An electron microscope study of arteriolar branching sites in the normal gastric submucosa of rats and in experimental gastric ulcer

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Summary. To observe the branching site of the rat gastric submucosal arteriole toward the mucosal capillary network, we used vascular corrosion casting, scanning electron microscopy (SEM) and transmission electron microscopy (TEM), under various conditions, including the normal state, water immersion restraint stress for 24 h, ethanol-induced ulcer and administration of low and high doses of noradrenaline. In normal rats, the branching site of the submucosal arteriole toward the mucosa was slightly narrowed, as seen in the cast observations. The SEM and TEM observations revealed that this narrowing was due to the presence of the so-called "intra-arterial cushion". In the restraint stress rats, this narrowing was increased. TEM and direct SEM observation of the intra-arterial cushion showed much the same findings. In the noradrenaline administered rats, similar changes were observed but not so in the rats with an ethanol-induced ulcer. Arterio-venous-anastomoses (AVA) were not observed in the submucosa, under any of the conditions used. We suggest that the submucosal intra-arterial cushions occurring at the branching sites of the submucosal arterioles may play an important role in regulating blood flow to the gastric mucosa.

Key words: Stomach – Submucosal arterioles – Mucosal blood flow – Intra-arterial cushions – Vascular corrosion cast

Introduction

The aetiology of gastric ulcer has not been clearly defined. Currently, the areas most commonly ex-

plored in the search for the aetiology of ulcer disease are mucosal ischaemia and mucosal barrier breakdown (Lanciault and Jakobson 1976). Blood flow in the gastric mucosa is regulated by neurogenic and hormonal factors and focal auto-regulatory systems, such as the submucosal vascular network, the submucosal arterio-venous anastomosis (AVA), the precapillary sphincter and so on.

There is an extensive literature dealing with vascular anatomy of the mammalian stomach (Barlow et al. 1951; Boultar and Parks 1960; Oka 1970; Piasecki 1975). These studies revealed connecting arterioles located between both the mucosal capillary network and the submucosal arteriolar network in the mammalian stomach, running much like pillars between the mucosa and the submucosa. In addition, physiological studies revealed that a gastric submucosal arteriolar network plays an important role in controlling blood flow to the mucosa (Delaney and Grim 1965; Guth et al. 1972, 1975, 1984).

Gannon et al. (1982) examined the microvascular architecture of rat stomach by SEM, using a vascular corrosion cast technique (Murakami 1970). They suggested that sphincter-like constrictions were present in the branching sites of terminal arterioles from the submucosal arterioles.

Since the report of Barlow et al. (1951), it has been believed that the submucosal AVA regulates mucosal blood flow. Guth and Smith (1975) reported evidence refuting the existence of submucosal AVA, as deduced from in vivo microscopic observations. Gannon et al. (1982) also reported the absence of the AVA in normal rats, as determined by vascular cast observations.

Thus, we considered it important to examine the fine morphology of the branching site of the connecting arterioles arising from the submucosal arteriolar network towards the mucosal capillary

network, and to investigate the functional significance in mucosal blood flow.

Materials and methods

Forty male Wistar strain rats weighing 150 to 200 g were used. All rats were housed two per cage in an air conditioned room and were fed rat cubes and water ad libitum. These rats were fasted for 24 h prior to experiment. Five groups were prepared; (1) normal; (2) water immersion restraint stress for 24 h; (3) oral administration of absolute ethanol of 10 ml/kg. bw; (4) intra-arterial injection of noradrenaline of 2 μg/min.kg.bw, with heparinized saline for 10 min (low dose group); (5) intra-arterial injection of noradrenaline of 0.2 mg/min.kg.bw, with heparinized saline for 10 min (high dose group). Four rats in each group were used for corrosion cast observations and four for SEM and TEM observations.

