

# **PATHOPHYSIOLOGY OF GASTROESOPHAGEAL REFLUX: A COLLECTIVE REVIEW**

Pages with reference to book, From 44 To 49

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Gastroesophageal reflux is a very common disease. Almost everybody experiences heartburn from time to time but with different degree of severity. How does reflux occur, and which factors encourage or work against reflux is a very controversial matter. This article covers all controversial issues about the pathophysiology of gastroesophageal reflux and discusses the old and recent understanding of the disease.

## **PHYSIOLOGY**

### **Esophageal Peristalsis**

The esophagus functions primarily to conduct food from the pharynx to the stomach. It has two types of peristaltic movements<sup>1</sup>, primary and secondary, where the former is simply a continuation of the peristaltic wave that begins in the pharynx, spreads down the esophagus, and reaches the stomach in 5 to 10 seconds<sup>2</sup>. However, the food usually reaches the stomach a little quicker due to the additional effect of gravity<sup>2</sup>. The secondary peristalsis originate in the esophagus in response to any food retained in the esophagus. Both types of peristalsis are controlled by the vagal reflexes<sup>3</sup>.

### **The lower esophageal sphincter (LES)**

This is a zone of increased pressure, about 3 to 5 cm long, at the lower end of the esophagus<sup>4,5</sup>. Like the upper sphincter, it is always in a state of contractions<sup>6</sup>, generating this high pressure zone to prevent the reflux of stomach contents into the esophagus. The sphincter relaxes with swallowing and returns back to its high basal pressure as the wave of peristalsis passes. There has been considerable controversy regarding the nature of this sphincter, and the way it generates this high pressure inspite of the fact that there is no anatomical component to this sphincter. At this time<sup>7</sup> it appears that the basal LBS pressure is due to its intrinsic myogenic activity and that the increase in pressure (contraction) or the decrease in pressure (relaxation) is under neural and hormonal mechanisms<sup>7</sup>. The neural control is through the vagus nerve which transmit both excitatory and inhibitory impulses to the sphincter<sup>8-11</sup>, so both contraction and relaxation is due to these neural impulses, which is now believed to be modulated also by the sympathetic nerves<sup>9</sup>. The basal tone, however, is not dependent on the vagal innervation<sup>10</sup>, as it has been shown that cutting the vagi does not abolish the basal LBS pressure in either animals<sup>12</sup> or humans<sup>13</sup>. The basal LBS pressure also is not dependent on the high intra abdominal pressure as the basal LES pressure is maintained when the LBS happens to lie above the diaphragm<sup>14</sup>. The hormonal factor<sup>15</sup> has been studied in detail in the last 20 years, and many agents were found either to raise or lower the basal LBS pressure. These are shown<sup>6</sup> in Table.

**TABLE. Substances altering the LES pressure.**

	Increase	Decrease
Hormones	Gastrin	Secretin
	Motilin	Cholecystokinin
	Substance P	G.I.P.
	Vasopressin	V.I.P.
	Glucagon	Progesterone
Drugs	Adrenergic agonist:	Adrenergic antagonist:
	Norepinephrine	Isoproterenol
	Phenylephrine	
	Cholinergic:	Anticholinergic:
	Bethanechol	Atropine
	Methacholine	
	Betazole	
Miscellaneous	Metaclopramide	Theophylline
	Prostaglandin F <sub>2</sub>	Prostaglandin E <sub>1</sub> , E <sub>2</sub> , A <sub>2</sub>
	Protein meal	Nicotine
	Gastric alkalization	Ethanol
		Fat meal
Chocolate		
	Gastric acidification	

The LBS maintains the ability to raise its resting tone in response to any increase in the intragastric pressure, and this is believed to be mediated by the vagus nerve<sup>13,16</sup>. However, others still think that this is mainly due to the mechanical compression by the diaphragm or other anatomical structures<sup>17,18</sup>. The LBS pressure is asymmetric<sup>19,20</sup> in both its length and pressure profile. At the lower half, higher pressures are observed on the left side, which is again probably a reflection of the anatomical position of the distal esophagus. Normal values are thus approximations, usually in the range of 15mm Hg to 22mm Hg and is affected by inspiration also, being higher with inspiration and lower with expiration<sup>21</sup>.

**Pathogenesis of gastroesophageal reflux**

A positive pressure gradient exists between the abdominal and thoracic cavity, where the mean pressure in the thoracic esophagus is -15mm Hg to + 5mmHg<sup>2</sup> and the mean pressure in the fundus and proximal stomach ranges from 7 mmHg to 50mmHg and is increased while straining and coughing<sup>22</sup>. Therefore mechanisms must exist to prevent the gastroesophageal reflux.

