

Clinical review

Extraesophageal Manifestations of Gastroesophageal Reflux Disease

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Gastroesophageal reflux is frequently viewed as a "nuisance" problem that affects a large number of individuals with variable frequency. When physicians conceptualize the complications of gastrointestinal reflux, they generally consider them a localized esophageal problem resulting in irritation of the esophagus, bleeding esophagitis, occasional stricture formation, and the development of Barrett's esophagus. However, attention has again been focused on the potential relationship between gastroesophageal reflux and pulmonary diseases (cough, asthma, recurrent pneumonia), chest pain, and hypopharyngeal or oral disease. This paper reviews our current understanding of the extraesophageal manifestations of gastroesophageal reflux.

INTRODUCTION

Gastroesophageal reflux (GER) is defined as the movement of gastric contents into the esophagus. This material, which may contain acid, pepsin, bile acids, and pancreatic enzymes, has the ability to irritate or injure tissues not adapted to the presence of this potentially noxious material. Since reflux may proceed more proximal than the esophagus, other tissues may be affected. Both clinical and experimental data have demonstrated that these events may lead to a variety of esophageal, head and neck, and pulmonary complications, as well as chest pain, although the exact frequency of these events is not clearly established. To begin to understand these conditions, we must start with definitions. One method of classifying reflux, shown in Table 1, serves as a starting point for understanding these processes.

It has become increasingly clear, using 24-h pH monitoring, that virtually all normal individuals have regular episodes of reflux as part of normal digestion, occurring postprandially in the upright position (physiologic reflux) (1-3). This reflux represents transient

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exposure with limited contact time to the esophageal mucosa. The degree of reflux may be increased with belching or with the ingestion of a fatty meal (4, 5). Many individuals have "heartburn" or symptomatic gastroesophageal reflux (SGER) without any evidence of esophageal or extraesophageal "disease" (6). Acid sensitivity of the esophagus without esophagitis, as manifested by heartburn, is extremely common. In addition, reflux may be the most prevalent cause of noncardiac chest pain, more common than esophageal motility disorders (7). Conversely, pathological reflux leading to esophageal and/or extraesophageal manifestations with tissue injury may occur with or without pain or the sensation of heartburn (8, 9). Actual disease due to gastroesophageal reflux [gastroesophageal reflux disease (GERD)] occurs in a minority of individuals and should be documented either through direct evaluation of the esophageal mucosa or by establishing a connection between episodes of reflux and the presence of extraesophageal disorders.

GASTROESOPHAGEAL REFLUX DISEASE

Disease due to reflux is best understood in the esophagus itself, where symptoms are well recognized and where the correlation between an illness and a reflux event is anatomically logical. This association has been corroborated by information obtained through 24-h esophageal pH monitoring (10, 11). Although literature exists suggesting the association between reflux and diseases outside the esophagus, all too often physicians do not make this potential connection when evaluating patients. This review will therefore be directed toward those extraesophageal manifestations of GERD that are now being rediscovered.

Esophageal

The esophageal manifestations of GERD are those caused by the contact of gastric contents with esopha-

TABLE I
Classification of Gastroesophageal Reflux

Physiologic gastroesophageal reflux
Symptomatic gastroesophageal reflux (SGER)
Gastroesophageal reflux disease (GERD)

geal mucosa. The results of acid contact to the esophagus are highly variable. Many individuals experience symptoms, classically heartburn, when acid is present in the esophagus. Others, for reasons that are not clearly understood, but probably represent a combination of aggressive factors (*e.g.*, concentration of acid, contact time) and defensive factors (*e.g.*, esophageal sensitivity, epithelial integrity, epithelial growth factor), may develop complications ranging from acute esophagitis with bleeding and odynophagia to chronic peptic stricture, and even Barrett's esophagus with its risk of adenocarcinoma. Many of these individuals are not aware of the presence of refluxed gastric contents, even with the development of the most severe forms of esophageal injury (*e.g.*, as many as one-third of Barrett's patients are not aware of reflux symptoms).

