal incision was kept closed during the experiment except during the collection of ascites and pathologic specimens.

### **Physiologic examination**

The mean blood pressure was monitored throughout the experiment. Arterial blood gas analysis was performed using the ABL510 (Radiometer Co., Copenhagen, Denmark) before (at 0 hour), and at 2, 4, 8, 12, 16, 20, and 24 hours after ligation of the arteries.

### **Measurement of tissue blood flow**

In six dogs in the SMAO group, tissue blood flow was measured at the liver, stomach, duodenum, jejunum, mid-portion of the small intestine, ileum, ascending colon, and descending colon using a Laser Doppler Flowmeter (ALF21N, Advance Co., Tokyo, Japan) before and after ligation of the arteries. The mean tissue blood flow was determined by averaging the data at six optimal points in each organ. Tissue blood flow after arterial ligation was expressed as a percentage of the initial value.

### **Determination of ammonia concentration**

Arterial blood was sampled for determination of ammonia concentration in the blood because venous ammonia concentrations sometimes vary from vein to vein. In both groups, the arterial ammonia concentration was measured before (at 0 hour), and at 2, 4, 8, 12, 16, 20, and 24 hours after ligation of the arteries. The ammonia concentration in the ascites was also measured in both groups at 2, 4, 8, 12, 16, 20, and 24 hours after ligation of the arteries. The FUJI DRI CHEM 5500 was used for determination of the ammonia concentrations. A multilayer-film slide for whole blood (NH<sub>3</sub>-W II) was used for the blood sample<sup>12</sup>. A slide for plasma (NH<sub>3</sub>-P II)

was used for the ascites sample.

### Biochemical examination

The plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, blood urea nitrogen (BUN), and creatine phosphokinase (CPK) in arterial blood were measured before (at 0 hour), and at 4, 8, 12, 16, 20, and 24 hours after the arteries were ligated.

### Pathologic study

In the SMAO group, a small portion of the anti-mesenteric wall was sampled at the ileum for pathologic study before (at 0 hour), and at 4, 8, 12, 16, and 20 hours after the arteries were ligated. The ileum was repaired after each sampling. The liver was also biopsied prior to ligation of the arteries and at the time the dogs were killed. These specimens were treated in the same manner as described in the *in vitro* experiment for light microscopic examination.

### Statistical analysis

The data are expressed as the mean  $\pm$  the standard error of the mean. The difference between three or more groups was examined by one-way analysis of variance, followed by Scheffe's test (post hoc). The difference between two groups was examined by a paired or unpaired *t* test. The difference was considered to be statistically significant when the probability value was less than .05. When the unpaired *t* test is repeated to examine the serial difference between two groups, total  $\alpha$  error should be diminished. In this case, the difference was considered to be statistically

significant when the probability value was less than .01.

## RESULTS

### *In vitro* experiment

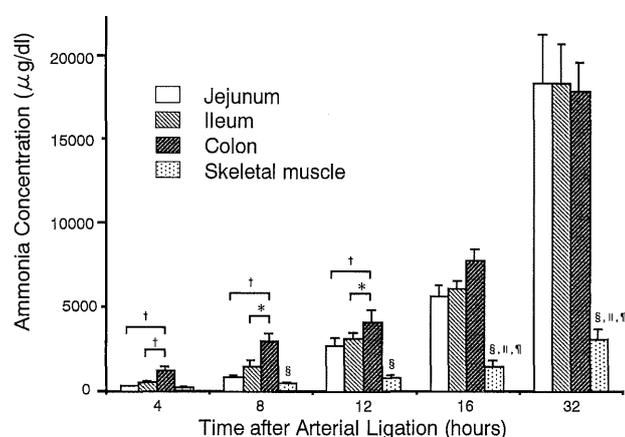
#### Ammonia concentration

The ammonia concentration in the saline was increased in every intestinal sample while the increase in the ammonia concentration in the saline around the skeletal muscle remained small. In a comparison among the intestinal samples, it was significantly highest in the sample from around the ascending colon and lowest in the sample from around the jejunum at the beginning of the experiment (at 4 hours:  $1264 \pm 235$   $\mu\text{g}/\text{dl}$  (ascending colon),  $544 \pm 93$   $\mu\text{g}/\text{dl}$  (ileum),  $311 \pm 37$   $\mu\text{g}/\text{dl}$  (jejunum),  $p < .01$  ascending colon vs. ileum and jejunum). The ammonia concentration in the saline in each sample increased to almost the same level and the differences among them became insignificant toward the end of the experiment (Fig. 1A).

