Review Article on Novel Insights into Chronic Cough

Pathogenesis and management of gastroesophageal reflux disease-associated cough: a narrative review

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Background and Objective: Gastroesophageal reflux disease (GERD)-associated cough is defined as a special GERD with a predominant cough symptom and is a common cause of chronic cough. This review summarizes our current understanding on the pathogenesis and management of GERD-associated cough.

Methods: Main literatures on the pathogenesis and management of GERD-associated cough were reviewed and our understandings derived from the published studies were showed then.

Key Content and Findings: Although esophageal-tracheobronchial reflex mainly underlies the pathogenesis of GERD-associated cough, its counterpart-tracheobronchial-esophageal reflex might exist and initiate the cough due to reflux induced by upper respiratory tract infection through the signaling of transient receptor potential vanilloid 1 linking airway and esophagus. The presence of reflux-associated symptoms such as regurgitation and heartburn along with coughing suggests an association between cough and GERD, which is supported by the objective evidence of abnormal reflux as detected by reflux monitoring. Although there is no general consensus, esophageal reflux monitoring provides the main diagnostic criteria for GERD-associated cough. Despite that acid exposure time and symptom associated probability are useful and mostly employed reflux diagnostic criteria, they are imperfect and far from being the gold standard. Acid suppressive therapy has long been recommended as the first choice for GERD-associated cough. However, the overall benefits of proton pump inhibitors have been controversial and need to be further assessed, especially in patients with cough due to non-acid reflux. Neuromodulators have demonstrated potential therapeutic effects for refractory GERD-associated cough, for which anti-reflux surgery may also be a promising treatment option.

Conclusions: Tracheobronchial-esophageal reflex might initiate reflux-induced cough provoked by the upper respiratory tract infection. It is necessary to optimize the current standards and to explore new criteria with higher diagnostic potency. Acid suppressive therapy is the first choice for GERD-associated cough, followed by neuromodulators and anti-reflux surgery for refractory GERD-associated cough.

Keywords: Anti-reflux treatment; chronic cough; gastroesophageal reflux; reflux monitoring

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Introduction

Chronic cough is a common extraesophageal symptom of gastroesophageal reflux disease (GERD) and occurs in about one-third of patients with GERD (1). GERD-associated cough, also known as reflux cough syndrome, is considered to be a special type of GERD, which is characterized by a predominance of cough (2,3). It accounts for 10–40% of chronic cough and has been increasingly recognized by physicians and researchers (1). The international guidelines for the diagnosis and treatment of cough have included the management of GERD-associated cough as an important component (4,5).

Although GERD-associated cough is a common cause of chronic cough worldwide, it was considered to be relatively rare in China. In 2013, a multi-center survey of the etiologies of chronic cough reported that GERD-associated cough only accounted for less than 5% of chronic cough in China (6). In our specialist cough clinic, GERD-associated cough was found in 9% of patients with chronic cough from 2004 to 2008 (7), which increased to 33% from 2009 to 2016 (8). The increasing prevalence of GERD-associated cough may reflect the changes in lifestyle and obesity rates due to social and economic development in China (8). This is also complicated by regional differences in the etiological distribution of chronic cough, the diagnostic thinking of physicians and the available diagnostic techniques in medical institutions.

This review summarizes our current understanding on the pathogenesis and management of GERD cough. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1757/rc).

Methods

The main literatures regarding the pathogenesis and management of GERD-associated cough were searched in PubMed and reviewed comprehensively as detailed in *Table 1*. We derived our understanding and insights on these issues from the published data, especially our studies conducted between 2009 and 2023.