Extraesophageal

The effects of refluxed gastric contents may extend beyond the esophagus itself, and may include a number of remote manifestations through anatomic or neural connections to the esophagus (Fig. 1). Osler (12), in his 1892 text, noted the risk of asthma in the overfilled stomach. Since then, the association between reflux and episodes of asthma has been documented in the pediatric and adult literature (13-17). Likewise, recurrent pneumonia or "dysphagia pneumonitis" (18), a term coined in 1949, has long been known to be a complication of obstructing esophageal processes such as carcinoma or achalasia. Over the last 30 yr, the pediatric and adult literature have gradually recognized reflux without structural or functional esophageal obstruction as being responsible for recurrent pneumonia in some patients (19-27). At our current level of understanding, the extraesophageal manifestations of GERD can be divided into gastropulmonary reflux, chest pain, cardiac complications, and head and neck manifestations.

Gastropulmonary reflux. Lung and airway involvement during reflux may take several forms, including pneumonia, chronic cough, interstitial fibrosis, and asthma. Indeed, pulmonary complications may be the presenting symptom in GERD (2).

Recurrent lung injury and pneumonia in GER may result from direct contact with the caustic refluxed gastric contents (acid and pepsin), and possibly aspirated gastric, esophageal, or pharyngeal bacteria. The frequency of dysphagia pneumonitis due to reflux without obstruction has not yet been defined (27), although, with improvement in the techniques of radionuclide

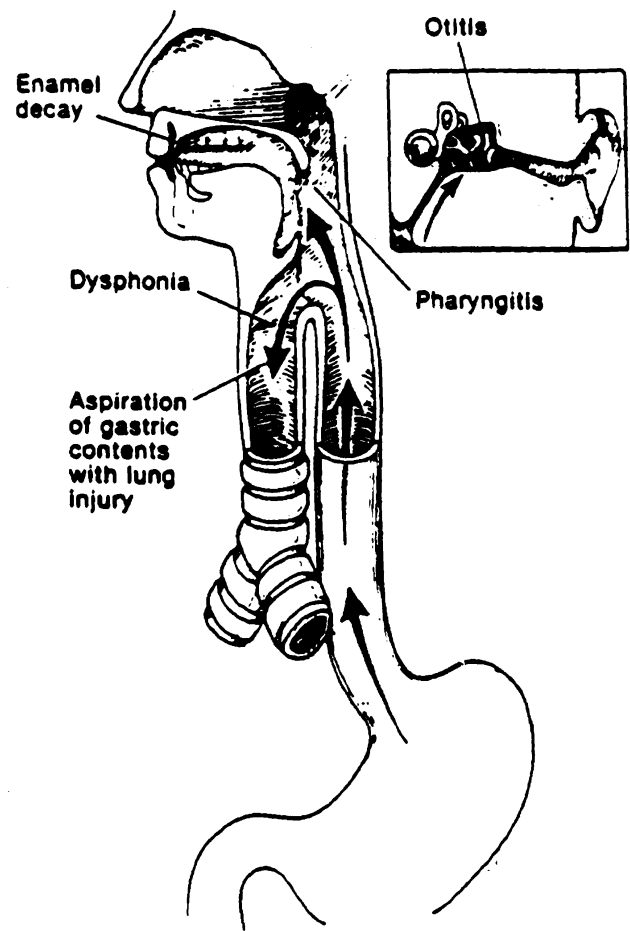


FIG. 1. A summary of extraesophageal manifestations of GER. Aspiration of gastric contents may result in chronic dysphonia and a number of forms of pulmonary injury. Oropharyngeal contact with gastric contents may result in enamel loss, otitis, and pharyngitis.

reflux scanning and dual-probe 24-h pH monitoring, this complication of GERD is more amenable to study. Such studies should be included in patients with appropriate clinical indications.

There is a small body of data to suggest a relationship between GERD and chronic interstitial lung disease. While this has been documented in humans by individual case reports, animal experiments have, in fact, shown that reflux may lead to pulmonary interstitial fibrosis (28-30). This association in humans has been supported by Johnson *et al.* (31), who studied 13 patients with progressive systemic sclerosis (scleroderma) a disorder known to be associated with esophageal reflux and interstitial lung disease. Eleven of these 13 patients had proximal esophageal reflux and interstitial lung disease, and a distinct correlation was found between the degree of esophageal reflux and the severity of pulmonary fibrosis as assessed by decreased carbon monoxide diffusion capacity. Although a causative link cannot be firmly established, there are certainly grounds for further investigation.

