

Autonomic dysfunction in gastroesophageal reflux disease. The neurogastro-cardiac axis: friend or foe?

La disfunción autonómica en la enfermedad por reflujo gastroesofágico. El eje neurogastro-cardíaco: ¿amigo o enemigo?

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Abstract

Gastroesophageal reflux disease (GERD) is a complex and highly prevalent entity. Impaired gut-brain communication is associated with autonomic dysfunction. Modulation of the autonomic nervous system controls gastrointestinal functions. In GERD, a decrease in vagal tone (parasympathetic activity) and an increase in sympathetic activity with autonomic balance shifted towards the sympathetic system have been reported. Clinical questionnaires and non-invasive measurement of heart rate variability may be useful in patients with GERD to detect autonomic dysfunction. Restoration of parasympathetic system activity (mainly neuromodulation), with subsequent improvement of parasympathetic activity, will reduce the intensity of autonomic symptoms and GERD, improving quality of life.

Keywords: Autonomic nervous system. Heart rate variability. Gastroesophageal reflux disease. Autonomic dysfunction.

Resumen

La enfermedad por reflujo gastroesofágico (ERGE) es una condición compleja y altamente prevalente. El deterioro de la comunicación intestino-cerebro está asociado a la disfunción autonómica. La modulación del sistema nervioso autónomo controla las funciones gastrointestinales. En la ERGE se han reportado una disminución del tono vagal (actividad parasimpática) y un aumento de la actividad simpática, con el equilibrio autónomo desplazado hacia el sistema simpático. Los cuestionarios clínicos y la medición de la variabilidad de la frecuencia cardíaca, método no invasor, pueden ser útiles en los pacientes con ERGE para detectar la disfunción autonómica. La restauración de la actividad del sistema parasimpático (principalmente neuromodulación), con la subsecuente mejoría de la actividad parasimpática, disminuirá la intensidad de los síntomas autonómicos y de la ERGE, mejorando la calidad de vida.

Palabras clave: Sistema nervioso autónomo. Variabilidad de la frecuencia cardíaca. Enfermedad por reflujo gastroesofágico. Disfunción autonómica.

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Date of reception: 10-01-2025

Date of acceptance: 21-01-2025

DOI: 10.24875/CIRUE.M25000835

Cir Cir (Eng). 2025;93(2):209-217

Contents available at PubMed

www.cirugiaycirujanos.com

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Introduction

Gastroesophageal reflux disease (GERD) is a complex clinical condition in which the reflux of gastroduodenal content into the esophagus causes symptoms or complications, affecting the quality of life and incurring a high management cost exceeding 12 billion dollars annually in the United States of America¹⁻⁴.

In Latin America, its prevalence has been described between 15% and 25%⁵. In the United States of America, GERD is the most prevalent gastrointestinal disorder, affecting one-third of the adult population⁶. In the Western world, the prevalence in adults has been reported at 20%^{6,7}.

Gastroesophageal reflux (GER) is a physiological phenomenon. The Lyon Consensus 2.0 defined "proven GERD" when there is conclusive evidence of GER, including the presence of erosive esophagitis (grades B, C, and D of the Los Angeles classification), Barrett's esophagus, and peptic stricture, and an acid exposure time in the distal esophagus > 6% measured by 24-hour ambulatory pH and impedance monitoring. The absence of significant esophagitis and an acid exposure time in the esophagus < 4% rule out the disease. However, it is important to clarify that objective evidence of GERD has little correlation with the frequency and intensity of symptoms, as these depend not only on the intensity of the esophageal stimulus but also on the degree of esophageal sensitivity of each individual^{4,5}.

Pathogenesis of gastroesophageal reflux disease

The pathophysiology of GERD is complex (Fig. 1)⁸. The constant exposure of the esophagus to GER (gastric acid, bile, pepsin, and pancreatic enzymes) can cause damage to the esophageal mucosa (initially related to pepsin and then to the inflammatory response mediated by cytokines and leukocyte infiltration)⁹.