The ammonia concentrations in the luminal contents of the ascending colon, ileum, and jejunum were  $865.3 \pm 155.6$   $\mu\text{g}/\text{g}$ ,  $501.2 \pm 162.2$   $\mu\text{g}/\text{g}$ , and  $175.8 \pm 30.0$   $\mu\text{g}/\text{g}$  respectively. It was highest in the ascending colon and lowest in the jejunum. There was a significant difference between the ascending colon and the jejunum ( $p < .01$ ) (Fig. 1B).

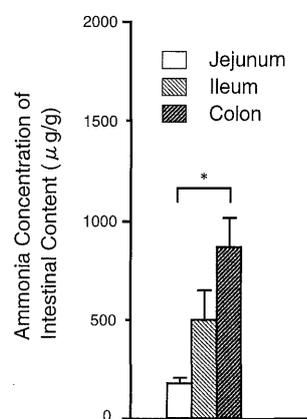
### Pathologic study

Similar pathologic changes occurred in the jejunum, ileum, and ascending colon. Cellular autolysis and interstitial degeneration were observed at



**Fig. 1A.** Change of ammonia concentration in saline in the *in vitro* experiment (n=13).

\* $p < .05$ , † $p < .01$ . The difference between each intestine was examined by one-way analysis of variance. § $p < .01$  muscle vs. colon. || $p < .01$  muscle vs. ileum. ¶ $p < .01$  muscle vs. jejunum. The difference between the muscle and each intestine was examined by unpaired *t* test. Mean  $\pm$  SEM is shown.



**Fig. 1B.** Ammonia concentration of intestinal content in the *in vitro* experiment (n=13).

\* $p < .01$ . Mean  $\pm$  SEM is shown.

the tips of the intestinal villi at 4 hours. These necrotic changes progressed toward the base of the villi. Most of the villi collapsed at 12 hours, and all of the intestinal layers became necrotic at 16 hours. Bacterial proliferation in the necrotic tissue was seen at 8 hours. These findings typify the progression of necrosis and putrefaction. Necrotic changes were also seen in the skeletal muscle. However bacterial proliferation was scarcely seen at 8 hours.

### *In vivo* experiment

In the SMAO group, three dogs were killed between 20 and 24 hours. The remaining eight dogs were killed between 24 and 28 hours. The mean survival time was  $24.6 \pm 0.8$  hours (range: 20.5 to 27 hours). The infusion rate of saline was significantly higher in the SMAO group than in the control group ( $26.2 \pm 1.9$  ml/kg/hr vs.  $16.2 \pm 1.7$  ml/kg/hr, respectively ( $p < .01$ )).

### Physiologic examination

The mean blood pressure was stable in the control group. However, in the SMAO group, it began to decrease at 12 hours and dropped significantly at 16 hours in comparison with the control group (mean blood pressure at 16 hours:  $81.7 \pm 4.8\%$  vs.  $103.0 \pm 3.1\%$ , respectively ( $p < .01$ )) (Fig. 2).

While arterial blood gas analysis revealed no metabolic acidosis in the control group, a progressive metabolic acidosis was seen in the SMAO group (pH at 8 hours:  $7.31 \pm 0.02$  vs.  $7.40 \pm 0.01$ , respectively ( $p < .01$ ), base excess (BE) at 2 hours;  $-7.37 \pm 0.57$  mEq/liter vs.  $-4.58 \pm 0.31$  mEq/liter, respectively ( $p < .01$ )) (Fig. 3).

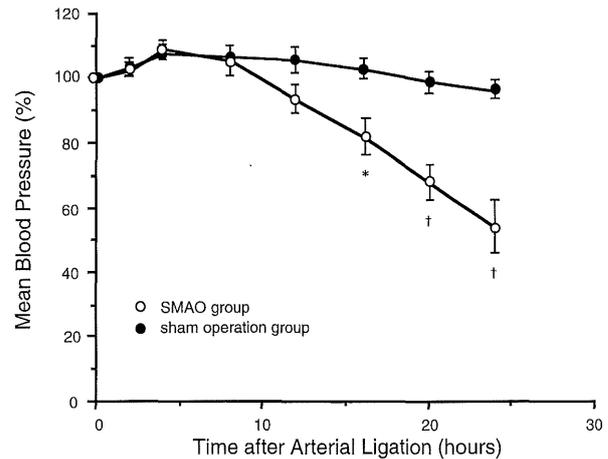
### Tissue blood flow in the SMAO model

In the jejunum, the mid-portion of the small intestine, the ileum, and ascending colon, the tissue blood flow was significantly reduced to less than 20% of the initial flow after arterial ligation ( $p < .0001$ ). It remained unchanged at the liver, stomach, duodenum, and descending colon (Table 1).