For the production of vascular corrosion casts, the abdominal and thoracic walls were incised and opened under ether anaesthesia. The abdominal aorta just proximal to the origin of the common iliac artery was ligated and the bilateral renal arteries were then ligated. Cannulation of the thoracic aorta just proximal to the diaphragm was performed and the superior vena cava was cut in the thoracic cavity. Blood was flushed out with heparinized (10 IU/ml) saline (0.5 ml/s, total 100 ml), then half strength Karnovskys fixative was infused via the implanted cannula (0.5 ml/s, total 200 ml). A colored methacrylated resin (Mercox CL-2R, Japan Vilene Hospital, Co. Ltd, Tokyo) was then infused, under constant manual pressure (0.5 ml/s), through a cannula, until the resin flowed out continuously from the cut end of the superior vena cava. After complete polymerization of Mercox (50–60° C, 12–24 h), the stomach was corroded in 20–30% KOH for 24–48 h at 50–60° C. The casts were rinsed in several changes of water, and dried at room temperature. A few casts were frozen in water, and with the aid of a stereomicroscope, were sliced with a razor blade through the mucosa perpendicular to the gastric glands. Casts were mounted on scanning electron microscopic aluminum stubs, using double-sided gum tape, coated with gold in an Eiko IB-5 ion coater and examined in a Hitachi S-430 scanning electron microscope at an accelerating voltage of 15–20 kv.

For SEM, immediately after flushing with heparinized (10 IU/ml) saline (0.5 ml/s, total 100 ml) and perfusion with half strength Karnovskys fixative (0.5 ml/s, total 200 ml), small pieces of the glandular stomach were removed and placed in the same fixative for 2 h at 4° C. Materials were then rinsed in 0.1 M cacodylate buffer (pH 7.4), fixed in 1% osmium tetroxide in the same buffer for 2 h, dehydrated in a graded series of ethanol, and dried in a Hitachi HCP-2 critical point dryer. Some specimens were cut through the level between the muscularis mucosa and the muscular layer, parallel to the mucosal surface, under a stereomicroscope for direct observation of the branching sites in the submucosal arteriolar lumen. Others were used for subsequent observation by SEM.

For TEM, immediately after removal from the same rats perfused as for SEM, small pieces of the glandular stomach were transferred into the same fixative for 2 h at 4° C, rinsed in 0.1 M cacodylate buffer (pH 7.4), and then fixed in 1% osmium tetroxide in the same buffer for 2 h. After fixation, specimens were dehydrated in a graded series of ethanol, and embedded in epoxy resin. Thick sections for light microscopy were prepared using a glass knife and were stained with toluidine blue. The branching sites of the submucosal arterioles were identified and trimmed down in each resin block. Thin sections of these areas were cut with a diamond knife, stained with

2% uranyl acetate and lead citrate, and examined in a Hitachi H 300 transmission electron microscope. We observed some specimens by serial sections of TEM and LM.

Results

The wall of the glandular stomach of rats is supplied by branches arising from both the left gastric and gastroepiploic arteries. The whole view of vascular corrosion cast of the stomach shows that each pair of subserosal arteries and veins runs at regular intervals over the outer surface of the stomach wall, sending their branches to form an arteriolar and venular network to the submucosa. These submucosal vessels send their connecting branches to capillary networks of both the muscular coat and the mucosa (Fig. 1). In the corrosion cast of vessels, the arterioles can be easily identified by virtue of their characteristic impression patterns of endothelial nuclei embossed on the surface of the cast (Figs. 2, 3). The submucosal arterioles are 40 to 80 μm in diameter, and the branching arterioles connecting the mucosal capillary network are 10 to 50 μm. These connecting arterioles appear to join the mucosal capillary network in the following fashion; after leaving the submucosal arterioles, the connecting arteriole is abruptly divided into several capillaries after penetrating the muscularis mucosa to join the mucosal network, and sends several terminal arterioles along its course to the mucosal capillary networks at the base of the lamina propria, or after sending these terminal arterioles, returns to the submucosal arteriolar network within the muscularis mucosa.

In the corrosion casts from normal rats, a minor partial or circumscribed impression is observed at the branching portions from the submucosal arterioles toward the mucosa as shown in Figs. 8A, 10A, however, this type of constriction is never observed at the bifurcations of the submucosal arteriolar network (Fig. 2). SEM observations on the fractured surface of the stomach wall (direct SEM observation) revealed that the branching arteriolar orifices from the submucosal arterioles are provided with a protruding wall (Figs. 1A, 9A, 11A). This protrusion seems to cause the constriction seen in the cast preparation.