Pathogenesis of GERD-associated cough

The mechanisms underlying GERD-associated cough mainly include reflux theory and reflex theory (2). Historically, reflux theory proposes that the acid refluxes (gastric acid and pepsin) rising to proximal esophagus directly injure laryngopharyngeal mucosa and are microaspirated into the lower airways, which irritate the innervating cough receptors and arise cough. Reflex theory suggests that the irritants derived from reflux in distal esophagus may also trigger cough indirectly through esophageal-tracheobronchial reflex. It is generally believed that reflex theory is more important than reflux theory in the pathogenesis of GERD-associated cough since only 32–37% of patients with GERD were observed having reflux reaching the upper esophagus (9,10), and the distal esophagus is the mandatory route for all refluxes traveling up to the proximal end of esophagus as well. Therefore, reflux theory actually contains the components of reflex theory. In addition, the disorder of esophageal dysmotility, which is also common in patients with GERD-associated cough (11), can amplify the noxious response of abnormal reflux by delaying esophageal clearance and prolonging acid exposure (*Figure 1*). Why only some patients develop chronic cough in the presence of GERD remains to be elucidated. One possible explanation is that patients with cough and abnormal reflux are highly responsive to the effects of both acid and non-acid reflux. Cough hypersensitivity underlied by airway neurogenic inflammation is responsible for the exaggerated cough reactivity to reflux, which is non-tussive in physical state but is violently tussive in patients with GERD-associated cough (12). Currently, how GERD-associated cough initiates remains unclear.

Both the tracheobronchial tree and the esophagus originate from the embryonic foregut and are innervated by the vagal C-fibers, which express the transient receptor potential vanilloid 1 (TRPV1) (13). The stimuli sensed and transmitted by the nerve endings innervating both esophagus and airway converge in the primary cough center and may have a neural crosstalk. This may produce the initiation of the cough reflex in response to the reflux-mediated irritation (14). In an intact vagal network, persistent excitation of one peripheral end may prime another distant peripheral end by sensitizing the neural circuit. There has been growing evidence to support that the esophageal-tracheobronchial reflex is mediated by the vagal C-fibers innervating the tracheobronchial and esophageal mucosa (15). Since GERD-associated cough is often provoked by a previous upper respiratory tract infection (16), it is conceivable that nociceptive irritants in the airway caused by the infection might enhance the excitability of C-fibers in the esophageal mucosa and elicit the esophageal

Table 1 The search strategy summary

Items	Specification
Date of search	September 25th, 2022–January 5th, 2023
Databases and other sources searched	PubMed
Search terms used	"Chronic cough", "Gastroesophageal reflux", "Cough due to reflux"
Timeframe	1988–2023
Inclusion and exclusion criteria	The main literature review about the pathogenesis and management of GERD-associated cough were included; case reports and similar review articles were excluded
Selection process	Li Zhang and Alimire Aierken searched and reviewed all initial articles, and conferred with Mengru Zhang, with additional selection by Zhongmin Qiu. Ultimate final article inclusion was determined by all authors

GERD, gastroesophageal reflux disease.