The mechanisms that most contribute to the development of GERD are 1) the increase in the number of transient lower esophageal sphincter (LES) relaxations, 2) the increase in abdominal pressure, and 3) the decreased LES pressure. The pathophysiology of GERD includes a malfunction of the esophagogastric junction, a decrease in esophageal clearance, and alterations in the integrity of the esophageal mucosa².

The antireflux barrier is composed of the LES and the crural diaphragm. The LES has an intrinsic component,

formed by the esophageal muscle fibers under neuro-hormonal control, and an extrinsic component, formed by the diaphragmatic pillars and the phreno-esophageal ligament, which provide anatomical support to the LES and greater protection against GER^{3,10,11}.

Typical symptoms and extraesophageal signs

The typical and most common symptoms of GERD are heartburn (substernal burning sensation) and regurgitation (effortless return of gastric content to the mouth). The therapeutic target in acid-related diseases is the pharmacological suppression of gastric acid secretion. The control of intragastric pH is related to mucosal healing and symptomatic relief¹. The pH scale is logarithmic (values from 0 to 14), with a pH of 4 being 10 times less acidic than a pH of 2, 100 times less than a pH of 3, and 1,000 times less than a pH of 1¹¹. Although heartburn and regurgitation are common symptoms of GERD, they are poor predictors of the presence of severe esophagitis. These symptoms alone are not sufficient to confirm or rule out the presence of esophagitis. The diagnostic sensitivity and specificity for heartburn have been reported at 30-76% and 62-96%, respectively¹².

To understand the disease, the Montreal Consensus divided GERD into syndromes¹³:

- Esophageal:
 - Symptomatic: typical reflux and reflux chest pain.
 - Esophageal mucosal damage (reflux esophagitis, reflux stricture, Barrett's esophagus, and adenocarcinoma).
- Extraesophageal:
 - Established association: chronic cough, asthma, laryngitis, and dental erosions due to GER.
 - Proposed association: laryngitis, sinusitis, recurrent otitis media, idiopathic pulmonary fibrosis.

In GERD, patients with mucosal damage are more likely to have abnormal esophageal acid exposure (71% vs. 40%). In the erosive phenotype, greater dilation of intercellular spaces has been reported. The decrease in tissue resistance, the increase in permeability, and the passage of H⁺ ions are associated with a greater inflammatory response, sensitization of afferent sensory nerve endings, and neural dysfunction^{14,15}. The erosive phenotype can be subdivided into 3 groups:

- Alteration of esophageal clearance due to altered esophageal motility.

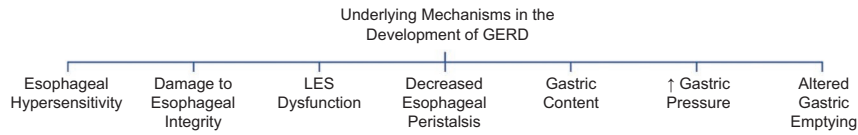


Figure 1. Underlying mechanisms in the development of gastroesophageal reflux disease (GERD)⁸. LES: lower esophageal sphincter.

- Dysfunction of the esophagogastric junction or the antireflux barrier due to LES hypotension, transient LES relaxations, or dyssynergia between the LES and the crural diaphragm (e.g., presence of hiatal hernia).
- Posterior gastric factors, including delayed gastric emptying and the presence of a gastric acid pocket⁷.

Non-erosive reflux disease (NERD) is the most common phenotype and represents up to 70% of GERD cases, while erosive esophagitis represents approximately 30%, and Barrett's esophagus 6-8% of the GERD patient population⁷.