In thin sections through these orifices of branching arterioles, the protruding walls are packed with smooth muscle cells surrounded by elastic elements in an area where the internal elastic lamina cannot be identified as a single layer of elastin, yet the smooth muscle cells appear to be embedded in an internal elastic lamina (Fig. 6A). This type of protrusion was never observed on the
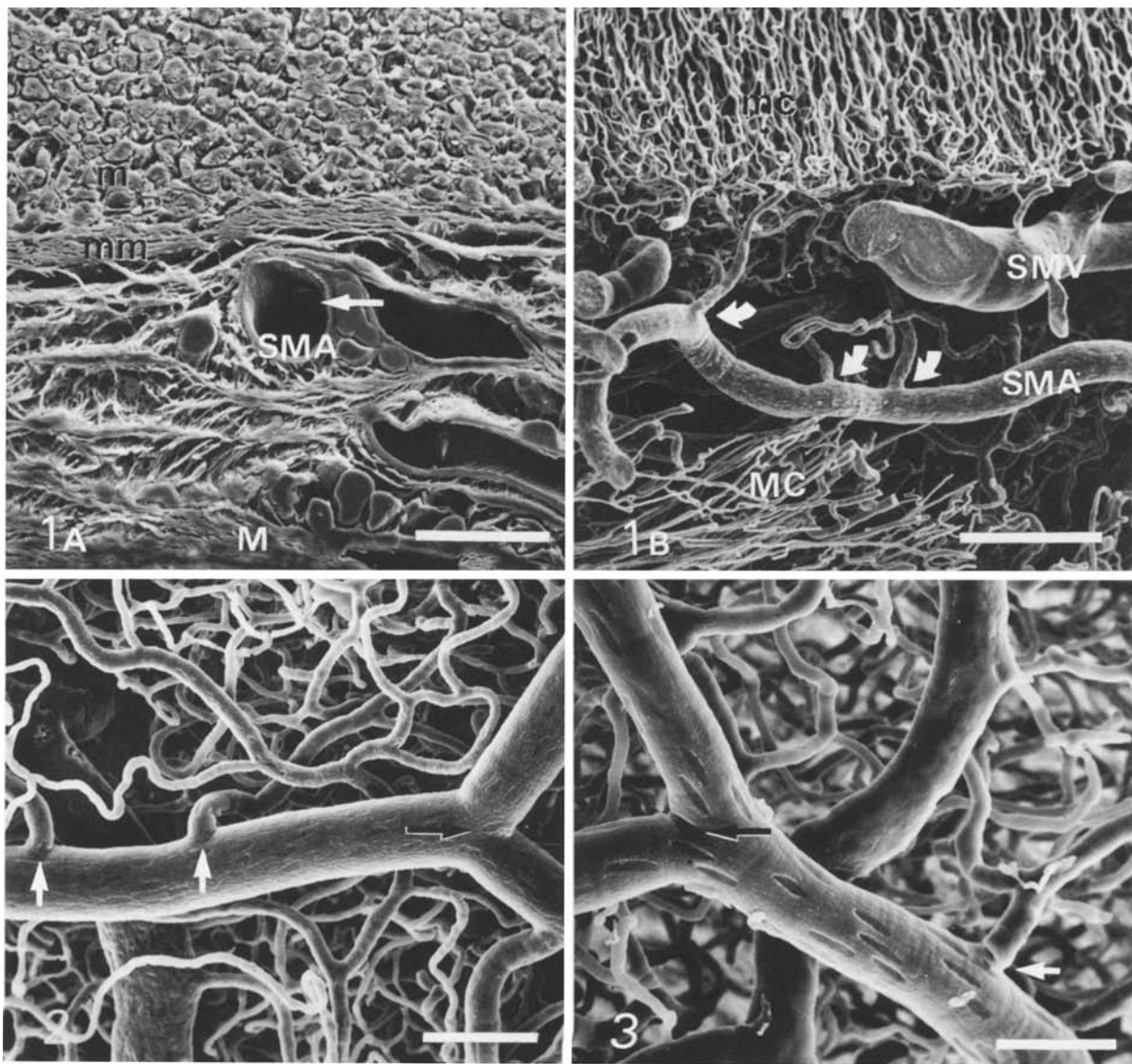
Fig. 1.A SEM of the sagittal section of the rat gastric glandular regional tissue. The branching arteriolar orifice is seen in the submucosal arteriolar lumen (*arrow*). *m* mucosa, *mm* muscularis mucosa, *SMA* submucosal arteriole *M* muscle layer. Bar = 100 μm. B Sagittal aspect of the gastric vascular cast. The branching arteriole runs to the mucosa from the submucosal arteriole almost at a right angle (*arrows*). *mc* mucosal capillary network, *SMA* submucosal arteriole, *SMV* submucosal venule, *MC* muscle layer capillary network. Bar = 250 μm