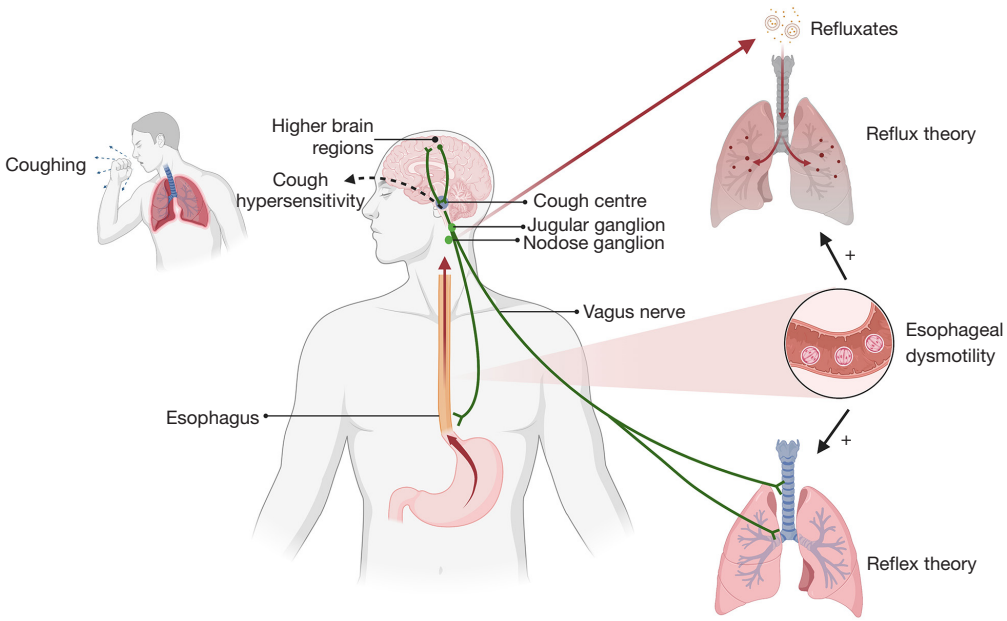

Figure 1 Possible underlying mechanisms of GERD-associated cough. GERD, gastroesophageal reflux disease.

hypersensitivity via the tracheobronchial-esophageal reflex (neuronal pathways that link the airway to the esophagus) as a mirror of esophageal-tracheobronchial reflex (neuronal pathways that link the esophagus to the airway) (*Figure 2*). Our study demonstrated tracheobronchial-esophageal reflex did exist and was mediated by TRPV1 signaling in the guinea pigs with repeated capsaicin inhalation (17). The tracheobronchial-esophageal reflex might provide a plausible explanation for how airway diseases, especially upper respiratory tract infection, initiated the reflux-related cough, thus producing a vicious cough-reflux loop (17).

Diagnosis of GERD-associated cough

Symptom features

Clinical features of patients with GERD-associated cough include diet-related cough (triggered or aggravated by meal), with or without typical reflux-associated symptoms such as regurgitation and heartburn. Moreover, hoarseness, postnasal drip and throat clearing may be a manifestation of reflux laryngitis. Generally, regurgitation and heartburn are present only in less than 60% of patients with GERD-associated cough and are more frequent in acid reflux-

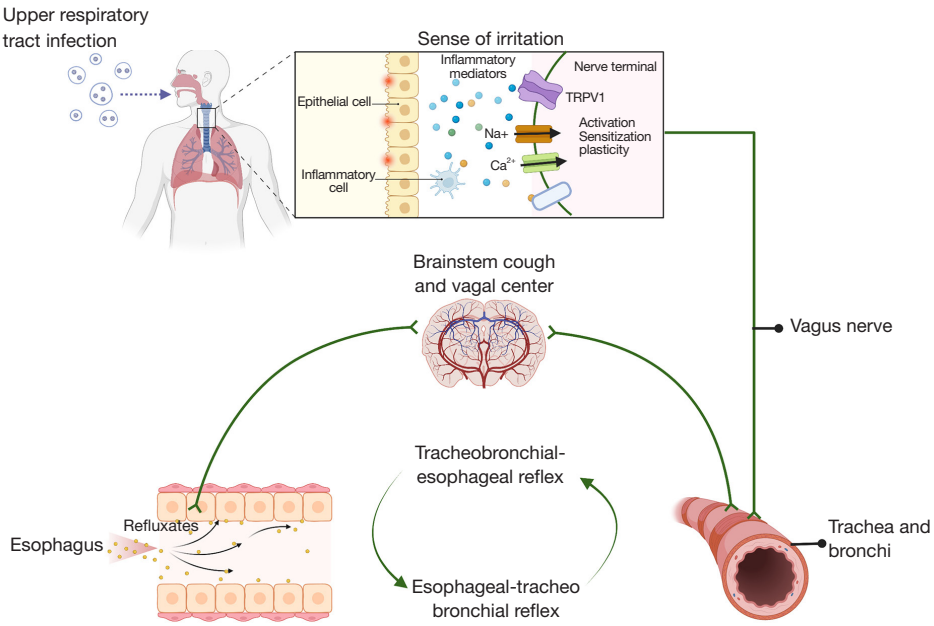

Figure 2 The pathogenic mechanism underlying tracheobronchial-esophageal reflex in GERD-associated cough. The upper respiratory tract infection is likely to induce the irritation by stimulation of inflammatory mediators and activation of sensory nerve endings which innervate the airway walls. Vagal sensory nerve endings within the airway mucosa express a range of receptors for these pro-inflammatory mediators. When these receptors are activated, neuronal ion channels (TRPV1) open, leading to alterations in sensory neuronal activity and a subsequent neural phenotype over time. Vagal sensory neurons input to the brainstem cough centre which connects to the vagal centre (neural crosstalk) and descend to the esophagus mucosa. This may produce esophagus hypersensitivity and the initiation of the cough reflex in response to reflux-mediated irritation by esophageal-tracheobronchial reflex. GERD, gastroesophageal reflux disease; TRPV1, transient receptor potential vanilloid 1.

induced cough (18). Therefore, the absence of classic reflux-associated symptoms is not rare, and it is impossible to rely solely on these symptoms to diagnose GERD-associated cough.