The non-erosive phenotype is an extraordinarily heterogeneous group that includes three subgroups (after objective reflux measurements) of patients: 1) true acid reflux (positive abnormal acid exposure [AAE] in 50%), 2) hypersensitive esophagus (negative AAE and symptom index > 50%), and 3) functional heartburn (negative AAE and symptom index < 50%)¹⁶. The symptom index is the ratio between heartburn and the number of acid reflux episodes. The non-erosive phenotype is more refractory to treatment, as it includes non-acid-related conditions (50%)¹⁷. In NERD, predictions of response to proton pump inhibitors (PPIs) are difficult, so a trial with a more potent suppressor would allow stratification of responding patients. Treatment failure can be explained because the diagnosis is based on symptoms, the persistence of weakly acidic reflux events with extensions to the proximal esophagus, and visceral hypersensitivity¹. However, when patients with objective evidence of acid reflux (multichannel intraluminal impedance with 24-h pH-metry) are selected, the response rate to PPIs is similar in erosive phenotypes and true NERD (72% vs 73%)¹⁸. Functional heartburn and reflux hypersensitivity represent > 90% of patients with heartburn unresponsive to twice-daily PPI treatment¹⁸.

The underlying mechanisms of extraesophageal airway manifestations are not yet well understood. Two hypotheses have been proposed: 1) direct contact of gastric acid with the upper airways and 2) a vagal reflex triggered by acidification of the distal esophagus,

causing bronchospasm¹³. Sensitization of the pulmonary tree can cause the airways to become reactive to other stimuli, producing bronchospasm through a vagal mechanism^{19,20}.

Of note, a higher frequency of autonomic nervous system (ANS) dysfunction (dysautonomias) has been reported in patients with GERD symptoms; the pathophysiology of GERD has been related to alterations in ANS activity^{21,22}.

Patients report that GERD symptoms occur more frequently in the postprandial period. Precipitating factors of GERD symptoms (refluxed material) and factors that modify the response to treatment, such as altered esophageal clearance and mucosal sensitivity, have been reported. It is estimated that between 10% and 40% of GERD patients have an incomplete or no response to a standard dose of PPIs¹.

Although there are no data confirming the higher frequency of autonomic symptoms in the early or late postprandial period in patients with GERD, many will appear after the ingestion of fat or condiments (larger volume), even in patients under treatment with acid suppressants. During the evaluation of GERD, the presence and intensity of autonomic symptoms (dry oral mucosa, hypersalivation, alterations in heart rate, sudden dyspnea, anxiety, depression, orthostatic intolerance, alertness or hypervigilance, and chest pain) are not usually considered.

Autonomic nervous system and gastroesophageal reflux disease

The ANS is composed anatomically and functionally of 2 divisions: 1) the sympathetic nervous system (SNS) and 2) the parasympathetic nervous system (PNS) (Figs. 2-4 and Table 1). Both are tonically active and provide a variable frequency of neuronal inputs (increase or decrease) to tissues (potentiation or diminution). This characteristic improves the ability to regulate the functional activity of a tissue more precisely. Without tonic activity, the neural input to a tissue could only increase. The SNS and PNS work in a coordinated manner and generally have opposite effects²³.