Perhaps the most actively studied pulmonary complication of GERD is asthma and/or chronic cough. There are two postulated mechanisms that would lead to these reflux-induced symptoms. One mechanism may be microaspiration of gastric contents resulting in bronchial irritation, wheezing, and coughing. Aspiration of gastric contents has been demonstrated by radio-nuclide scans in patients with GERD, and may be more predictive of favorable asthmatic response to ranitidine than 24-h pH monitoring (32). In this situation, asthma and cough may occur independently, or the cough may be the result of asthmatic bronchospasm. However, asthma and/or coughing during reflux without microaspiration is probably mediated through reflex mechanisms (2, 15) (Fig. 2). Wright (33) recently reported the response of airway resistance and oxygen saturation to intraesophageal acid infusion in 108 patients. Arterial oxygen saturation and 1-s forced expiratory volumes were significantly reduced during esophageal acid infusion, suggesting a reflexive increase in airway resistance and, presumably, a tendency toward asthma. The response of asthmatics to anticholinergics (e.g., atropine) may be related to this phenomenon. Chronic cough may be a manifestation of GERD, not only because of aspirated gastric contents, but because of the existence of what has been called the "esophageal ptussive center" (15). Cough resulting from esophageal irritation without actual pulmonary aspiration would presumably be mediated through a reflex arc using vagal afferents and efferents with the esophagus initiating the "sensory" limb of the reflex (2, 15). A "vicious cycle" could be postulated in which reflux leads to cough which, by increasing abdominal pressure, produces more reflux. Even though the two mechanisms (microaspiration and esophageal reflux) may coexist in any individual, it appears that actual aspiration of gastric contents is not required for the precipitation of bronchospasm and/or chronic cough.

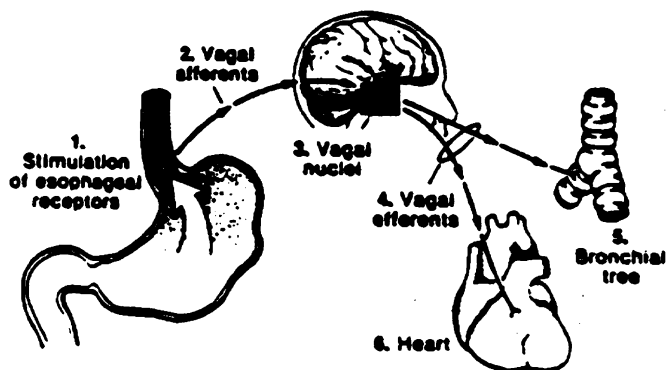


FIG. 2. A postulated mechanism of reflex cardiac and pulmonary response to GER. An esophageal "receptor" (1) senses refluxed gastric material and initiates a reflex arc with vagal afferents (2), vagal nuclei (3), and vagal efferents (4). The effects on the bronchial tree (5) may result in reflex coughing or bronchospasm. The effects on the heart (6) may lead to angina-like symptoms or arrhythmias.

Asthmatics treated with bronchodilators may decrease the lower esophageal sphincter pressure and encourage reflux (34, 35). Cimetidine has been shown to be beneficial in some patients with asthma, presumably by reducing the quantity or potency of refluxed acid (36, 37). Sontag *et al.* (16) recently published the results of antireflux surgery in 13 asthmatics with symptoms refractory to histamine 2 receptor antagonists. Six patients were relieved of all symptoms and were able to stop all bronchodilators, while six others had a marked reduction in symptoms and bronchodilator dose.

It would appear then that, in patients with refractory asthma, recurrent pneumonia, or chronic cough, an evaluation for reflux would be prudent, if not mandatory, especially in situations in which symptoms are poorly responsive to therapy. When a relationship between GER and pulmonary disease is found, antireflux surgery should be strongly considered, given the chronic nature of reflux and the fact that complete elimination of reflux is rarely accomplished with medical therapy alone.

Chest pain manifestations. By definition, symptomatic gastroesophageal reflux (SGER) is manifested by heartburn, the major symptom associated with reflux (1). However, it is becoming increasingly well documented that chest pain indistinguishable from angina may be of esophageal origin (38-40). Indeed, it is now known that reflux, rather than primary esophageal motility disorders, is probably the most common cause of noncardiac chest pain (7, 41). Attempts have been made to isolate patients with reflux-induced chest pain by defining certain symptom characteristics (8, 42, 43), but with the advent of 24-h pH monitoring, the ability to collect direct pathophysiological data has been substantially improved (7, 41, 44). Mellow *et al.* (40) demonstrated the onset of typical angina in patients with established coronary artery disease and a known abnormal rate pressure product (RPP) while having Bernstein testing. The postulated mechanism was a neurally mediated reflex vasoconstriction or increased sympathetic tone initiated by esophageal irritation.