Reflux monitoring

Abnormal reflux and its association with cough are important objective evidence for the diagnosis of GERD-associated cough. Currently, 24-hour ambulatory esophageal pH monitoring and impedance-pH monitoring are recommended as first choice to measure reflux in China (19). When these investigations are unavailable, upper endoscopy and barium esophagography can be alternative options. However, although these two methods have a relatively high specificity in detecting GERD-associated cough, the sensitivity remains quite poor (20).

High resolution manometry is worthy of attention and is now the most useful of the available esophageal manometry techniques due to its ability to describe the anatomy of the esophagus and accurately assesses esophageal peristalsis (3). European Respiratory Society (ERS) guideline for cough management has first advocated its application to the evaluation of GERD-associated cough (5). With this technology, esophageal dysmotility was found in two thirds of patients with chronic cough (11).

Esophageal impedance-pH monitoring is superior to 24-hour ambulatory esophageal pH monitoring. It has the ability to identify both acid and non-acid reflux, provide information on the temporal link between reflux and cough, accurately distinguish reflux from swallowing, precisely locate the height of the reflux reaching the esophagus (proximal and distal reflux) and determine the nature of the reflux (liquid, gas and liquid-gas mixture) (21). Furthermore, impedance-pH monitoring can be performed on or off the use of proton pump inhibitors, and in combination with high resolution manometry to assess the esophageal dysmotility. At present, it has been recommended as the gold

standard for reflux detection by the Lyon Consensus (3). Since there is no general agreement on how to interpret the test of esophageal reflux monitoring in patients with chronic cough, esophageal impedance-pH monitoring is not accepted as a mandatory laboratory investigation for the diagnosis of GERD-associated cough in the international guidelines for the cough management (4,5).

Reflux diagnostic criteria

Diagnostic criteria for reflux usually utilize acid exposure time (AET), symptom associated probability (SAP) and total reflux episodes (3). These impedance-pH variables have individual inherent clinical values in establishing a causal relationship between cough and reflux. AET is defined as total percentage of time that the esophagus is exposed to pH <4.0 throughout monitoring time, with a value of <4% being definitively normal (physiological) and >6% being absolutely abnormal, and the intermediate value between these two limits being indeterminate. SAP reflects the likelihood of the reflux being the cause of coughing, and a value of ≥95% is considered positive. Total reflux episodes represent the total number of refluxes over 24 hours, with a number of >80 times being definitively abnormal, <40 being physiological and the intermediate values being indeterminate (3). In the early years, DeMeester score, a composite algorithmic score of six parameters measuring acid reflux, was commonly used to identify potential pathological esophageal acid exposure and predict response to PPI therapy (22), but now is recommended to be replaced by AET due to its poor repeatability (3,23).

According to the latest Chinese cough guidelines (updated in 2021), the diagnostic criteria for GERD-associated cough include (I) chronic cough, with or without concomitant classic reflux-association symptoms such as regurgitation and heartburn; (II) abnormal acid or non-acid reflux detected by esophageal reflux monitoring, as evidenced by AET >6% or SAP ≥95%; and (III) complete relief or marked improvement of cough in response to anti-reflux treatment (19). It is the only cough guideline worldwide that attempts to set up the clear reflux criteria for the diagnosis of GERD-associated cough. However, the application of the diagnostic criterion is only limited to a few cough research centers across China in real-world clinical practice because esophageal impedance-pH monitoring is expensive and time-consuming, In our cough clinic, approximately 70% of patients with suspected GERD-related cough have undergone esophageal impedance-pH monitoring for the establishment of the diagnosis (8,21), which is much higher than in the other clinics in China and in the other countries where the empirical anti-reflux therapy is used as the preferred mainstream diagnostic approach.

