Sleep and the Gastrointestinal System

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Sleep Related Changes in Upper Gastrointestinal Physiology

Sleep has a profound influence on the physiology of upper gastrointestinal tract and these state-dependent dynamic changes lead to marked alteration of esophageal and gastric function. There is reduction in upper esophageal sphincter pressure, decreasing from 40 mm during wakefulness to 10 mm with sleep onset [1]. The circadian rhythm of basal gastric acid secretion peaks between 8.00 pm and 1.00 am [2]. Sleep disrupts gastroenteric function leading to delayed gastric emptying [3]. There is a marked decrease in swallowing during sleep (an average of 2 swallows per hour during total sleep time) with almost no deglutition during stages 3 and 4 [4, 5]. Along with decreased deglutition frequency during sleep, saliva production was found to be essentially absent [4, 6]. Normal saliva production and deglutition are vital mechanisms in the process of esophageal acid clearance, a pivotal defense mechanism against the development of GERD-related symptoms and inflammation. Thus, sleep hinders the normal clearance mechanisms and leads to prolonged acid clearance time [7]. A summary of these changes is listed below.

Sleep related changes in upper gastrointestinal physiology
Fall in upper esophageal sphincter tone
Reduced swallow frequency
Decreased salivary secretion
Prolonged acid clearance time
Delayed gastric emptying

Sleep and Gastroesophageal Reflux: Sleep Is a Vulnerable State for GERD

Gastroesophageal reflux (GER), the retrograde passage of gastric contents into the esophagus, is a normal physiologic process that occurs in all age groups. The main protective barrier for GER is the lower esophageal sphincter (LES), which consists of a 2–4 cm high-pressure zone at the level of the gastroesophageal junction. The LES operates as a dual sphincter mechanism consisting of a ring of thickened circular muscle and the diaphragmatic crura. The LES receives cholinergic innervation and the crural diaphragm receives bilateral phrenic nerve innervation. The occurrence of a vagally mediated and transient LES relaxation (TLESR) constitutes the primary mechanism for GER; these TLESRs events are brief, are not related to weak lower esophageal sphincter pressure, and occur independent of swallowing [8]. Esophageal clearance factors are important defensive mechanisms that neutralize the acid refluxate and minimize acid exposure to esophageal and extra-esophageal structures. These include salivation and primary peristaltic contractions triggered by saliva-stimulated swallowing. In addition, salivary bicarbonate also neutralizes the acid refluxate [9]. When awake, GER is most likely to happen in the post prandial period when there is abdominal distention and TLESR. These episodes are short and are rapidly cleared as the acid mucosal contact enhances salivary flow also stimulates a higher frequency of swallowing. However, the swallow frequency and salivary production are almost nonexistent during stable sleep [4, 5], and sleep related reflux events will occur predominantly during arousals and awakenings and, if recurrent in sufficient frequency, can lead to mucosal injury as a result of impaired clearance mechanisms.

A pediatric based survey has estimated that vomiting, a common symptom GER, occurs in 50% of infants in the first 3 months of life, in 6% of 4-month-old infants, and in 5% of 10–12 month old infants [10, 11]. Most episodes of GER last <3 minutes, occur in the postprandial period, and cause few or no symptoms. However, a subset of children develops

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pathologic gastroesophageal reflux disease (GERD) which is associated with plethora of gastrointestinal and extra gastrointestinal symptoms. These symptoms include feeding difficulties, failure to thrive, heartburn/chest pain, dystonic posturing, and recurrent respiratory symptoms of coughing, stridor, and wheezing. The estimated prevalence of GERD in infants 0–23 months, children 2–11 years old, and adolescents 12–17 years old is 2.2–12.6%, 0.6–4.1%, and 0.8–7.6%, respectively [12, 13]. It is important to realize that in healthy persons, sleep is relatively free of GER events.