### Ammonia concentration

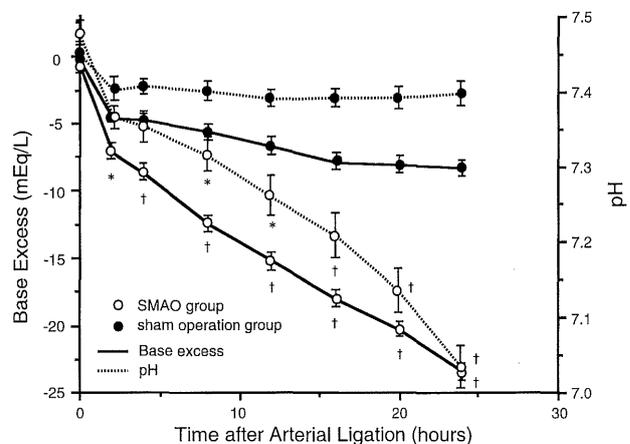
While the arterial ammonia concentration was unchanged in the control group, it increased significantly at 2 hours in the SMAO group in comparison with the control group (arterial ammonia concentration at 2 hours;  $71.9 \pm 3.8$   $\mu\text{g/dl}$  vs.  $42.6 \pm 2.5$   $\mu\text{g/dl}$ , respectively ( $p < .0001$ )). It steeply increased after 12 hours until the dogs were killed (Fig. 4).

Only a small amount of ascites was present in the control group. On the other hand, ascites increased gradually in the SMAO group, and became brown and had a foul odor after 12 hours. While the ammonia concentration in the ascites



**Fig. 2.** Change of mean blood pressure in SMAO group ( $n=11$ ,  $n=8$  at 24 hours) and sham operation group ( $n=10$ ).

Value is expressed as % of each initial value. \* $p < .01$ , † $p < .0001$  SMAO group vs. sham operation group. Mean  $\pm$  SEM is shown.



**Fig. 3.** Change of base excess (BE) and pH in SMAO group ( $n=11$ ,  $n=8$  at 24 hours) and sham operation group ( $n=10$ ).

\* $p < .01$ , † $p < .0001$  SMAO group vs. sham operation group. Mean  $\pm$  SEM is shown.

remained unchanged in the control group, it was significantly higher from 8 hours in the SMAO group than in the control group and continued to increase until the end of the experiment (ammonia concentration in the ascites at 8 hours:  $1056.9 \pm 224.2$   $\mu\text{g/dl}$  vs.  $127.7 \pm 8.4$   $\mu\text{g/dl}$ , respectively ( $p < .01$ )) (Fig. 5).

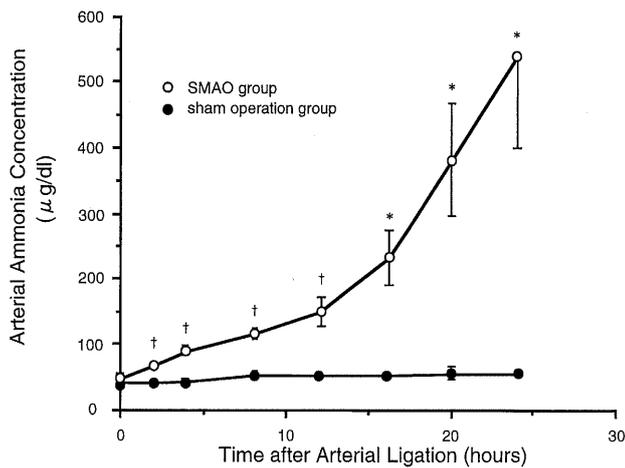
### Biochemical examination

The plasma levels of AST and ALT increased in both groups. However, there was no significant difference between the SMAO and control groups. The plasma BUN level was significantly higher after 8 hours in the SMAO group than in the

