

RRVIEW ARTICLE

Intestinal morphomechanical remodeling caused by partial obstructionYue Liu^{1,*}, Xingyu Liu²¹Zhuhai Da Hengqin Technology Development Co. Ltd., Zhuhai 519031, Guangdong, China. ²Graduate school, Chongqing Normal University, Chongqing, Sichuan, China.

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Intestinal obstruction is a rather common surgical emergency, accounting for up to 20% of admissions with acute abdominal pain. Mechanical small bowel obstruction remains a common clinical problem. The cardinal features of obstruction are abdominal pain, vomiting, distension, and constipation. In order to study pathophysiological characteristics of intestinal obstruction, researchers use animal models to learn more about mechanisms in obstruction of the human gastrointestinal (GI) tract. Several models to create intestinal obstruction exist. The most common method is to place a silk thread or plastic loop around the intestine. Partial intestinal obstruction changes (remodels) morphohistology and neuromechanosensory properties. Histologic examination reveals that the thickness of the muscle layer, especially the circular smooth muscle layer, massively increases. Furthermore, the collagen content proximal to the obstruction site is significantly larger. The opening angle and residual strain mainly depend on the thickness of the muscle layer whereas the wall stiffness mainly depends on the thickness of the submucosa layer. The partial obstruction of the small intestine also leads to severe hypertrophy of smooth muscle cells, dilatation, and functional denervation, and the interstitial cells of Cajal (ICCs) phenotype are lost. The purpose of this paper is to provide a review of the scientific literature related to GI obstruction with focus on data morphologic, biomechanical remodeling, and changes of neuromechanosensory function. This article also proposes how the data obtained in animal experiments can be used to improve the clinical condition.

Keywords: intestine; partial obstruction; animal models; histomorphology; biomechanics; remodeling.***Corresponding author:** Yue Liu, Zhuhai Da Hengqin Technology Development Co. Ltd., Zhuhai 519031, Guangdong, China. Email: yue_liu@aliyun.com.**Introduction**

Intestinal obstruction is a blockage that keeps food or liquid from passing through the small intestine or large intestine (colon). Intestinal obstruction can be divided into complete and partial intestinal obstruction according to its degree. Statistics indicate that 3% of all emergency patients are admitted to the hospital due to intestinal obstruction [1]. The current mortality rate of intestinal obstruction patients is about 3% [2]. But, when intestinal resection is needed as intestinal obstruction progresses to

strangulated one, the operative mortality rate rises to 30% [3, 4]. Therefore, the following questions have become special concerns for doctors as (1) how to predict the occurrence of intestinal obstruction? (2) how to accurately determine the situation of intestinal injury? (3) how to avoid intestinal resection? (4) how to reduce the mortality of patients? and so on. The establishment of animal models can help researchers to know more clearly on the pathophysiological and biochemical changes in the evolution of intestinal obstruction. It is meaningful to study the influence of intestinal

obstruction on intestinal barrier function, intestinal tissue morphology, and intestinal mechanics. The results of animal experiments can reveal the characteristics of intestinal obstruction and it can provide a theoretical basis for the clinical staging and severity of intestinal obstruction. This article mainly focuses on partial obstruction and the aim is to introduce some common animal models of intestinal obstruction and to show the influence of intestinal obstruction on intestinal barrier function, tissue hyperplasia, collagen content, tissue histomorphological and biomechanical remodeling.

Common animal models of intestinal obstruction

Currently, the established animal models of intestinal obstruction from previous studies are mainly divided into two categories. One is the intestinal ischemia while the other is the intestinal obstruction. The animal model of intestinal ischemia mainly simulates the intestinal ischemia state by ligating the mesenteric blood vessels or restricting the blood flow of the mesenteric vessels [5-9]. The animal model of intestinal obstruction is to directly intervene in the intestine through physical means, which makes the passage of intestinal contents being blocked. The latter model is more widely used by researchers as it can better study the intestinal obstruction characteristics.