Our previous study has demonstrated that AET has a high sensitivity but low specificity for the prediction of GERD-associated cough, while SAP has a low sensitivity but high specificity (21). AET and SAP have limited diagnostic efficacy when used alone, however, this can be improved greatly by combined use. Overall, the diagnostic value of AET and SAP remains suboptimal (21). Although AET and DeMeester present a comparable diagnostic efficacy and AET is able to replace DeMeester score, AET is not superior to DeMeester score in identifying GERD-associated cough (24). Compared to AET >6%, AET >4.8% appears to be a more optimal cut-off point to predict GERD-associated cough with a higher sensitivity and roughly equivalent specificity (24). Therefore, 6% may be a too stringent cut-off point for diagnosing GERD-associated cough. An optimal pathological AET needs to be sought to further improve its diagnostic accuracy.

There are two methods of imputation for SAP: the first is to count all the recorded reflux-related symptoms which include cough; and the second is to count only the cough symptom. While the former is widely used in the diagnosis of GERD, the latter has only been used for determining the relationship between reflux and chronic cough in several studies (25,26), but has not been applied in clinical practice to identify GERD-associated cough. Our recent study on 105 patients showed that SAP calculated only by cough was superior to SAP involving all the reflux-related symptoms, with the former demonstrating a higher sensitivity and diagnostic accuracy for both acid reflux and non-acid reflux induced cough (27). In contrast, SAP is inferior to AET in terms of diagnostic efficacy, but is particularly suitable for predicting GERD-associated cough with obvious non-acid reflux or without abnormal acid reflux.

Our previous study also demonstrated a limited predictive value of the total reflux episodes in GERD-associated cough, with the cut-off point >97 times (28). Mean nocturnal baseline impedance and post-reflux swallow-induced peristaltic wave index have demonstrated the ability to enhance the diagnostic yield of impedance-pH monitoring in GERD-associated cough as well (29).

The summary of reflux diagnostic criteria for GERD-associated cough can be seen in *Table 2*.

Table 2 Summary of reflux diagnostic criteria for GERD-associated cough

Diagnostic indicator	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	References
AET	6%	0.613–0.768	42.5–63.2	63.6–93.0	(21,24,29)
	4.8%	0.827	73.3	88.4	(24)
SAP[a]	95%	0.561–0.714	22.1–25.7	87.8–100	(21,24)
SAP[b]	95%	0.757	53.9	97.5	(27)
Total reflux episodes	97	0.684	46.6	83.1	(28)
DeMeester score	14.7	0.818	70.0	89.6	(24)
AET and SAP	6%, 95%	0.863	92.6	63.6	(21)
DeMeester score and AET	14.7, 4.8	0.809	72.7	75.3	(24)
MNBI	2,292 Ω	0.748	65.0	75.5	(29)
PSWI index	61%	0.732	79.3	87.5	(29)

[a], SAP involving all the reflux-related symptoms; [b], SAP calculated only by cough. GERD, gastroesophageal reflux disease; AUC, area under the curve; AET, acid exposure time; SAP, symptom associated probability; MNBI, mean nocturnal baseline impedance; PSWI, post-reflux swallow-induced peristaltic wave.

Treatment of GERD-associated cough

The aim of treatment for GERD-associated cough is to relieve cough symptoms and improve the patients` quality of life by minimizing reflux episodes and eliminating the factors precipitating reflux (2). Relief of cough that responds to anti-reflux therapy is a key outcome to definitely confirm the diagnosis of GERD-associated cough (*Table 3*).

Lifestyle modification

Lifestyle modifications are essential for the long-term management of GERD-associated cough, which include weight loss for patients who are overweight or have recently gained weight, quitting smoking and alcohol, and avoiding foods or drugs which may trigger or aggravate reflux (30). Head elevation during sleep may also reduce reflux (31), but whether it can improve GERD-associated cough remains to be proven.