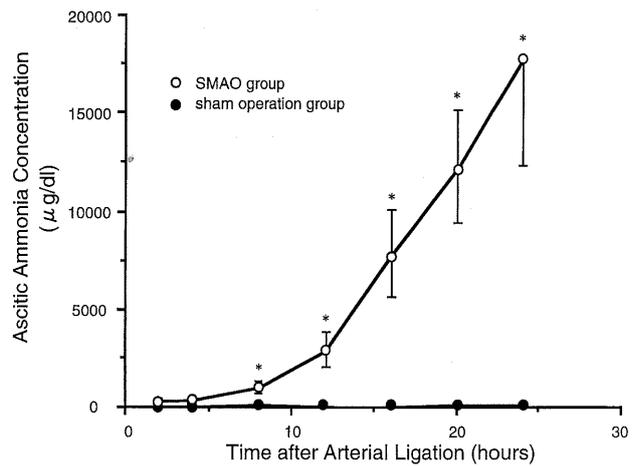
**Table 1.** Tissue Blood Flow Change

	liver	stomach	duodenum	jejunum	mid-portion of small intestine	ileum	ascending colon	descending colon
before arterial ligation(%)	100	100	100	100	100	100	100	100
after arterial ligation(%)	104.4±8.9	87.8±7.3	91.3±20.0	16.6±1.5*	13.0±0.8*	13.8±0.8*	16.3±2.8*	90.9±9.8

\*p&lt;.0001 versus data before arterial ligation

**Fig. 4.** Change of arterial ammonia concentration in SMAO group (n=11, n=8 at 24 hours) and sham operation group (n=10).

\*p&lt;.01, †p&lt;.0001 SMAO group vs. sham operation group. Mean±SEM is shown.

**Fig. 5.** Change of ascitic ammonia concentration in SMAO group (n=11, n=8 at 24 hours) and sham operation group (n=10).

\*p&lt;.01 SMAO group vs. sham operation group. Mean±SEM is shown.

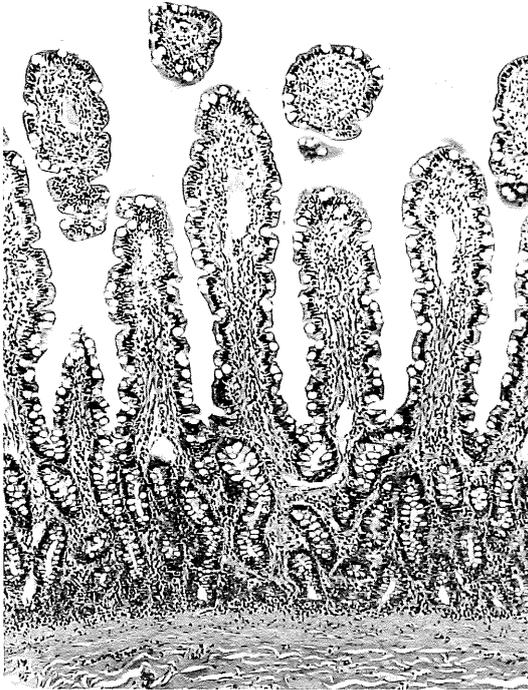
**Table 2.** Biochemical Examination

time (hour)		0	4	8	12	16	20	24
AST (IU/liter)	SMAO group	33.6±2.8	72.9±9.6	127.0±19.8	163.0±30.6	209.0±42.5	255.0±67.5	282.0±92.1
	sham operation group	39.2±2.9	69.0±9.5	84.3±10.0	93.8±11.2	123.0±13.8	140.0±15.8	153.0±16.0
ALT (IU/liter)	SMAO group	32.1±7.3	34.6±7.1	39.1±8.9	43.0±9.4	47.8±11.0	53.3±11.6	50.2±10.7
	sham operation group	21.8±3.4	41.0±11.5	35.2±9.5	40.7±10.3	41.8±11.1	51.2±12.8	50.7±11.8
creatinine (mg/dl)	SMAO group	0.97±0.06	0.74±0.03	0.73±0.06	0.74±0.05	0.78±0.06	1.02±0.18	1.08±0.11
	sham operation group	1.00±0.06	0.83±0.03	0.68±0.06	0.68±0.03	0.70±0.06	0.73±0.08	0.73±0.08
BUN (mg/dl)	SMAO group	15.0±1.5	11.2±0.6	13.5±0.7*	15.2±1.0*	16.7±1.2*	19.0±1.6*	22.5±2.2*
	sham operation group	16.4±1.0	12.4±0.7	10.5±0.6	10.4±0.5	10.5±0.8	11.0±1.1	10.8±1.2
CPK (IU/liter)	SMAO group	143.8±38.8	270.6±93.0	264.8±91.5	208.8±92.6	85.8±32.1*	27.4±9.3*	16.9±6.3*
	sham operation group	166.3±53.2	488.7±59.6	573.7±11.5	712.6±11.5	909.7±80.3	898.7±182.4	901.3±129.7