Fig. 2. Submucosal aspect of the vascular cast in a normal rat. The branching site of an arteriole from the submucosal arteriolar network to the mucosa is slightly narrowed (*white arrows*), but this narrowing is not seen at the bifurcation within the submucosal arteriolar network (*black arrow*). Bar = 100 μm

Fig. 3. Submucosal aspect of the vascular cast in a restraint stressed rat. The narrowing in the branching arteriole is increased compared to that in the normal rat (*white arrow*). The narrowing is not present in the bifurcation within the submucosal arteriolar network, as in normal rat (*black arrows*). Bar = 50 μm

luminal surface of other arteriolar walls. The smooth muscle cells of the cushions are not distinguishable in fine structure and innervation from those of the arteriolar media. (Figs. 4, 6A). Thus, these protrusions apparently correspond to the intimal cushions noted at the branching sites of other

arteries (Moffat and Creasey 1971; Takayanagi et al. 1972; Stehbens and Ludatscher 1973; Yohro and Burnstock 1973; Suzuki et al. 1979; Kojimahara and Ooneda 1980).

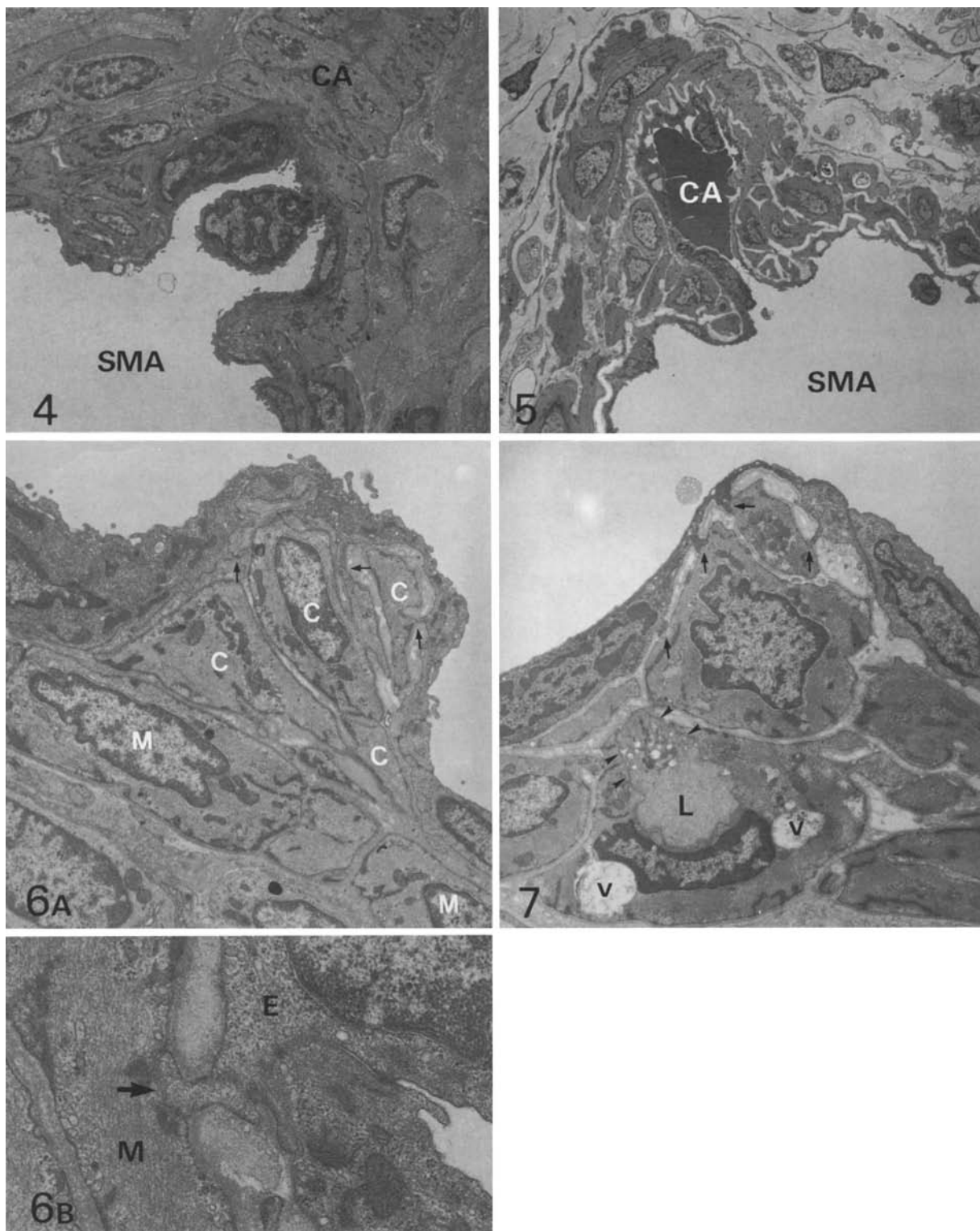The cushions are not always uniform in shape in both the long and short axis of the submucosal