Anti-reflux medicinal treatment

Several studies have confirmed that acid suppressive therapy can significantly reduce the damage and irritation of the esophagus and airway mucosa from gastric acid and pepsin in the refluxates, and alleviate cough by inhibiting micro-aspiration and esophageal-tracheobronchial reflex (2,4). Proton pump inhibitors are the first choice since they potently block the secretion of gastric acid and provide rapid relief of reflux-associated symptoms, such as cough (30). However, the antitussive efficacy of proton pump inhibitors on GERD-associated cough is inconsistent between clinical observations and randomized clinical trials (40,41). Meta-analysis also showed that proton pump inhibitors have not been universally beneficial for GERD-associated cough (32) and only work in some patients with pathologic esophageal acid exposure (33). Therefore, the overall benefits of proton pump inhibitors have been controversial (34). The latest American College of Chest Physicians (ACCP) and ERS guidelines for cough management did not recommend the universal use of proton pump inhibitors to treat GERD-associated cough. Proton pump inhibitors have been considered only suitable for patients with typical reflux-related symptoms (e.g., regurgitation and heartburn) or with the subjective evidence of abnormal acid reflux. However, their therapeutic benefits may also be limited (4,5). In contrast, the updated Chinese, Japanese and Korean guidelines for the management of cough advocated acid suppression therapy as the first-line treatment for GERD-associated cough (19,42,43). Since all the guidelines for GERD have recommended anti-acid therapy as the primary treatment (30), it is difficult to understand why proton pump inhibitors are ineffective for GERD-associated cough (34). Even for cough due to weakly acidic reflux, a slight increase in the pH value of refluxates in response to a trial of proton pump inhibitors may significantly reduce the acid signaling in the hypersensitive esophagus and

Table 3 Evaluation of therapeutic options for GERD-associated cough

Treatment	Patient selection	Representatives	Outcomes	Side effects
Lifestyle modification	Overweight, unhealthy eating and lifestyle habits	Healthy eating and living, head elevation (30,31)	Unclear	N/A
Medicinal treatment				
PPI	Typical reflux-related symptoms or abnormal acid reflux	Omeprazole, rabeprazole, esomeprazole	Controversial; benefits 10–70% of cough patients (32,33)	No available data
Prokinetics	Esophageal dysmotility and impaired gastric emptying	Metoclopramide, domperidone and mosapride	Lack of sufficient evidence for cough patients; when added to PPI, may be effective (34)	No available data
Double dose of PPI	Refractory GERD-associated cough, severe esophageal acid exposure	Omeprazole, rabeprazole, esomeprazole	Cough controlled in 20–40% of patients (35)	No available data
Neuromodulators	Refractory GERD-associated cough	Baclofen, gabapentin	50–70% of success rates for cough patients (36-38)	Central nervous system-related side effects (somnolence, dizziness, fatigue)
Anti-reflux surgery	Refractory GERD-associated cough	laparoscopic fundoplication	Cough resolved in 85% of patients (39)	Complications (dysphagia, dyspepsia, reflux esophagitis)

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; N/A, not applicable.

relieve cough (12). Ideally, the first-best option for GERD-associated cough is to minimize the excessive reflux burden by rebuilding normal anti-reflux barrier. Therefore, acid suppressive therapy is currently the second-best option because the structural and functional abnormalities of the lower esophageal sphincter and esophagogastric junction do not get treated (34). The failed response to proton pump inhibitors should not rule out the possibility that patient's cough is triggered by reflux.

There is no clear consensus regarding the course of acid suppressive therapy, with little evidence on the optimal duration of treatment for GERD-associated cough. Generally, a trial of proton pump inhibitor for 8–12 weeks is recommended to define extraesophageal GERD symptoms (30). In our practice, we usually shorten the duration of treatment to 4–8 weeks for suspected GERD-associated cough. Since a variety of conditions other than GERD can also produce a cough, a prolonged anti-reflux trial may delay the diagnosis and treatment of the true cause (18,21). If the initial trial could provide cough resolution, a further 3–6 months' supply can be given. The treatment can be maintained indefinitely or used as needed afterwards, depending on the relapse and persistence of cough symptoms (30).