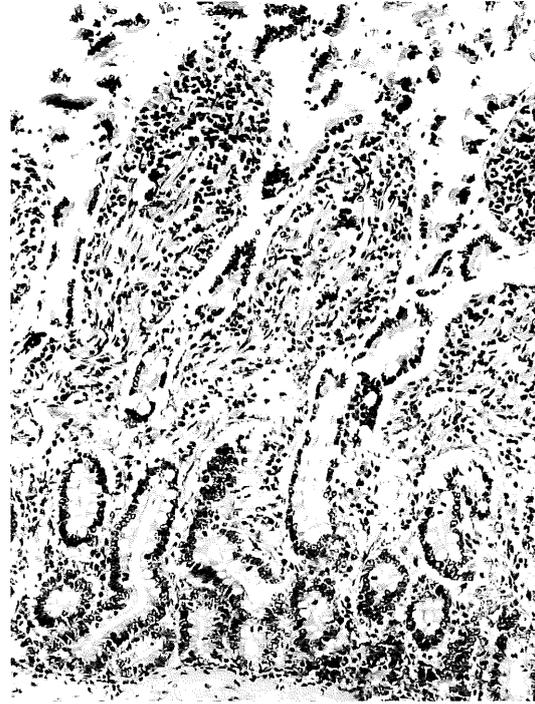
\*p&lt;.01 versus sham operation group.

control group (BUN at 8 hours;  $13.5 \pm 0.7$  mg/dl vs.  $10.5 \pm 0.6$  mg/dl, respectively ( $p < .01$ )). There was no significant difference between two groups in the plasma creatinine level. The plasma CPK level was significantly lower after 16 hours in the

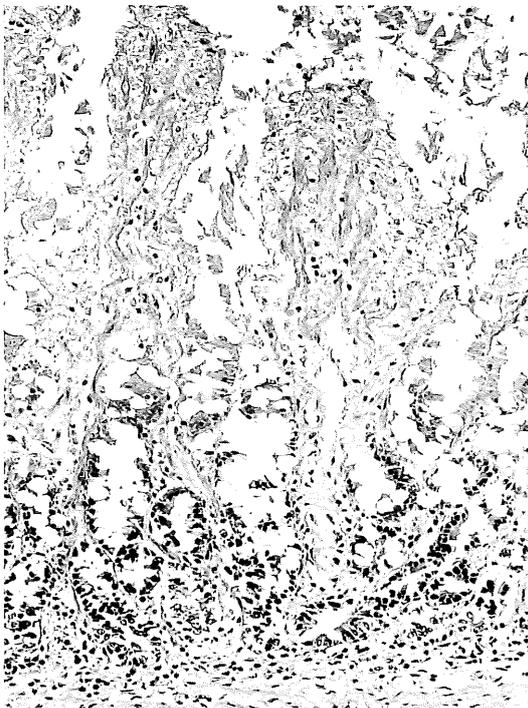
SMAO group than in the control group (CPK at 16 hours;  $85.8 \pm 32.1$  IU/liter vs.  $909.7 \pm 80.3$  IU/liter, respectively ( $p < .01$ )) (Table 2).



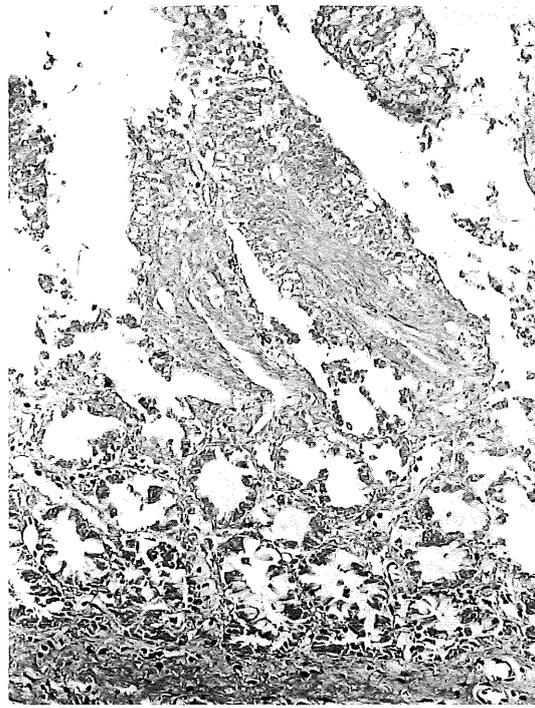
**Fig. 6A.** The mucosal epithelium and interstitial tissue were well preserved at 0 hour (H&E,  $\times 80$ ).