To the beginning of this century, researchers such as Ahmet *et al.* introduced a method for establishing a strangulated intestinal obstruction model [10]. The method was as follows. Briefly, an opening with a length of about 0.5 cm was cut in the abdomen of the rat. Then, a part of the small intestine tube was taken out through the incision. This part of the intestine was buried under the skin with a purse string suture to simulate strangulated intestinal obstruction (Figure 1). On the other hand, some researchers use the exfoliation method to establish a model of partial intestinal obstruction [11]. They wiped

the ileum with gauze and peeled off the serosal layer of the intestinal tube in order to cause mechanical damage. When the body repaired itself, many fibrous tissues proliferated, resulting in intestinal tissue adhesion and intestinal stenosis. The advantages of the above two methods are that they both close to the actual clinical situation. However, this type of model method requires higher technical skills for the surgeon. Therefore, the uniformity of the model and the experimental results may be affected by the strength and techniques of different surgeons. In addition, after the operation is completed, the intestinal peristalsis becomes active after the animal eats, which may develop into a complete intestinal obstruction and lead to the death of the experimental animals and increase the experimental cost.

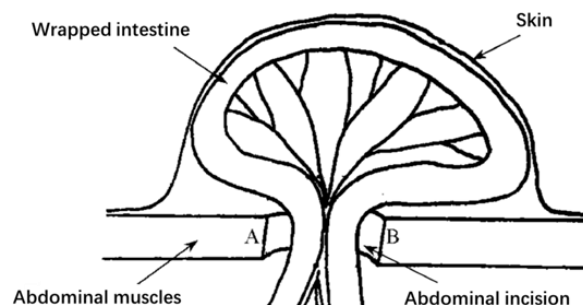


Figure 1. Schematic diagram of a strangulated intestinal obstruction model developed by Ahmet *et al.* [10].

Currently, the ligation method and the loop method are widely used by researchers (Figure 2). The principles of these methods are to wrap the intestines with silk threads or plastic loops to simulate partial intestinal obstruction. The ligation method is to use a silk thread through the mesentery and then incompletely ligate the intestine [12]. The loop method puts a sterile plastic loop through the mesentery and puts it around the intestine and sutures the loop incision [13]. The silk thread method is relatively simple. However, the silk thread is very thin and inelastic, which can easily cause a large volume of intestinal contents to accumulate in the obstructed site and cause serious disease. In

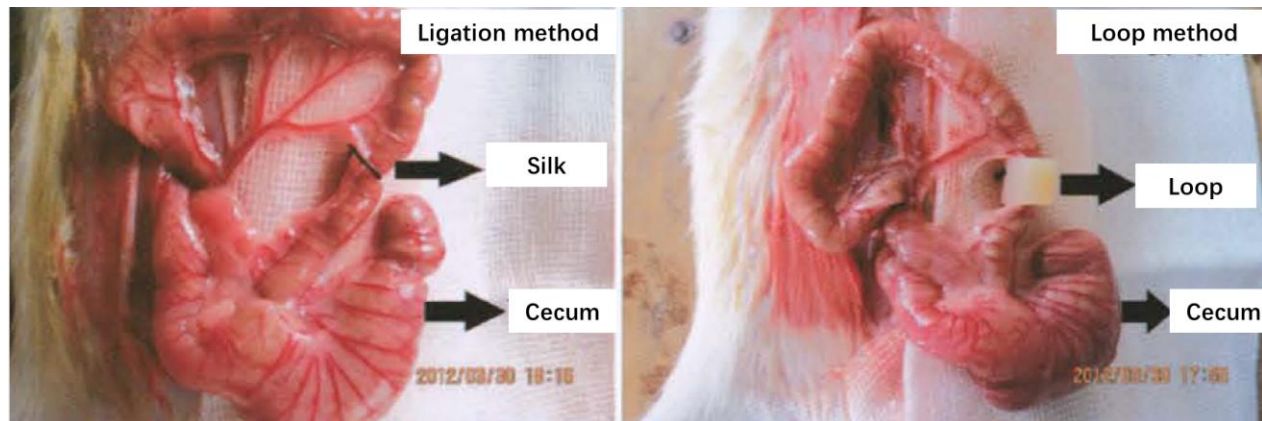


Figure 2. Schematic diagrams of the methods of partial intestinal obstruction model in rats (**Left:** ligation method; **Right:** loop method) [14].

addition, different degrees of ligation will cause uneven obstruction, and excessive ligation will cause a complete intestinal obstruction model. The loop method has less damage to the intestinal tissue than the silk thread one. It has a higher success rate and strong reproducibility, which is more in line with the pathological characteristics of partial intestinal obstruction.