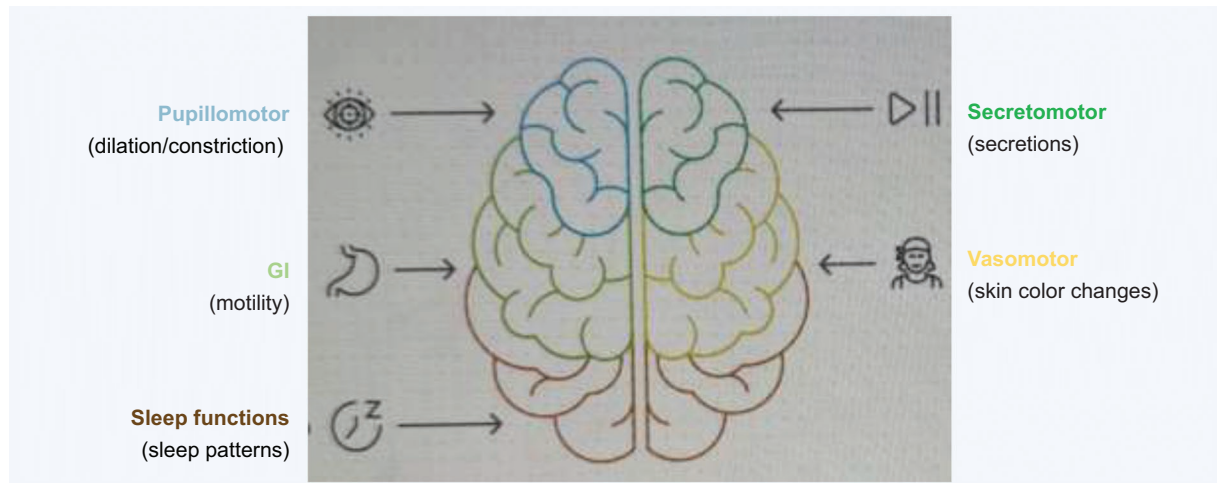


Figure 2. Effects of the autonomic nervous system²²⁻²⁶.

Sympathetic (mainly splanchnic) and parasympathetic (vagal) fibers innervate the LES, with parasympathetic activity being essential for its reflexive relaxation. Vagal sensory afferents originate from the LES and the distal esophagus and synapse in the nucleus of the solitary tract of the rhombencephalon. Vagal efferents originate in the dorsal motor nucleus and synapse with the myenteric plexus of the enteric nervous system. The PNS contributes to both inhibitory and excitatory neurons. Excitatory fibers arise from the rostral portion of the dorsal motor nucleus, and inhibitory fibers arise from the caudal portion. The dorsal motor nucleus and the nucleus of the solitary tract form a dorsal vagal complex in the rhombencephalon that coordinates the reflex control of the LES²³.

Milovanovic et al.²¹ reported that patients with GERD symptoms have distortion of the components of the SNS and the PNS. Impaired parasympathetic function has been associated with GERD. The association between gastrointestinal symptoms and cardiac arrhythmias, as one of the impairments of the ANS in GERD, has been described as the gastroduodenal syndrome. The ANS has effects on different systems; autonomic neuropathy can manifest in almost any system. Orthostatic hypotension is one of the most common manifestations of autonomic dysautonomia, but others may occur²⁴.

Dysautonomia

The ANS controls vital bodily functions (blood pressure, breathing, gastrointestinal system, heart rate,

body temperature control, and bladder activity). The central nervous system provides its inputs to the enteric nervous system by modulating the ANS to control GI functions. The ANS is composed of a network controlled by physiological systems through inputs (internal and external) to maintain homeostasis. The central nervous system network, together with the SNS and the PNS, regulates bodily functions, and when it fails, it is expressed by various clinical signs²²⁻²⁵ (Table 1):

- Cardiovascular: fixed heart rate, postural hypotension, resting tachycardia.
- GI: dysphagia, gastroparesis, nausea, vomiting, abdominal fullness, constipation.
- Genitourinary: bladder atony.
- Pupillary: absent or delayed light reflexes, decreased pupil size.
- Sexual: erectile dysfunction, retrograde ejaculation.
- Sudomotor: anhidrosis, salivation.
- Vasomotor: cold extremities (due to loss of vasomotor responses), edema (due to loss of vasomotor tone and increased capillary permeability).

The most frequent symptoms of dysautonomia are orthostatic hypotension, confusion, tunnel vision, and discomfort in the head, neck, or chest. It can present concomitantly with supine hypertension due to increased peripheral resistance, which induces natriuresis, exacerbating orthostatic hypotension. There are many other more benign stimuli that can decrease blood pressure (standing, swallowing, Valsalva maneuver, dehydration, exercise, hyperventilation, heat, etc.) or increase it (supine rest, water or coffee intake, head-down tilt, hypoventilation, etc.)²⁵.