Fig. 4. TEM of the intra-arterial cushion of the branching arteriolar orifice from submucosal arteriolar network in a normal rat. The structure and shape of the cushion were not symmetrical. *SMA* submucosal arteriolar lumen *CA* branching arteriole ×2200

Fig. 5. TEM of the intra-arterial cushion of the branching arteriolar orifice from submucosal arteriolar network in a restraint stress rat. The cushion constricted and the branching arteriolar orifice was narrow. *SMA* submucosal arteriolar lumen *CA* branching arteriolar lumen ×1500

arterioles: some are partially well-developed and others are not. In serial sections, the smooth muscle cells within the cushion are arranged circular to the long axis of branching arteriole (Fig. 4). Thus, these smooth muscle layers are thought to be protrusions of the media of branching arterioles. The endothelial cells covering the cushion frequently extend their cytoplasmic processes to the smooth muscle cells in the cushion to form myo-endothelial-junctions. These junctions are more frequently observed in the cushion than in other parts of submucosal arteriole (Figs. 6, 7A, B).

In rats subjected to water immersion restraint stress, multiple erosion and ulcers accompanied by hemorrhage were observed in the gastric glandular mucosa. Casts of the vessels showed an increase in the degree of narrowing in the orifice of branching arterioles, when compared with findings in normal rats (Figs. 3, 8B, 10B). These narrowings are caused by a partial or complete belt-like constriction. These narrowings were not observed in the bifurcation within the submucosal arteriolar network, as in normal rats. In the SEM observations of the orifice (Figs. 9B, 11B), we noted a septum-like structure protruding from the one or both poles of the orifice. In thin sections (Figs. 5, 7), structural organization of these cushions was much the same as in the normal rats, but the smooth muscle cells in the cushions show perinuclear vacuoles (Takeuchi et al. 1973) or cell-to-cell hernias (Joris and Majno 1981), vesicles, and electron lucent areas. Similar changes were also evident in the smooth muscle cells of media adjacent to the cushions, but were rarely found in other parts of the arteriolar media.

In rats with ethanol-induced ulcer, diffuse and multiple erosions plus haemorrhage were observed in the mucosa of the glandular stomach, as was also the case in the restraint stress rats. In the vascular casts (Figs. 8C, 10C), direct SEM (Figs. 9C, 11C) and TEM observations, however, changes in vascular morphology seen in the restraint stress rats were not evident.

In rats given a low dose of noradrenaline, nar-

rowing of the orifice in the branching arterioles was observed in the corrosion cast (Figs. 8D, 10D), but was apparently higher in degree than in the normal rats. Direct SEM observation demonstrated a similar septum-like structure protruding toward the branching arteriolar lumen, as seen in the restraint stress rats. In thin sections, smooth muscle cells in the cushion showed no changes, except for frequent perinuclear vacuoles.

In the rats given a high dose of noradrenaline, corrosion casts of arteries in the serosa and muscular coat showed a remarkable constriction due to so-called "spasm". The submucosal arteriolar network was also partially constricted. In orifices of the branching arterioles, narrowings seemed to be similar in degree to those in the cases of restraint stress and administration of a low dose of noradrenaline. In the direct SEM observation (Figs. 9D, 11D), the diameter of the branching arteriolar orifice was markedly narrowed. In thin sections, the perinuclear vacuoles of smooth muscle cells in the cushion were more numerous than in other groups.

We carefully examined whether or not the AVA was evident in the glandular stomach of either the normal or experimental rats, using a vascular cast technique; however, the occurrence of AVA as noted by Barlow et al. (1951) could not be confirmed.