However, given the dynamic changes in sleep as they relate to alteration in clearance mechanisms, it is not surprising that many patients experience frequent nighttime symptoms of regurgitation, heart burn, insomnia, and poor quality of sleep. These symptoms cumulatively grouped as a distinct diagnostic entity as "Sleep Related Gastroesophageal Reflux" in International Classification of Sleep Disorders (ICSD) [14]. Essential features of this diagnosis include heartburn, substernal burning, chest discomfort, coughing, choking, or unexplained excessive day time sleepiness, even in the absence of typical reflux symptoms. Sleep related GER is also associated with sleep onset and sleep maintenance insomnia, early morning awakenings, sleep disturbances, arousals, unrefreshing sleep, daytime dysfunction. A national random sample telephone survey to estimate the prevalence of frequent GERD and nocturnal GERD concluded that over all prevalence of frequent GERD was 14% and nocturnal GERD was 10%. Seventy four percent of those with frequent GERD symptoms reported nocturnal GERD symptoms [15]. Similarly, in a Gallup survey of 100 adults conducted on behalf of the American Gastroenterological association, 79% respondents had nighttime symptoms and 40% reported that these nighttime symptoms diminished their ability to function well the next day [16]. Despite the fact that GERD is common in children of all ages, the exact prevalence of nighttime symptoms and sleep disturbance in children has not been well studied, and there is paucity of information and minimal research on the bidirectional relationships of GERD and sleep in pediatric population. Indeed, the recently published clinical practice guidelines on Pediatric Gastroesophageal reflux did not specify any sleep-related symptoms [17]. A questionnaire-based study identified infants and young children with pathologic reflux, compared with population norms, as having a greater prevalence of nighttime awakenings, delayed onset of sleep during the night, and greater prevalence of daytime sleep [18]. Another large-scale cross-sectional study on Japanese junior high school students found that problem behaviors in adolescents are associated with some sleep problems, including sleep bruxism, as well as several lifestyle and food habits and GERD symptoms [19]. In another study of snoring obese children without evidence of OSA, simultaneously performed polysomnographic and MII-pH studies concluded that acid GER caused increased arousals and awakenings sleep interruptions [20]. Assessing the impact of GERD treatment in improving the sleep quality in adolescents, 8 weeks of esomeprazole improved the sleep dysfunction domains of quality of life in a prospective randomized controlled study [21].

GERD and OSA: Bidirectional Relationship?

In patients with obstructive sleep apnea, the increased collapsibility of the upper airway leads to progressive increases in respiratory effort during periods of heightened upper airway resistance, thereby generating very large intrathoracic pressure swings. Such intrathoracic pressure swings may promote reflux of gastric contents into the distal esophagus. With the impaired clearance mechanisms that characterize the sleep state, such reflux episodes can be prolonged, leading to increased mucosal damage and thus symptoms of esophagitis. Such effects can be compounded by the supine position during sleep, and these effects can be further multiplied by the concurrent presence of obesity, a common co-morbid condition in patients with obstructive sleep apnea. Thus, from a physiological perspective, it is natural to assume that three pathophysiological consequences in the relationship with GERD and OSA are present, namely a) gastroesophageal reflux is estimated to occur with higher degree of prevalence in patients with obstructive sleep apnea, b) there will be temporal relationship between respiratory events and reflux parameters, and c) the severity of OSA will correlate with the severity of GERD.

The frequency of nocturnal GER in adult patients with obstructive sleep apnea ranges from 54% to 76%, and application of nasal CPAP resulted in marked improvement of nocturnal GER [22]. One study found that five of six patients with OSA who underwent pH monitoring had markedly abnormal nocturnal GER, and that application of CPAP reduced GER frequency [23]. Graf and coworkers found that 11 of 17 patients with OSA had abnormal GER but failed to establish a temporal relationship, as well as any other relation between GER and the severity of OSA [24]. In addition to these small studies, Ing and colleagues compared nighttime pH monitoring results in patients with AHI <5/ hrTST ($n = 41$) to those with and AHI index >15 /hrTST ($n = 63$). Patients with AHI >15 /hrTST experienced more GER events, and nasal CPAP reduced GER in both groups suggesting a nonspecific effect [25]. Additionally, CPAP reduced the mean duration of reflux episodes, as well as the total percentage time of reflux in six non OSA patients with GER, further confirming the non-specific effect of CPAP in reducing nocturnal GER [26]. Unfortunately, few studies are available in children on this specific issue. In a small sample of otherwise healthy children referred to sleep laboratory to

rule out OSA, a high prevalence of GER was observed in children with OSA [27]. In addition, and similar to the aforementioned studies in adult patients, no time-based or severity-based relationships emerged between OSA events and reflux episodes [27]. In another small series of 18 children with obstructive sleep apnea, gastroesophageal reflux was frequent and occurred in 41% children. However, no temporal relationship was observed between the respiratory events and reflux events and furthermore, there was no correlation between the severity of OSA and the presence and severity of GERD [28].