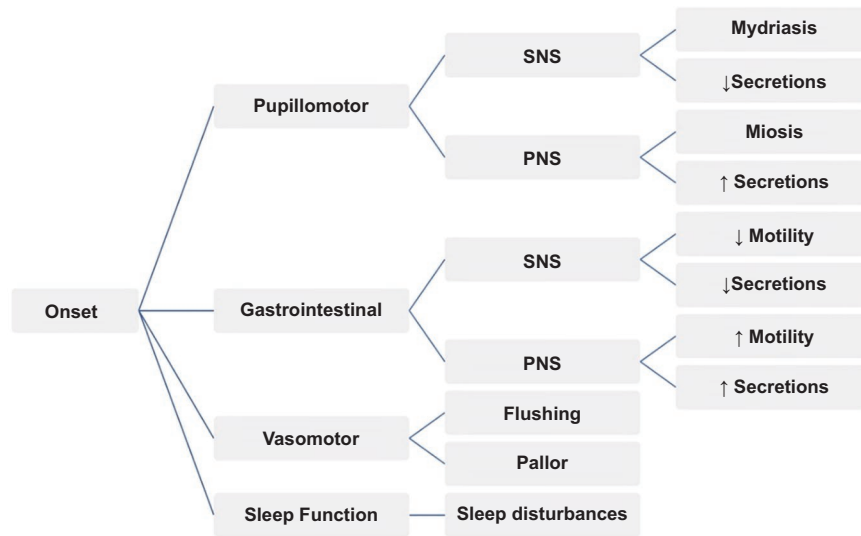


Figure 3. Effects on specific systems²²⁻²⁶. PNS: parasympathetic nervous system; SNS: sympathetic nervous system.

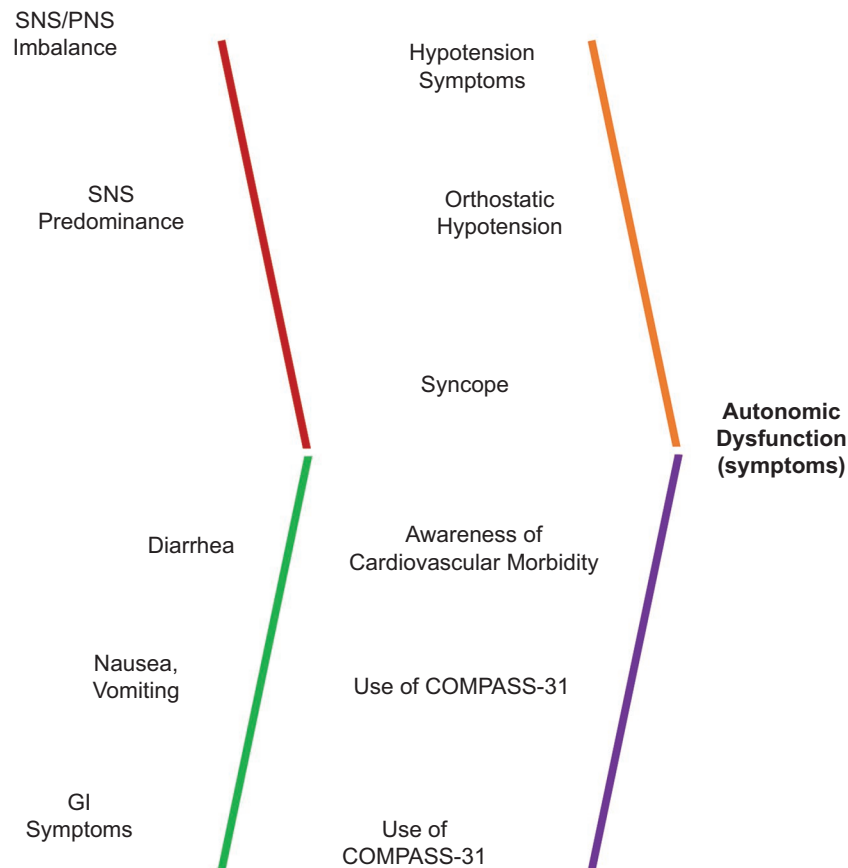


Figure 4. Understanding autonomic dysfunction²²⁻²⁶. PNS: parasympathetic nervous system; SNS: sympathetic nervous system.