Effect of intestinal obstruction on intestinal barrier function

The intestine is not only an important place for digestion and absorption of nutrients, but also an important immune metabolic system [15]. The intestinal barrier function mainly includes four parts including (1) the mechanical barrier formed by mucosal epithelial cells and their surface mucus; (2) the immune barrier formed by immunoglobulin A (IgA) on the mucosal surface produced by lymphoid tissue; (3) the biological barrier formed by normal physiological flora; (4) the chemical barrier formed by antibacterial substances secreted by the digestive tract. The intestinal barrier function can separate the contents, and, at the same time, effectively prevent pathogenic bacteria from entering the blood circulation. When the barrier function is impaired, the multiple organ dysfunction syndrome (MODS) could be led as the translocation of bacteria and endotoxins in the

intestine. Intestinal obstruction can cause severe endometrial damage, causing abnormalities of barrier and absorption [16-18]. Normal bowel motility can effectively reduce content retention and prevent long-term contact between intestinal mucosa and bacteria, thereby reducing bacterial colonization on the inner wall. However, the intestinal epithelial cell damage after obstruction causes permeability changes, and bacteria and endotoxins migrate into the blood. At the same time, obstruction can also reduce the secretion of IgA and weaken the ability of mucosa to resist bacterial adhesion.

Some researchers found that the concentration of diamine oxidase (DAO) in the serum increased after intestinal obstruction occurred through blood ELISA experiments of intestinal obstruction model [19]. This was due to the dilatation of the intestinal cavity caused by obstruction. In the early stage of obstruction, the increase in intraluminal pressure triggered the loss of intestinal mucosal epithelium, changed the permeability of the mucosa, and caused DAO to be released into the blood. Due to the increase in the permeability of the intestinal mucosa, a large amount of D-lactic acid produced by the fermentation of intestinal bacteria entered the blood circulation. The acid content increased with the obstruction time [20]. Studies have shown that, comparing to the control group, the content of blood tumor necrosis factor- α (TNF- α)

Table 1. The mean serum D-lactate concentrations for control group and Intestinal obstruction group [8].

Group		t = 0 min	t = 5 min	t = 2 hr	t = 4 hr
Control group	Unoperated controls	0.51 ± 0.30	-	-	-
	Controls	-	1.32 ± 0.29	0.50 ± 0.24	1.04 ± 0.21
Intestinal obstruction group	Nonischemic obstruction	-	1.58 ± 0.71	1.03 ± 0.38	1.14 ± 0.048
			NS	NS	NS
	Ischemic obstruction	-	2.33 ± 0.45	1.77 ± 0.27	2.22 ± 0.38
			P < 0.0005	NS	P < 0.0005
	SMA ligation	-	2.06 ± 0.44	4.97 ± 0.84	6.21 ± 0.55
			P < 0.0005	P < 0.0005	P < 0.0005

Note: Number expressed as $\mu\text{g/ml} \pm 1 \text{ SEM}$. NS: no significant.

in the obstruction group increased over time, indicating that endotoxin had shifted after intestinal obstruction, causing systemic inflammation [21]. At the same time, many studies have confirmed that obstruction can affect the content of D-lactic acid in plasma, and the study of D-lactic acid content has important clinical value [22-24] (Table 1). It is worth noting that although blood DAO content and plasma D-lactic acid content can be used as assessments of mucosal damage [8, 25], some conditions will affect the accuracy of bowel function evaluation, such as intestinal infections and flora disorders.