Recently, however, evidence of changes in cardiac microvascular flow during esophageal stimulation has caused this area to be reexamined (45-47). Ducrotte *et al.* (45) demonstrated an association between esophageal motor disorders and an increase in coronary sinus lactate during esophageal provocative testing, in spite of normal coronary arteriograms. Cattau *et al.* (47) have also reported the coexistence of microvascular angina (as evidenced by a paradoxical increase in cardiac vascular bed resistance during overdrive pacing) and esophageal motility disorders. It is not clear whether these findings represent coincidental esophageal and cardiac disease, an esophageal/cardiac reflex, or an overlying neural or smooth muscle disorder that becomes manifest in both the esophagus and the cardiac

circulation. The possibility that GER might trigger these same events has yet to be confirmed.

Cardiac complications. A variety of interrelationships between GER and cardiac events has been demonstrated, in addition to those cited above. These may be mediated through vagal pathways (Fig. 2). The pediatric literature reveals an association in children between gastroesophageal reflux and bradycardia (48) which has been implicated as one possible cause of sudden infant death syndrome (49, 50). Axelrod *et al.* (51) reported the case of a patient with familial dysautonomia who displayed reflux-induced bradycardia and became asymptomatic after fundoplication. Wright (33) has reported bradycardia in adults during esophageal acid infusion. It appears, therefore, that gastroesophageal reflux in patients with poorly developed autonomic control (neonates and patients with familial dysautonomia) may lead to profound bradycardia. Further evidence for the connection between esophageal stimulation and vagal reflexes can be found in the syndrome of "swallow syncope" (52, 53). In this disorder, swallowing or pharyngoesophageal stimulation can lead to profound, even lethal, bradycardia, presumably through a vagal mechanism. We have observed one such patient whose syncope required a pacemaker. During intraesophageal balloon distension, her EKG would reflect a conversion from 100% sinus rhythm to 100% paced rhythm. This change totally reversed with balloon deflation. Rarely, patients in our laboratory have demonstrated a variety of tachyarrhythmias or conduction defects during esophageal provocation (acid, drugs, and/or balloon distention) that reversed at the end of the stimulus. It is open to speculation as to whether or not there exists a more subtle cardiac response to reflux in patients with an unsuspected subclinical autonomic disorder.

Head and neck manifestations. Although the organ primarily damaged in GER is the esophagus, reflux-induced pulmonary aspiration disease implies that contiguous organs may also be affected. It is that concept that has brought diseases of the head and neck under closer scrutiny in search of a reflux etiology. Bain *et al.* (54) implicated GERD as being associated with sore throat, hoarseness, dental injury, and possible otitis media. Steigman *et al.* (55) reported that these symptoms may be present in 5.8% of GERD patients and may be the presenting symptom of GERD. Other authors have supported the association of reflux with head and neck symptoms (42, 56). However, the correlation between the severity of symptoms and the degree of reflux found during 24-h pH monitoring (using a dual esophageal probe, with one lead proximal and one distal) has been weak. Baldi *et al.* (8) noted that 83% of proximal reflux episodes were asymptomatic, although 70% of symptomatic episodes were associated with reflux. Katz *et al.* (57) evaluated nine patients with

chronic dysphonia, using dual probe 24-h pH monitoring. They demonstrated proximal reflux in most of these patients, especially upright reflux, and commented on the necessity of using a proximal pH probe when evaluating for head and neck symptoms. It appears, therefore, that there is a positive association between reflux and some head and neck diseases. Evaluation of a causative relationship between head and neck symptoms and contact peptic irritation remains a fertile area of clinical research. The technology to facilitate these evaluations exists, and hopefully will clarify the issue in the near future.

SUMMARY

Whereas the esophagus is the primary target of injury in GER, any contiguous structure can be affected due to the direct contact of gastric irritants or due to neurally mediated mechanisms. Reflux may result in chronic cough, aspiration pneumonia, and perhaps chronic interstitial lung disease. It may also produce disease of the head and neck, presumably by bathing these structures with gastric contents. However, it appears that some manifestations of GER, most notably bradycardia and asthma, may be reflex mediated through some specific esophageal receptors. The expanding use of new diagnostic technologies should provide future clarification of pathophysiology and, perhaps, direct successful therapy. In an individual with unexplained symptoms in areas proximal to the esophagus, gastroesophageal reflux should be considered, even if "classic" symptoms of reflux are not present.

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