Autonomic symptoms have been observed to be more frequent in patients with GERD than in healthy volunteers. In the study by Milovanovic et al.²¹, severe

autonomic dysfunction was detected in 44.4% of patients with GERD vs 7.9% of controls ($p < 0.001$). Similarly, 24-h ambulatory blood pressure measurement showed

Table 1. Sympathetic and parasympathetic symptoms affecting humans²

System/organ	Effect of stimulation	
	Sympathetic effect	Parasympathetic effect
Eye	Contraction of radial iris muscle (pupil dilation: mydriasis) Relaxation of ciliary muscle (far vision)	Contraction of sphincter iris muscle (pupil constriction: miosis) Contraction of ciliary muscle (near vision)
Heart	↑ Heart rate ↑ Contractile strength ↑ Conduction rate	↓ Heart rate
Blood vessels	Vasoconstriction (most vessels), ↑ blood pressure	Vasodilation (some vessels)
GI tract	↓ Motility and secretions	↑ Motility and secretions
Bladder	Relaxation of detrusor muscle	Contraction of detrusor muscle
Sweat glands	↑ Sweating (diaphoresis)	No direct effect
Piloerector muscles	Contraction (goosebumps)	No direct effect
Bronchi	Relaxation (bronchodilation)	Contraction (bronchoconstriction)
Pupilmotor	Pupil dilation (mydriasis)	Pupil constriction (miosis)
GI (again)	↑ Motility and secretions, potentially leading to constipation	↑ Motility and secretions, facilitating digestion
Secretomotor	↓ Secretions (except sweat)	↑ Secretions
Vasomotor	Skin color changes (redness, pallor)	
Genitourinary	Erectile dysfunction	Normal sexual function
Sleep function	Sleep disturbances	

significantly higher values of systolic blood pressure and pulse pressure in the GERD group compared to the control group²¹.

It has been suggested that parasympathetic dysfunction is not only a consequence of chronic esophageal inflammation but also the main factor in the etiology of GERD. Alterations in ANS activity affect both the contraction and transient relaxation of the LES (which acts as a reflux barrier), leading to the onset and progression of GERD^{23,26}.

The distal esophagus and the heart share vagal afferent innervation, which makes it difficult to distinguish between ischemic chest pain of esophageal and cardiac origin; esophageal pain mimics ischemic cardiac discomfort. In clinical contexts, this leads to the misdiagnosis of chest pain due to GER as angina pectoris, and vice versa²⁷. The presence of GERD may predispose to myocardial ischemia by altering the sympathetic-parasympathetic balance due to

impaired parasympathetic function. This mechanism could trigger an esophagogastric-cardiac reflex, resulting in decreased myocardial perfusion. GERD and disorders of the brain-gut interaction could be associated with autonomic dysfunction, which can be identified by heart rate variability²⁸.

The ANS, with its 2 branches, the SNS and the PNS, also plays a fundamental role in the modulation of cardiac functions, such as arrhythmogenesis. There is evidence that hyperactivity of the PNS can trigger “vagal” arrhythmias (e.g., paroxysmal atrial fibrillation, Brugada syndrome, idiopathic ventricular fibrillation)²⁹.

Heart rate variability is lower in patients with GERD symptoms compared to controls, indicating severe autonomic dysfunction. Patients with more severe symptoms exhibit greater sympathetic dominance²⁹. Other authors report similar data^{30,31}.

Based on an analysis of heart rate variability, Ali and Chen³² reported that disorders of the brain-gut interaction

(formerly functional gastrointestinal disorders) and GERD were associated with decreased parasympathetic activity and increased SNS activity, with the autonomic balance shifted towards the sympathetic system. These conditions were associated with autonomic dysfunction, mainly due to the suppression of vagal tone and a hyperactive sympathetic system. It can be assessed non-invasively using heart rate variability measurements.

Dysautonomia, gastroesophageal reflux disease, and long COVID-19 symptoms

A systematic review reported that heart rate variability analysis was consistent in detecting reduced parasympathetic activity and sympathetic dominance in patients with brain-gut axis disorders. Some studies have reported heart rate ratios (maximum/minimum) during postural change, Valsalva maneuver, handgrip, and deep breathing to record heart rate variability instead of time or frequency domain parameters. Six of 15 studies concluded that patients had low heart rate variability compared to controls. Four studies reported a decrease in PNS and SNS activity³³. Djeddi et al.³³ studied autonomic activity before, during, and after the GER event and found that PNS activity is significantly suppressed before the reflux event. Jones et al.³⁴ indicated that better control of autonomic dysfunction has a positive effect on symptomatic improvement in GERD.