Effect of intestinal obstruction on tissue hyperplasia and collagen content

The hyperplasia of muscular layer is one of the main manifestations of chronic intestinal obstruction. The circular muscle layer has a larger increase than the longitudinal one. The main reason may be that the increased intestinal contraction characteristics increase the circumferential stress of the intestine [26, 27]. The hyperplasia of muscle layer is not only manifested as an increase in the number, but also as a feature of hypertrophy in the volume of a single muscle cell [28]. Excessive growth of cells causes changes in microstructures, such as sarcoplasmic reticulum, gaps, cytoplasm, and the ratio of myofilaments to intermediate fibers [29-32]. The relatively reduced amount of myofilament indicates partial loss of contractile function of a single cell. However, due to the

increase in the number of smooth muscle cells, the overall contractility of the muscle layer is increasing [33]. The proliferation of the submucosa is related to the accumulation of collagen, which can cause a significant increase in the stiffness of the intestinal wall. According to the study of Chen *et al.* on the dynamic transformation among the differentiation, proliferation, and hypertrophy of intestinal obstructive muscle cells, serum response factors, cardiomyocin, transferred into the nucleus to activate transcription factors (Elk-1) and proto-oncogenes (C-fos) may play an important role in these phenotypic changes [34]. Figure 3 shows the HE staining of the hyperplasia of the intestinal obstruction site and adjacent segments after the obstruction occurs.

It is known that the function and morphology of organs mainly depend on the collagen content, distribution, structure, and type in the extracellular matrix [35]. The change in collagen characteristics is one of the main reasons that affect tissue remodeling. Any of these elements may lead to abnormal organ structure and function. For example, diseases that promote collagen production or accumulation can significantly increase intestinal wall stiffness, such as diabetes [36-38], obstruction [39], and epithelial growth factor (EGF) intervention [40, 41]. Conversely, physiological interventions that inhibit collagen production or accumulation can reduce intestinal wall stiffness, such as fasting [42] and low-protein diet [43]. Collagen content has a close positive correlation with tissue