Prokinetics should be a reasonable option of anti-reflux medicinal therapy since they increase the pressure of lower esophageal sphincter and promote gastric emptying. However, there is no evidence currently to show that metoclopramide, domperidone and mosapride can alleviate GERD-associated cough. Prokinetics are usually used in combination with antacids, and are especially indicated in patients with esophageal dysmotility and impaired gastric emptying (5,34).

For the refractory GERD-associated cough, intensified anti-reflux medicinal therapy such as the double dose of proton pump inhibitors or neuromodulators can be tried (35). Besides the adjustments in dosage and brand, the optimization of proton pump inhibitor therapy also includes ensuring good compliance and correct usage, such as taking the drugs 30–60 minutes before meals, switching to a different proton pump inhibitor and co-administration with a histamine H2 receptor antagonist (35). This proved effective in the management of refractory GERD-associated cough (44). The other antiacids, such as novel potassium-competitive acid blockers and alginates, have the potential to achieve effective and durable acid suppression as well, thus addressing the specific therapeutic needs of GERD patients (30). Although there is a wealth of available data

on the intractable GERD, studies on refractory GERD-associated cough are absolutely lacking. Baclofen and gabapentin are the neuromodulators commonly off-label used for cough, but they do not work perfectly (45). Theoretically, baclofen should be superior to gabapentin since it inhibits the transient relaxation of the lower esophageal sphincter and blocks both acid and non-acid reflux in addition to having a comparable antitussive effect to gabapentin (45). However, our previous study showed that as the add-on therapy of omeprazole, baclofen and gabapentin achieved a similar therapeutic success in 53–58% of patients with refractory GERD-associated cough, but gabapentin had fewer central nervous system-related side effects and was more tolerable than baclofen (36). Given the failure of the treatment with baclofen or gabapentin in approximately 40% of patients with refractory GERD-associated cough and the limitations of frequent central nervous system-related side effects, it is of great clinical value to find a way to screen patients most likely to respond to baclofen and gabapentin to improve the success rates to avoid drug abuse or minimize potential adverse effects. Our previous studies have demonstrated that the pressure (less than 11 mmHg) and length (less than 2.35 cm) of lower esophageal sphincter measured by esophageal manometry are useful indicators to predict the therapeutic success of baclofen treatment, while Hull airway reflux questionnaire score (more than 21.5) is a promising tool to predict a more favorable response to gabapentin treatment in patients with refractory GERD-associated cough (37,38).

Anti-reflux surgery

Anti-reflux surgery removes abnormal gastroesophageal reflux by artificially rebuilding the mechanical barrier at the gastro-esophageal junction, and may be a promising approach for refractory GERD-associated cough (4). As a commonly used anti-reflux operation, laparoscopic fundoplication can resolve coughing in 85% of patients who undergo this treatment (39). Given its invasive nature and the fact that efficacy cannot be guaranteed if GERD-associated cough is not definitively established, strict surgical indications are required. The following criteria may be useful in patient selection: patients who have (I) a clear diagnosis of GERD-associated cough and responded well to anti-reflux agents, but do not wish to be on long-term medications and would like the anti-reflux surgery; (II) failed anti-reflux trials, but have objective evidence of abnormal reflux which is associated with cough, as indicated by various laboratory investigations such as esophageal impedance-pH monitoring; (III) no peristaltic dysfunction of the esophagus (4,19).

Conclusions

Tracheobronchial-esophageal reflex might initiate reflux-induced cough provoked by the upper respiratory tract infection through a central crosstalk between the neural pathways linking the airway and esophagus in a manner similar but opposite to esophageal-tracheobronchial reflex. Esophageal reflux monitoring provides the main diagnostic criteria for GERD-associated cough. AET and SAP have demonstrated significant diagnostic efficiency as reflux diagnostic parameters, but they are not yet perfect and far from being the gold standard. It is necessary to optimize the current standards and explore new criteria with higher diagnostic potency. Acid suppressive therapy is the first choice for GERD-associated cough but needs further evaluation. Neuromodulators may be potential therapeutic options for refractory GERD-associated cough, for which anti-reflux surgery may be also a promising treatment option.

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Footnote

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