Typical symptoms include chronic fatigue, GI symptoms, brain fog, orthostatic tachycardia, and exertional dyspnea. These can be severe and debilitating, and many patients are left with disability or modified independence. The underlying causes of the so-called post-acute sequelae of SARS-CoV-2 infection (PASC) are not yet clear, but given the evidence of the similarity between the clinical presentation of PASC phenotypes and postural orthostatic tachycardia syndrome, it has been postulated that dysautonomia may play a role in its pathophysiology. Compensatory activation of the sympathetic nervous system in postural orthostatic tachycardia syndrome can cause tachycardia, insomnia, gastrointestinal dysfunction, and anxiety, symptoms also common in PASC³⁵.

PASC presents in many forms and affects all organs of the body. This heterogeneous presentation suggests the involvement of the ANS. So far, studies on ANS dysregulation in people with PASC have been largely observational and descriptive, based on symptom inventories or objective but indirect measures of cardiovascular function, and have paid little attention to the adrenomedullary, hormonal, and enteric nervous components of the ANS³⁶.

Early detection (presence and intensity) of dysautonomic symptoms in patients with chronic GERD symptoms, whose prevalence in our country is high, regardless of cardiometabolic risk, may improve the response to treatment with acid-suppressing drugs, prokinetics, or neuromodulators, especially in patients with normal esophageal acid exposure (reflux hypersensitivity), which can contribute to improving the patients' quality of life.

The balance between the SNS and the PNS is crucial for maintaining homeostasis and preventing cardiac arrhythmias. Imbalance can manifest with a variety of symptoms, and its identification and treatment can be important in the management of various clinical conditions.

Autonomic symptoms occur more frequently in the postprandial period in patients with chronic GERD. Our group considers this to be a different phenotype in GERD that has not been adequately evaluated. The increase in the frequency and intensity of autonomic alterations in GERD (non-erosive, diabetic, obese, post-COVID-19) produced by the imbalance between the SNS and the PNS requires clinical studies with clinical questionnaires and heart rate variability measurements to evaluate the impact on health, treatment response, and quality of life. The Montreal Consensus should consider dysautonomic phenomena as a special subtype.

Clinical scenarios

Figure 5 shows the diagnostic approach in clinical scenarios of patients with GERD and autonomic symptoms.

Isolated autonomic symptoms

Any healthy individual or someone with mild GERD may experience autonomic symptoms after a large intake of food (chili, fat, or condiments), which are infrequent, short-lived, and of low intensity. Hygienic-dietary measures and adequate control of acid suppression will be sufficient to relieve the symptoms.

Chronic GERD with autonomic symptoms

Patients may report a greater intensity of autonomic symptoms in the intermediate postprandial period (associated with the volume and type of food), of sudden onset, difficult to explain, and triggering anxiety due to fear of suffering a cardiac disease (chest pain, tachycardia or bradycardia, dyspnea, dry mouth, or mental confusion) or complications of GERD (odynophagia,