Discussion

Intra-arterial cushions have been reported to occur in the branching sites of various arteries (Yohro and Burnstock 1973; Kojimahara and Ooneda 1980; Gorgas and Bock 1975 1976). Kardon et al. (1982) studied the cushions of the uterine artery of rats, utilizing for the first time SEM and vascular corrosion casts in various physiological states of uterine blood flow. Their studies suggested a dynamic role for intra-arterial cushions in the regulation of uterine blood flow. Casellas et al. (1982) also examined the morphology and organ distribution of arterial intimal cushions in rats by SEM of the vascular corrosion casts. They reported that

Fig. 6. A TEM of the intra-arterial cushion in a normal rat. Cushion's smooth muscle cells (C) are arranged almost perpendicular to medial smooth muscle cells out of cushion (M). The internal elastic lamina is divided and/or splitted for several layers and distributed in the space between each smooth muscle cells within the cushion. Their numerous cytoplasmic processes show formation of myo-endothelial-junctions (arrows). Fine structure of the smooth muscle cells is not distinguishable from that of the media. × 6500. B High magnification of myo-endothelial-junctions (arrow). E endothelial cell M cushion's smooth muscle cell × 25000

Fig. 7. TEM of the intra-arterial cushion in a restraint stress rat. The arrangement of the smooth muscle cells and entire shape of the cushion are not so different from findings in the normal rat and numerous myo-endothelial-junctions (arrows) are also present, but perinuclear vacuoles (V), vesicles (arrow heads) and electron lucent area (L) are seen in smooth muscle cells of the cushion. × 6500
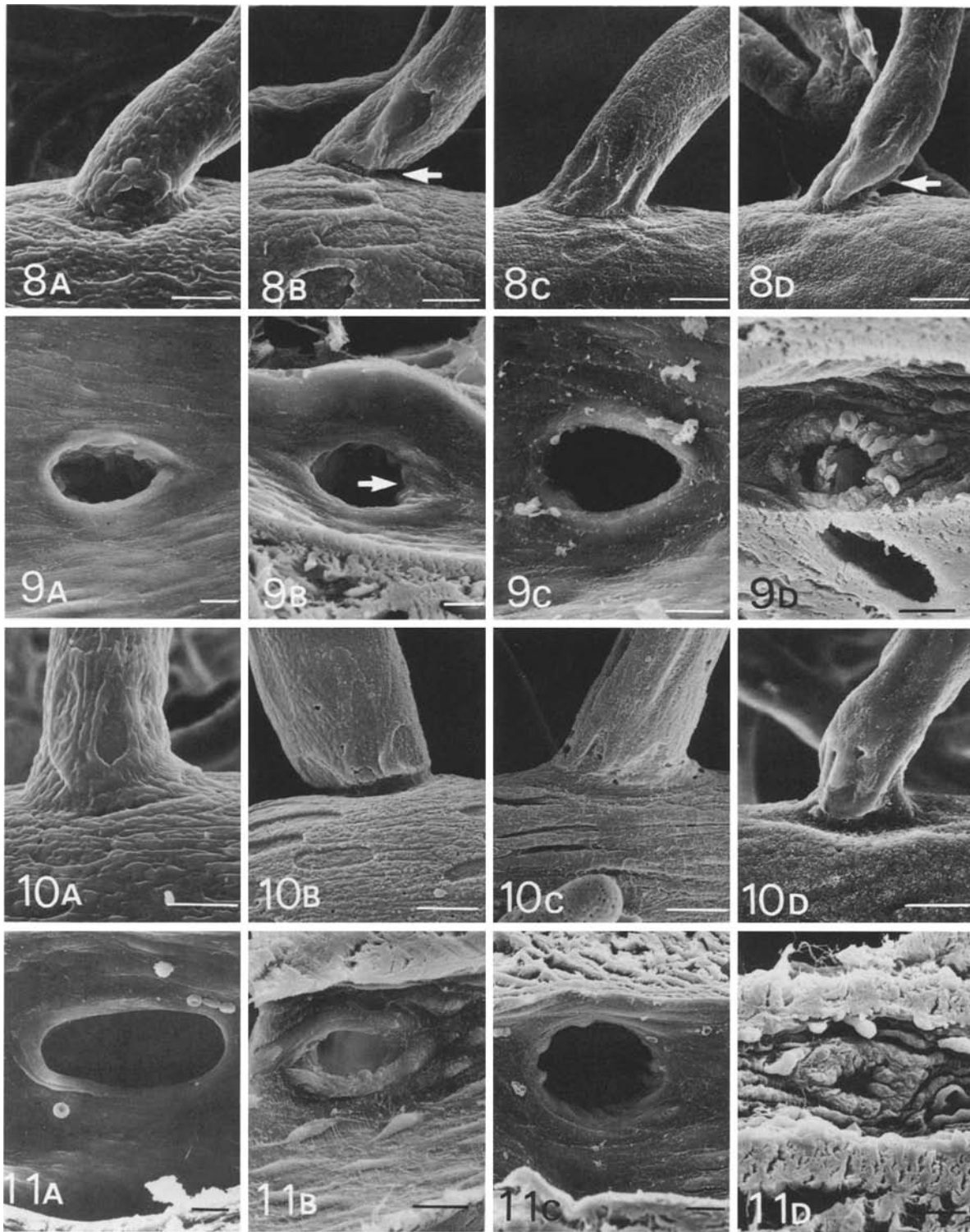
Fig. 8. A–D Vascular cast of the branching site of an arteriole from the submucosal arteriolar network to the mucosa. One sided narrowing of the branching arteriolar orifice in each experimental group. **A** Normal rat. **B** Restraint stress rat. One sided narrowing is prominent (*arrow*).**C** Ethanol-induced ulcer. **D** Low dose noradrenaline administered rat. The degree of narrowing is similar in the restraint stress rat (*arrow*). Bar = 10 μm