Laryngopharyngeal Reflux: LPR

Extraesophageal symptoms are common in patients with GERD. The principal protective barrier for the prevention of extraesophageal reflux is the Upper Esophageal Sphincter (UES), a zone of high pressure that includes the cricopharyngeus muscle. Due to sleep related changes in the decrease of upper esophageal sphincter tone in combination with prolonged clearance time, sleep state may promote proximal retrograde migration of gastric contents breaching the UES with the resultant pharyngolaryngeal injury. Recent studies in adults have identified that the etiology, pathogenesis, clinical manifestations, and the treatment of these symptoms are indeed unique, and significantly differs from conventional GERD, being actually viewed as a variant. Thus, the term LPR (laryngopharyngeal reflux) has been coined to describe this separate entity, and the abundance of publications in the recent literature justifies its consideration and discussion [29]. Indeed, while GERD represents the digestive manifestations of the disease, LPR represents the upper airway manifestations of this disease process. Hoarseness, dysphonia, sore throat, and dysphagia are common symptoms. Although GERD symptoms can be present in patients with LPR, symptoms related to LPR are exclusively extraesophageal, predominantly laryngopharyngeal in majority of cases, with no associated GI symptoms [30].

Although extraesophageal reflux and its associated laryngopharyngeal symptoms are well characterized in adults, recent reports seem to indicate that a similar presentation spectrum also occurs in children. Indeed, chronic rhinitis and rhinosinusitis and laryngeal disorders have been reported in children associated with laryngopharyngeal reflux [31]. Furthermore, an increased prevalence of GER has been associated with the presence of increased risk for adenoidal hypertrophy in young children [32]. This association strongly supports the role of chronic chemical irritation and ensuing inflammation resulting from GERD and promoting lymphoid hyperplasia in the upper airway, thus contributing to adenotonsillar hypertrophy. The putative role of extraesophageal reflux as a cause of adenotonsillar hypertrophy leading to OSA has been highlighted by a recent publication of a case report. A 7-year-old child with adenotonsillar hypertrophy and OSA had severe GERD confirmed by 24 hr. pH probe monitoring. This patient also had an endoscopically confirmed diagnosis of laryngopharyngeal reflux (Fig. 8.1). The adenotonsillar hypertrophy and laryngeal changes improved significantly with acid suppression therapy, and such changes were also associated with ameliorations in overnight polysomnographic findings [33]. Intuitively, one can propose that a subset of patients with OSA is likely to present with LPR, and that appropriate treatment of LPR may decrease the severity of OSA. Given that the treatment for OSA in children is surgical, it is imperative to look for evidence of GERD in general, and LPR in particular, in an effort to minimize the need for invasive surgical treatments.

While the diagnosis of GERD is based on well-established criteria based on 24 hr. pH probe monitoring, similar criteria are not present for defining LPR, and the diagnosis is often challenging and based on empirical assumptions, usually by incorporating the symptoms and upper airway endoscopic findings. Endoscopic abnormalities are often localized in regions of the larynx, particularly involving the posterior laryngeal wall, the arytenoid cartilages, interarytenoid areas, and the posterior third of the vocal cords. Although adding a hypopharyngeal sensor in the context of the conventional dual pH probe recording may increase the diagnostic yield of LPR, demonstration of reflux events can be best achieved by multichannel intraluminal impedance (MII) studies. Symptom-based diagnosis has low diagnostic specificity and laryngoscopic findings have low sensitivity. In addition, only 40% of patients with laryngeal findings attributed to LPR have objectively confirmed reflux events measured by MII pH [34]. Treatment is often lengthy, usually requiring 2–6 months administration of high dose, twice daily, acid suppression therapy [35].