## **Defense mechanisms against gastroesophageal reflux**

Before 1953, when the presence of the LES was demonstrated by Butin and Sanchez<sup>4,5</sup> anatomical factors were thought to be the sole mechanism against GE reflux<sup>23</sup>. Currently the wide spread belief is that multiple factors must be working together in preventing GE reflux<sup>6,24-29</sup> like:

### **1. Anatomical factors**

Although the presence of an anatomical sphincter has been postulated<sup>30</sup>, the consensus of opinion to date is that no such sphincter really exists<sup>31</sup>. The different anatomical factors that are thought to help against reflux have been divided into two groups. The first group, called the possible valve mechanism group, include: a mucosal flap<sup>32</sup> flutter valve<sup>33</sup> acute esophago gastric angle<sup>33</sup>, compression by gastric sling fibers<sup>34</sup> and the mucosal choke hypothesis proposing that adhesive mucosal forces exist during sphincter closure and help resist its opening<sup>25</sup>. The second group consists of mechanical factors that compress the distal esophagus at or near the hiatus. These include: the diaphragmatic pinch cock<sup>35</sup>, the phrenoesophageal ligaments<sup>35,36</sup>, the sling action of the right crus of the diaphragm<sup>37,38</sup> and the abdominal segment of the esophagus<sup>37,39</sup> being surrounded by the positive intra abdominal pressure.

#### **What gave the anatomical factors even more importance are the facts that:**

- a. The LES pressure is radially asymmetric<sup>19,22</sup> which cannot be accounted for by intrinsic squeeze alone, which theoretically should be symmetrical. This invites the idea of some mechanical factors<sup>28</sup> affecting the LES pressure.
- b. The fact that a modest high pressure zone exists at the hiatus level even when the LES herniates into the chest<sup>38,40</sup>, forces the idea that the extrinsic diaphragmatic forces must contribute to the intraluminal pressure measured at the hiatal level, when the LES is located within the hiatus.
- c. It has been found that when the LES pressure is reduced by atrophine, reflux is not enhanced<sup>41,42</sup> and that during relaxation of the sphincter, reflux is not always occurring which could be the enhancement of other mechanical factors.
- d. The fact that there is an overlap in the LES pressure values between symptomatic and asymptomatic patients suggests the role of factors other than LES pressure alone.

For a long time, hiatus hernia has been thought of as a major factor in the production of reflux. This assumption was based on the high incidence of sliding hiatal hernia in patients with gastroesophageal reflux<sup>43,44</sup> and according to this assumption, the mechanical factors described above are disrupted by the presence of such hernia<sup>35,45</sup>. Others, however, have negated the above assumption by providing the following facts: First, 30% to 50% of the general population have hiatus hernia, and yet only 5% have significant reflux<sup>46</sup>. Second, hiatus hernia may be the result of esophagitis caused by reflux<sup>47,48</sup>. Third, that LES pressure which is considered now as the main factor against reflux is not affected by its anatomical position, as it maintains its competence in the chest as well<sup>14</sup>. Fourth, even if we believe the assumption that hiatus hernia disrupts the anatomical factors, these factors themselves are only one acting defense force among the other five more important forces, which negate the attractive idea that hiatus hernia is a major cause of gastroesophageal reflux. Currently, the presence of hiatus hernia is believed not to be an important issue in the clinical evaluation of patients with gastroesophageal reflux<sup>49</sup> and at best is a very minor factor in the production of gastroesophageal reflux<sup>50,27</sup>.

### **2. The lower esophageal sphincter: LES**

Since early reports about the existence of the lower esophageal sphincter in man<sup>4,5,50-52</sup>, a great deal of research about the subject has occurred<sup>25-27,30,41,53</sup> where the innervation, and the hormonal control of the LES sphincter have been studied in detail. While twenty five years ago, anatomical factors were solely believed to be the main barrier against reflux<sup>23</sup>, it is now generally accepted that the major abnormality in patients with gastroesophageal reflux is the incompetence of the LES<sup>54-56</sup>. The causes

of this incompetence are not known. Cohen<sup>37</sup> has postulated that it may result from alterations of one or more of the mechanisms responsible for the sphincter competence and so it could result from abnormalities in the muscle, neural fibers, or gastrointestinal neuropeptides, alone or in combination, and so reflux can occur from decreased tonic activity of excitatory nerves or atrophy of the circular muscle layer as in scleroderma<sup>57</sup> or from a functional disorder of the circular muscle induced by circulating hormones<sup>27</sup>. Others have shown that GE reflux itself can damage the cholinergic innervation of the LES and the muscularis propria of the esophagus<sup>58</sup>. Practically speaking, reflux usually occurs in the recumbent position, while asleep, and in the fasting state and this is due to the decrease in the basal LES pressure which is found in most patients with symptomatic gastroesophageal reflux. The reduction is usually below 10mmHg and can be as low as 2 or 3mmHg. In some patients, reflux occurs while doing exercise, bending over, straining, or wearing tight garments or corsets, and this is explained by the fact that patients with gastroesophageal reflux don't have the adaptive mechanism that allows the LES pressure to increase to a greater degree when the intra abdominal pressure is increased during the above mentioned conditions. This adaptive response has been demonstrated clearly in healthy patients. However, its nature is still debated whether it is a neurogenic reflex<sup>13,16,59</sup> or purely a mechanical event<sup>17,18,60</sup>. Although the concept of the LES as the major barrier against reflux is generally accepted<sup>54-56,61</sup> and seems attractive, it has come under attack because of some of the discrepancies that have been found with the measurement of the LES pressure. In at least 25% of patients with reflux the basal LES pressure is in the normal range<sup>62,63</sup>. This has been explained<sup>28</sup> by the fact that the basal LES pressure as measured in the laboratory may not always reflect the pressure that is present when the reflux occurs, which is again affected by so many hormones, and the type of diet, e.g., fat, alcohol, etc. It can also be attributed to the fact that the sphincter tone varies considerably during the day, which means that a single measurement does not necessarily reflect the daily events. In a recent study<sup>64</sup> using prolonged intraesophageal PH and pressure monitoring, they showed that reflux occurred primarily when the sphincter pressure was low and that transient relaxation of the sphincter was responsible for the reflux esophagitis present in some of their patients with the LES pressure within the normal range. Another point is the occurrence of occasional reflux in healthy subjects, that have normal LES pressure, this was clarified again in many studies<sup>64-66</sup> where it was shown that transient relaxation of LES that occurred most frequently in subjects with normal LES pressure was responsible for 98% of the reflux episodes, and these were not related to swallowing which is also known to produce transient relaxation of the LES.