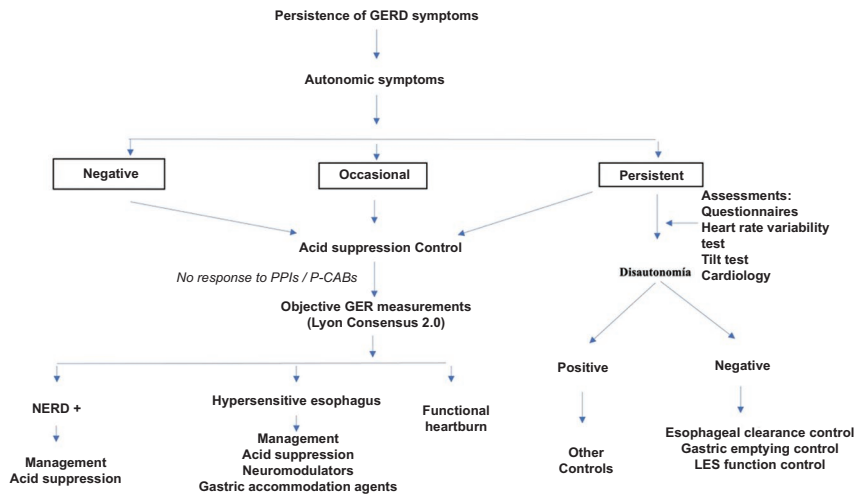


Figure 5. Proposed approach in patients with gastroesophageal reflux disease (GERD) and autonomic symptoms. LES: lower esophageal sphincter; NERD: non-erosive reflux disease; PPIs: proton pump inhibitors.

dysphagia, distension and epigastric abdominal pain, cancer). They are generally associated with triggering factors (sudden changes in diet, prolonged fasting, intake of analgesic, anti-inflammatory, steroid, or hormonal drugs, and post-traumatic stress). These symptoms may manifest occasionally or persistently.

If autonomic symptoms are persistent, the use of clinical questionnaires and heart rate variability testing should be considered²¹. Symptoms are triggered by the suppression of vagal tone and a hyperactive sympathetic system^{21,22,24}. Acid-suppressing drugs neutralize intragastric pH but have no significant effect in alleviating the symptoms. The following should be considered in this group:

- Typical GERD symptoms (heartburn and regurgitation): increased duration and intensity, even with the intake of water or non-irritating foods.
- Oppressive chest pain: it is complex to distinguish the cardiac from the esophageal origin, as they have the same innervation. Pain can be triggered by the intake of water or non-irritating foods. It shows a diffuse character (difficult localization), poor relationship with the disease (or the intensity of the stimulus) that originates it, the ability to produce high-intensity autonomic responses, and the ability to generate referred sensations (referred pain). In the gastrointestinal tract, the relationship between tissue damage and pain is not obvious; relatively mild stimuli (tonic contraction of smooth muscle, mild inflammation of the mucosa, or mild ischemia) can produce intense pain reactions³⁷.

- Dyspepsia: one of the most frequent symptoms is early satiety, followed by abdominal distension with or without epigastric pain, nausea, and belching.
- Dysphagia with or without globus sensation.
- Symptomatic overlap.

In this group, objective measurements of GER (endoscopy and multichannel intraluminal impedance with 24-h pH-metry)^{16,18} and optimization of acid-suppressing drugs, prokinetics, agents to improve gastric accommodation, or neuromodulators should be considered.

Dysautonomia (diagnostic test: tilt test)

The most frequent symptoms of dysautonomia are orthostatic hypotension, confusion, tunnel vision, and discomfort in the head, neck, or chest²⁶. Stress, heat, prolonged fasting, sleep deprivation, dehydration, and lack of adherence to cardiological treatment can cause an increase in the frequency, duration, and intensity of symptoms in different systems. The pathophysiological mechanisms in GERD (alterations in the LES, altered esophageal emptying, and delayed gastric emptying) are controlled by the ANS (vagal fibers). Parasympathetic innervation plays an important role in the regulation of LES tone³⁸, and this increases with poor control of dysautonomia. In these cases, it is difficult to try to prove causality, but they are associated diseases that influence a poor quality of life. Good control of GERD symptoms will improve autonomic control, and vice versa.

Conclusions

Human life depends on the ANS, as it controls involuntary bodily functions such as blood pressure, the gastrointestinal system, heart rate, and bladder activity. Therefore, it is suggested to evaluate the frequency and intensity of autonomic symptoms in individuals with GERD, and the presence of esophageal and extra-esophageal manifestations in patients with persistent and dysautonomic autonomic symptoms.

Funding

The authors declare that they did not receive funding for this study.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of persons and animals. The authors declare that no experiments have been performed on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal data of patients nor does it require ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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