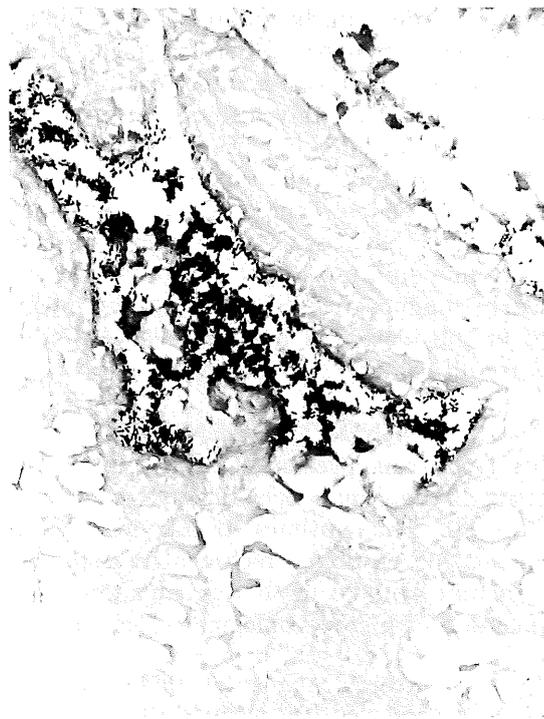
**Fig. 6B.** The covering epithelial cells were degenerated and detached at the tips of the villi at 4 hours (H&E,  $\times 160$ ).



**Fig. 6C.** Necrotic changes progressed toward the bases of the villi at 8 hours (H&E,  $\times 160$ ).



**Fig. 6D.** The entire mucosal layer became necrotic at 12 hours (H&E,  $\times 160$ ).



**Fig. 6E.** Bacterial proliferation was distinct at the necrotic villi at 12 hours (Gram's stain,  $\times 320$ ).

### Pathologic study

After the arteries were ligated, a substantial portion of the small intestine and ascending colon became severely cyanotic. Subserous petechiae and edematous changes appeared diffusely in the infarcted intestines within 4 hours. In the ileum, the pathologic specimen exhibited intraluminal hemorrhage at 4 hours. The dark hemorrhagic discoloration became distinct at 8 hours. Dark green necrotic spots appeared in a scattered pattern at 12 hours. These spots spread and fused, leading to perforation in some dogs. In the control group, little change was apparent.

Microscopic examination revealed that the structure of the villi was well preserved at 0 hour (Fig. 6A). However the covering epithelium was degenerated and detached at the tips of the villi at 4 hours (Fig. 6B). Cellular autolysis and interstitial degeneration progressed toward the bases of the villi (Fig. 6C). The entire mucosal layer became necrotic at 12 hours (Fig. 6D). Bacterial proliferation was recognized distinctly at the necrotic villi from 12 hours (Fig. 6E). In the liver, little change was observed macroscopically in either group, and microscopically, no remarkable change was noted except mild interstitial edema in the SMAO group.

### DISCUSSION

In the *in vitro* experiment, the ammonia concentration in the saline was highest in the sample around the ascending colon and lowest in the sample around the jejunum at the beginning of

the experiment. The ammonia concentration in the luminal contents was also highest in the ascending colon and lowest in the jejunum. These findings suggested the leakage of inherent ammonia into the saline in the early stages of the experiment, possibly caused by ischemic damage to the intestinal wall. Morphologic changes in the intestinal mucosal tissue (autolysis of mucosal villi) were already present at this time. In later stages of the experiment, the ammonia concentration in the saline was increased in every sample until the differences among them became insignificant. This appeared to be caused by a large amount of newly produced ammonia resulting from the decomposition of the necrotic tissues by the bacterial flora, because the progress of necrosis and putrefaction was evident on pathologic examination. On the other hand, the increase in the ammonia concentration in the saline around the skeletal muscle remained small. Thus, the increase in the ammonia concentration in the saline around the intestinal samples appeared to occur in two steps: leakage of inherent ammonia, and leakage of newly produced ammonia through the putrefaction of the necrotic intestinal tissue by the bacterial flora.