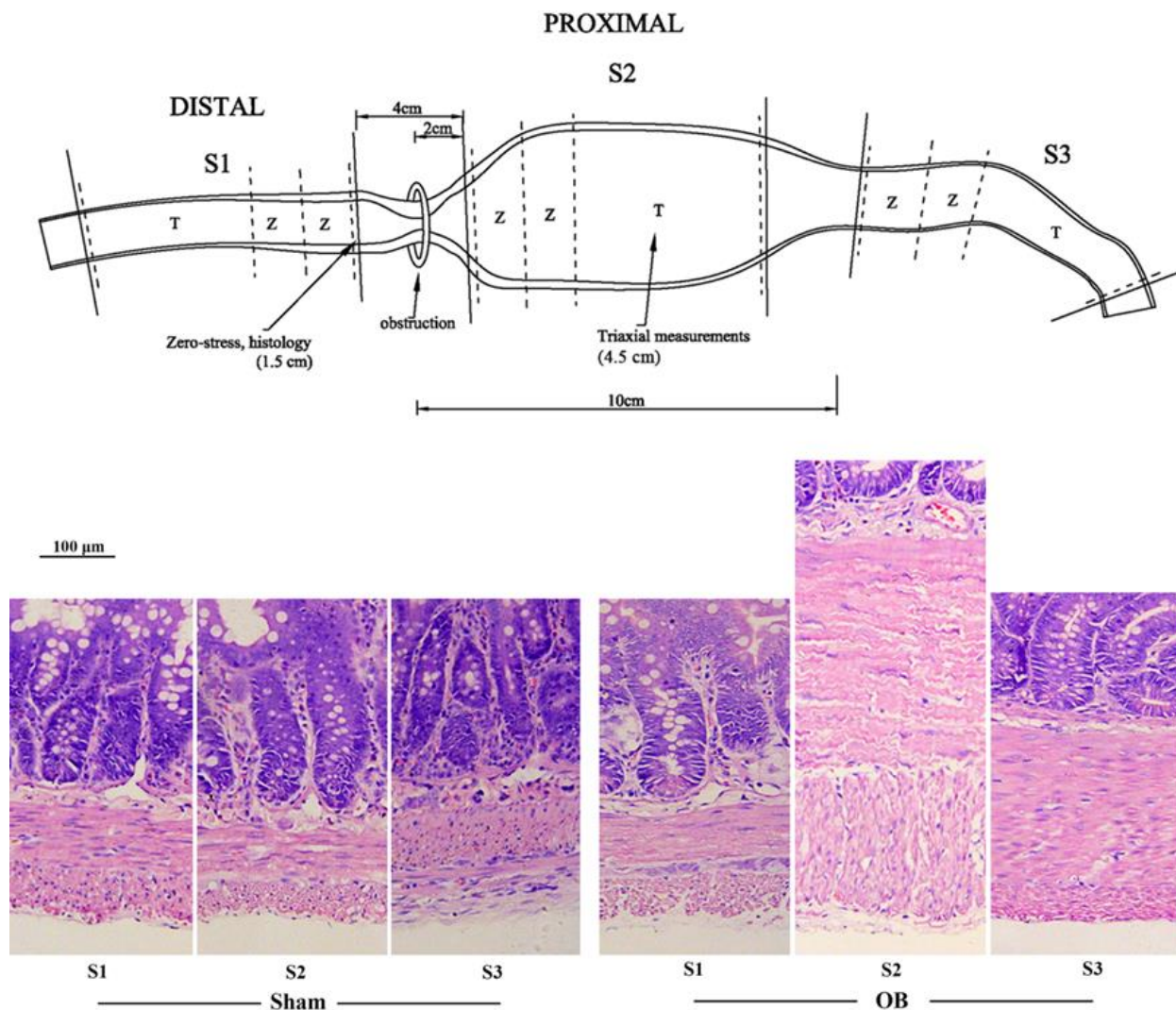


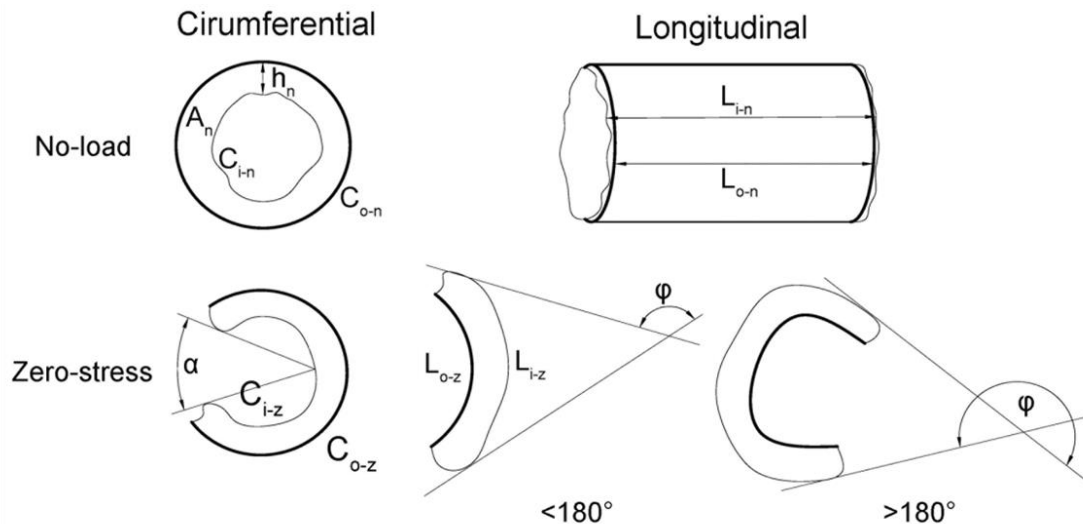
Figure 3. HE staining results of muscular layer hyperplasia. The circular muscle and longitudinal muscle of S2 part were proliferated significantly after 2 weeks of partial obstruction. **S1**: the proximal end of the obstruction; **S2**: the obstruction site; **S3**: the distal end of the obstruction. **Sham**: control group; **OB**: intestinal obstruction group [13].

hardness. Storkholm *et al.* found that comparing to the control group, the circumferential elastic modulus of the obstruction group increased in a time-dependent manner. They also found that the stress-strain curve of the obstruction group shifted to the left comparing to that of the control group, indicating an increase in intestinal wall stiffness. Histological results revealed a significant increase in collagen content in the proximal tissue of the obstruction. Correlation analysis proved that the circumferential elastic modulus was significantly correlated with collagen content under low and high stress

conditions [39]. The change of collagen content may be a physiological protection and regulation mechanism with the proposes to protect the integrity of the intestinal wall and to prevent intestinal tissue damage [44].