Fig. 9. A–D Direct SEM observation of the branching arteriolar orifice from the submucosal arteriolar lumen. The same type of narrowing as seen in Fig. 8. **A** Normal rat. **B** Restraint stress rat. Septum-like structure appeared from inside of the cushion of the arteriolar lumen at one side (*arrow*). **C** Ethanol-induced ulcer. The shape of the intra-arterial cushion is the same as in the normal rat. **D** High dose noradrenaline. The shape of the intra-arterial cushion is similar to that seen in the restraint stress rat and the submucosal arteriole is also constricted. Bar = 10 μm

Fig. 10. A–D Entire belt-like circumscribed narrowing of the branching arteriolar orifice in the vascular cast. **A** Normal rat. **B** Restraint stress rat. **C** Ethanol-induced ulcer. **D** High dose noradrenaline. Bar = 10 μm

Fig. 11. A–D Direct SEM observation of the branching arteriolar orifice from the submucosal arteriolar lumen. The same type of narrowing as in Fig. 10. **A** Normal rat. **B** Restraint stress rat. **C** Ethanol-induced ulcer. **D** High dose noradrenaline. Bar = 10 μm

the arterial intimal cushions in the stomach were much less frequent at branching sites, but often exhibited a striking sphincter-like appearance. Gannon et al. (1982) studied vascular corrosion casts of the stomach of rats by SEM and suggested the occurrence of sphincter devices at branching sites of terminal arterioles arising from the submucosal arteriolar network. Details on the morphology of these branching sites were not given.

Since a corrosion cast technique is likely to induce artifacts, because of viscosity, injection and shrinkage rates of resin, the casts obtained may not always represent the exact appearance of the vascular lumen. Therefore, the functional morphology of the gastric vasculature has been examined mainly by in vivo microscopy (Guth and Rosenberg 1972).It is, however, apparent that SEM studies on the corrosion casts of vasculature are highly advantageous in examining three dimensional ultrastructural architectures of the vascular branchings. To obtain artifact-less corrosion casts of microvasculature in the stomach, we examined the most desirable perfusion procedure of fixative and resin (Mercox), and a proper cannulation site. An attempt was also made to compare the cast images with the luminal aspects of the vasculature by direct SEM observation. We noted a fairly good correlation between cast and direct SEM images of the branching sites.

Our study demonstrated that almost all the branching orifices of the connecting arterioles from the submucosal arteriolar network are provided with a luminal fold, or intra-arteriolar cushion, albeit more or less variable in its degree of development. Corrosion casts of the microvasculature show incisures at the branching sites of connecting arterioles from the submucosal arteriolar network. When animals are exposed to stress or noradrenaline, these incisures or constriction patterns become deeper or prominent. This phenomenon is apparently due to the fact that the luminal fold of intra-arteriolar cushions extends into the lumen to narrow branching orifices, following such stimuli as stress or noradrenaline. In fact, the direct SEM observation clearly demonstrates the narrowing of branching orifices of connecting arterioles by expansion of the folds.