In the *in vivo* experiment, the SMAO model involved ligation of the anterior mesenteric artery and communicating branches. This procedure produced sufficiently low blood flow to mimic SMAO.

In the *in vivo* experiment, the ammonia level in the arterial blood was significantly higher in the SMAO group than in the control group as early as at 2 hours. And it increased steeply after 12 hours. The ammonia level in the ascites was also significantly higher from 8 hours in the SMAO group than in the control group. The two-step increase in ammonia shown in the *in vitro* experiment could be applied to the interpretation of the results of the *in vivo* experiment. At the early stages, ammonia appeared to leak through the ischemic intestinal wall into the circulation by any possible pathway including the lymphatic system, portal vein, systemic capillary vessels, and other routes. It also appeared to leak into the ascites directly. Later, as the putrefaction advanced, increased production of ammonia resulted in an increased ammonia level in the arterial blood and ascites.

Generally, in mammals, ammonia comes from the intestinal tract and amino acid metabolism. In the former, ammonia is produced from the dietary protein and secreted urea by bacterial decomposition. Ammonia is present only in trace amounts in the peripheral blood. It is rapidly removed from the circulation and converted to glutamine, or urea in the liver. However, blood ammonia levels rise to toxic levels with severely impaired hepatic function, the development of

collateral communications between the portal and systemic circulations, or with inborn errors of metabolism associated with the urea cycle. In the *in vivo* experiment in this study, the plasma levels of AST and ALT, which are indicators of liver damage, increased moderately in both the SMAO and control groups. However, there was no significant difference between the two groups in the plasma levels of AST and ALT. In the SMAO group, there was no pathologic evidence of the severe hepatic necrosis seen in fulminant hepatitis. Thus, the hyperammonemia seen in this study did not seem to be caused by hepatic impairment. Portosystemic shunting and congenital metabolic disorders of the urea cycle were also not present. The increase in BUN without changes in creatinine was probably caused by reactive acceleration of urea synthesis to compensate for the hyperammonemia. Therefore, the hyperammonemia seen in the *in vivo* experiment might have resulted from excessive ammonia influx into the circulation by any of the possible pathways described above.

In the *in vivo* experiment, the blood pressure began to decrease at 12 hours in the SMAO group, compared with the control group. Though the criterion of early diagnosis of SMAO has not been defined yet, the diagnosis should be made at least prior to this point, because no treatment is effective under the shock state. Thus we think the measurement of the arterial ammonia concentration, which began to increase as early as at 2 hours, would enable an early diagnosis of SMAO.

A number of indicators have been tried to make the diagnosis of acute mesenteric ischemia or SMAO, including metabolic acidosis<sup>3</sup>, elevated concentrations of phosphate<sup>7,15</sup>, lactate<sup>8</sup>, creatine phosphokinase<sup>17</sup>, alkaline phosphatase, BUN<sup>11</sup>, diamine oxidase<sup>18</sup>, and intestinal fatty acid binding protein<sup>5</sup>. Some imaging modalities have been suggested<sup>2,13,16</sup>. However, the mortality of SMAO has not been improved. In the *in vivo* experiment, the plasma level of CPK was lower in the SMAO group than in the control group through the experiment. While some researchers reported the plasma level of CPK as a good indicator, others did not<sup>14,17</sup>. It was unknown why the plasma level of CPK did not show any meaningful change in the early stage and why it significantly decreased in the later stage. Thus the value of CPK as an indicator remains controversial. On the other hand, because we thought arterial blood gas analysis was one of the most useful indicators, metabolic acidosis was examined and compared with the arterial ammonia concentration. The base excess changed significantly at 2 hours, as did the arterial ammonia level. However, base excess is affected by various

conditions, and can be changed or masked by therapeutic maneuvers. Therefore, we think the arterial ammonia level is superior in specificity because it is not acutely influenced by other factors, except in acute hepatic failure. Thus, this study showed that the ammonia levels in the blood and ascites increased in experimental SMAO, and that the measurement of the increased ammonia level in the blood would lead to an early diagnosis of SMAO and the measurement of the increased ammonia level in the ascites would confirm this diagnosis.

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