## **ESOPHAGEAL CLEARANCE**

Another important line of defense against gastroesophageal reflux and its consequences like esophagitis is the efficacy of esophageal clearance, which determines the duration of esophageal exposure to the noxious refluxed material, and the severity of esophagitis produced<sup>67-69</sup>. Esophageal clearance depends on three factors, one is the effect of gravity<sup>70</sup> second is primary and secondary peristalsis<sup>71</sup>. third is saliva<sup>72</sup>. During sleep, however, swallowing ceases almost completely<sup>73</sup> and the only mechanism available would be secondary peristalsis as the effect of gravity also disappears while awake, primary peristalsis, elicited by swallowing is the main factor that clears the esophagus<sup>66</sup> and although gastroesophageal reflux often elicits secondary peristalsis, the major mechanism eliciting peristalsis is the high frequency of swallowing and so primary peristalsis protects against reflux while the person is awake<sup>64</sup> and secondary peristalsis works during sleep<sup>70</sup>. Saliva is found to promote acid clearance from the esophagus<sup>72</sup> which can be attributed to the fact that it has a diluent and washing effect, and with its bicarbonate content (Ph of 7) can neutralize acid very well, in addition, it elicits deglutination<sup>71</sup>. In

patients with reflux, the abnormality is in the increased incidence of non peristaltic contractions at the lower esophagus which cause ineffective clearance of acid<sup>74,75</sup>.

### **Gastric volumes**

It has been shown that as gastric secretory volume is increased, gastroesophageal reflux is increased too<sup>76</sup> and that reflux increase significantly after meals<sup>64,77</sup>. Gastric volume can be increased due to the following<sup>53</sup>, (a) volume and composition of ingested material, (b) rate of gastric secretion, (c) rate of gastric emptying, and (d) rate and volume of duodenogastric reflux. So reflux is increased with large meals and fatty foods which in addition to lowering the LES pressure, take longer time to leave the stomach, and thus lead to more reflux<sup>78</sup>. Patients with duodenal ulcer also have high incidence of reflux disease<sup>79</sup> probably because of increased acid volume in the stomach. Delayed gastric emptying<sup>80</sup> and impaired antral motility<sup>81,82</sup> has been reported in up to 40 percent of patients with GE reflux, so more volume is available for reflux. Duodenogastric reflux leads to increased volume of the stomach and provides more of the harmful bile to the gastric juice<sup>83,84</sup>.

### **Potency of reflux material**

The composition of reflux material is very important in determining the severity of symptoms of gastroesophageal reflux and the degree of esophagitis<sup>26,27</sup>. It has been shown for example that bile with the gastric acid and pepsin can be more harmful and together form a potent combination that leads to reflux disease<sup>84</sup> as bile increases the permeability of esophageal mucosa to Hcl<sup>85</sup>.

### **Mucosal resistance**

The esophageal mucosa is very sensitive to damage from acid, pepsin or bile salts, and the degree of damage may depend on the ability of the mucosa to regenerate.

## **REFLUX ESOPHAGITIS**

Reflux esophagitis is a well documented manifestation of gastroesophageal reflux<sup>27,31,86,87</sup> and the severity of the esophagitis parallel the severity of the reflux. Some aspects remain controversial. Many cases are known where reflux can be demonstrated radiologically and symptoms are very severe yet with no evidence of esophagitis<sup>88</sup> on endoscopy. Other cases show severe esophagitis with the patient having minimal symptoms. This has been explained by the fact that esophagitis has so many factors that help against it such as the mucosal resistance of the esophagus<sup>49</sup>. its clearance ability, and the saliva<sup>71,72</sup> which make the injury variable from person to person. Esophagitis usually starts with very minimal changes in the basal cell layer of the epithelium, where the mucosa appears grossly normal on endoscopy<sup>89</sup>. There is increased activity and increased thickness of the basal layer; however, eventually superficial ulceration supervenes, followed by deep ones, this invites healing by granulation tissue which lead to stricture formation.

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