Thin section electron microscopy revealed that the core of cushion contains smooth muscle cells arranged in a circular fashion to the long axis of the branching arterioles. This arrangement of the smooth muscle cells explains the narrowing of the vascular lumen at the branching orifices when they contract in the presence of stimuli. It is of interest that the internal elastic lamina in the cushion can-

not be well defined as a single layer as observed in ordinary arterioles or small arteries. Instead elastic elements surround individual smooth muscle cells, forming an elastin network. This arrangement of elastin may play an important role in returning the cushion to a widened position when the smooth muscle cells relax.

It is difficult to know whether or not the cushions demonstrated in the present study regulate blood flow under physiological conditions, because we have no data. There are physiological studies (Fourman and Moffat 1961, Bergel et al. 1976; Langille and Adamson 1981) dealing with haemodynamics in arterial branches but apparently none in case of the gastric submucosal arteriolar branchings. Murakami et al. (1985) reported that the gastric mucosal blood flow decreased by 61.4% of the pre-stress value in water immersion restraint stressed rats. Delaney and Grim (1965) suggested that noradrenaline was the agent elevating the gastric vascular resistance and altering distribution of blood flow in the gastric wall.

We assume that the cushions play a role in regulating the blood flow toward the mucosa, not only the cases of intense stimuli, but also possibly in weak ones operating under physiological conditions.

Fluorescence histochemistry (Furness 1971) revealed that adrenergic innervation of the arterial branches in the stomach was dense, particularly in the submucosa, but no special innervation was noted at the branching points. In our TEM observations, the smooth muscle cells in the cushions lacked innervation but did have numerous myo-endothelial-junctions. Rhodin (1980) described that myo-endothelial-junctions may facilitate transport of transmitter substances across the endothelium to the smooth muscle cells in the vascular wall. The fact that the cushions in the present study are constricted remarkably by restraint stress and/or noradreanline, together with the observation that the cushions are devoid of nerve terminals, suggests that the smooth muscle cells here may be affected directly (possibly through myo-endothelial-junctions) by blood borne substances.

Barlow et al. (1951) described a considerable number of AVA in the submucosal vascular plexus in the human stomach, where as Guth and Smith (1975), Piascecki (1974, 1986) and Raschke et al. (1987) reported that submucosal AVA were not evident in the stomach of normal rats and humans. Gannon et al. (1982, 1984) also noted the absence of AVA in vascular corrosion casts. However Hase and Moss (1973) described submucosal AVA's measuring 20 to 40 μm in diameter and found that

in normal rasts these became prominent and appeared to be distended in stressed rats. As we found no AVA in normal, restraint stressed rats and other experimental groups, we assume that the so-called submucosal AVA may not be present or are less frequent. The submucosal AVA may not play an important role in regulating mucosal blood flow, at least in the rat. This assumption is supported by physiological studies that no more than 1 to 2% of gastric blood flow passes through AVA in the normal dog (Archibald et al. 1975; Delaney and Grim 1965).

Gastric mucosal ischaemia has attracted the attention of many investigators as a causative factor of gastric ulcer since Virchow (1853). Our present study suggests that water immersion restraint stress causes ischaemia in the mucosa by constriction of the intra-arteriolar cushions at the branching orifice from the submucosal arterioles, resulting in mucosal ischemia. However, gastric ulcer or erosion is not induced by noradrenaline, despite constriction of the orifice. This may possibly be due to the short duration of constriction by a more rapid elimination of noradrenaline action. Oral administration of ethanol also induces gastric haemorrhagic erosion (Szabo et al. 1985, Lacy and Ito 1984, 1985). However, this type of lesion may be caused by the direct action of ethanol on the gastric mucosa rather than by mucosal ischaemia, since no constriction can be found at the orifice of the connecting arterioles.

When the aetiology of gastric ulcer is being discussed, the intra-arteriolar cushions at the orifices of branches from the submucosal arteriolar plexus leading toward the mucosal capillary network, can be considered as a possible structural device for regulating gastric mucosal blood flow. This device is presumably controlled by blood borne substance such as vasoactive amines rather than by neuronal factors.

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