Effect of intestinal obstruction on intestinal histomorphological and biomechanical remodeling

Intestinal obstruction can cause many contents to accumulate in the proximal intestinal lumen. It



C , L , A , h , α and ϕ denote the circumferential length, longitudinal length, wall area, wall thickness, opening angle and bending angle. The subscripts i , o , n and z refer to the inner (mucosal) surface, outer (serosal) surface, no-load state and zero-stress state.

Figure 4. Illustration of no-load and zero-stress states [49].

can lead to the intestinal load increase and the deformation of intestinal wall. Long-term obstruction can also induce tissue remodeling and cause morphological changes, which lead to the expansion of the obstructed proximal intestine, muscularis hyperplasia, intestinal wall neuronal hypertrophy, and collagen content increase [39, 45-48]. The zero-stress state is the zero-point position of the mechanoreceptors of tissues, and its changes have a significant impact on the perception and movement of the GI tract. The zero-stress state of tissue is very sensitive to remodeling due to disease, growth, or others. The change of opening angle is caused by the reconstruction of non-uniform tissue layers. When the inner layer grows faster than the outer layer or the outer layer shrinks larger than the inner layer, the opening angle will increase [35]. The change of opening angle is a direct manifestation of the change of the residual strain that is mainly caused by the residual stress. Figure 4 shows some illustration of no-load and zero-stress state. Obstruction can cause the changes in the intestinal structure and morphology, thereby changing the tissue morphology and mechanical properties. Studies have shown that chronic partial intestinal

obstruction can induce thickening of the muscle layer, making the outer wall of the lumen grow larger than the inner wall, and reduce the residual strain and expansion angle of the inner wall. This change was time-dependent [13]. At the same time, the intestinal wall stiffness increased in obstruction group [48]. Sun *et al.* found that, through correlation analysis, the circumferential residual stretch rate of the mucosa was significantly positively correlated with the submucosal area, circular muscle area, and longitudinal muscle area. The axial residual stretch rate of the mucosa was significantly positively correlated with the thickness of the submucosa [49].

The main characteristic of intestinal obstruction is that the proximal intestinal motility is abnormal, just the changes in contraction amplitude and frequency. The change of biomechanical characteristics is the most direct manifestation of this process. The contraction movement of the obstructed bowel segment is dominated by the high amplitude irregular phase contraction near the obstruction site (approximately 2.5 times of the normal pressure) [50]. The contraction frequency and amplitude in

obstruction group are more than normal. However, this abnormal movement cannot be explained solely by changes in muscle characteristics. The increase in proximal propagation time indicates that this movement is also governed by the nervous system [51]. According to existing studies, the number of neurotransmitters and the interstitial cells of Cajal (ICCs) in intestinal neurons in the over-expanded ileum tissue was significantly reduced [52, 53]. In addition, in hypertrophic smooth muscle cells, the current density of voltage dependent potassium channel was significantly reduced. This electrophysiological remodeling can lead to an increase in the resting potential of hypertrophic smooth muscle cells and keep these cells at highly excited state to overcome the high impedance characteristics caused by the pressure surge in the obstructed intestinal cavity [54].

Conclusion

GI tract is an important system of human being. The root cause of most GI diseases is dysfunction of bowel motility. The partial intestinal obstruction is a clinically common surgical acute abdominal disease. The most obvious change in dynamic function is the obstruction of the passage of the contents, which causes a large amount of food to accumulate in the proximal intestine and lead to abnormal intestinal physiological state. As mentioned above, intestinal obstruction can affect the barrier function of the intestine, cause tissue hyperplasia and collagen accumulation in the intestine, reduce the intestinal tissue morphology and biomechanics. Studying the changes of intestinal obstruction in different pathophysiological processes can help to understand its pathogenesis, improve the levels of diagnosis and treatment on intestinal obstruction. The biomechanical study of obstructed intestine is one of the important methods to predict the pathogenesis or GI physiological behavior under therapeutic intervention. However, there are many other studies on intestinal obstruction in

both basic medical research (for example, pathology, biochemistry, biophysics, and pathophysiology, etc.) and clinical study (for example, clinical animal experiment, imaging, and GI dynamics, etc.) fields. Due to the limited space of this article, these fields are not covered in this review study.

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