Many of the published studies have investigated relationships between OSA and GERD, but very few studies have explored the relationship between LPR and OSA. It has been hypothesized that the causal relationship between LPR and OSA is actually bidirectional. The swings in negative intrathoracic pressure related to repetitive obstructive apneas promote reflux of gastric contents into the esophagus. Proximal migration of the refluxate into the laryngopharyngeal structures is promoted by sleep-related decrease in the clearance mechanisms, as well as by the sleep-associated decrease in upper esophageal sphincter tone, Over time, the pharyngeal inflammation related to LPR may then contribute to the progression of OSA by enhancing the collapsibility of the upper airway, likely mediated by the activation and propagation of local inflammatory and sensory neuropathic mechanisms [36] (Fig. 8.2). Indeed, significant improvements in the severity of OSA have been reported in adults by implementation of an aggressive anti-reflux therapy regimen [37].
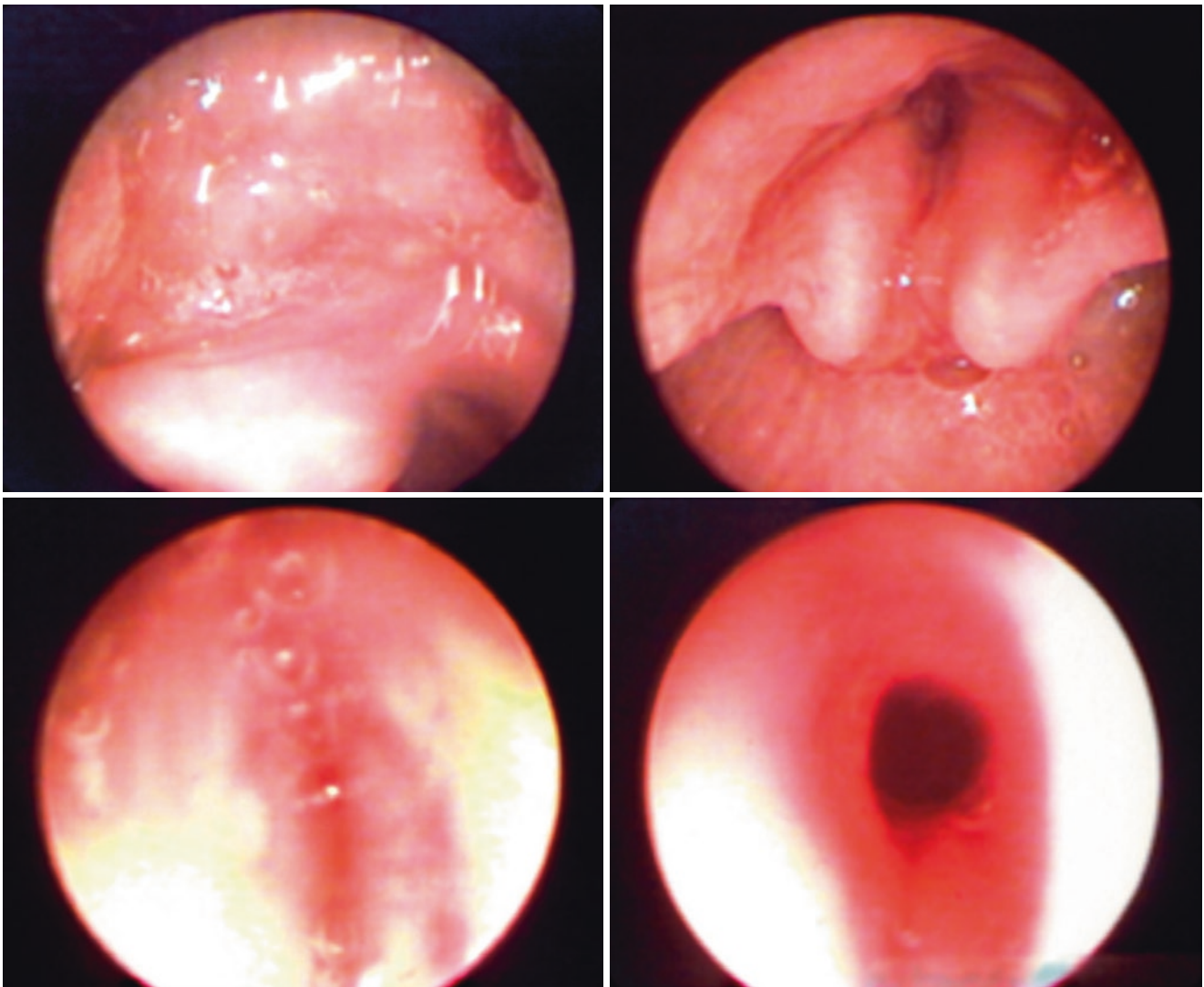
Fig. 8.1 Laryngopharyngeal Reflux. Endoscopic view of Laryngopharyngeal reflux reveals thickened epiglottis, posterior glottic swelling, and almost complete obstruction of the larynx with grade 3 subglottic stenosis. (From Stapleton and Brodsky [33]. Reprinted with permission from Elsevier)

Fig. 8.2 Schematic drawing of the relationship between OSA and LPR disease. (From Eskiizmir and Kezirian [36]. Reprinted with permission from Elsevier)
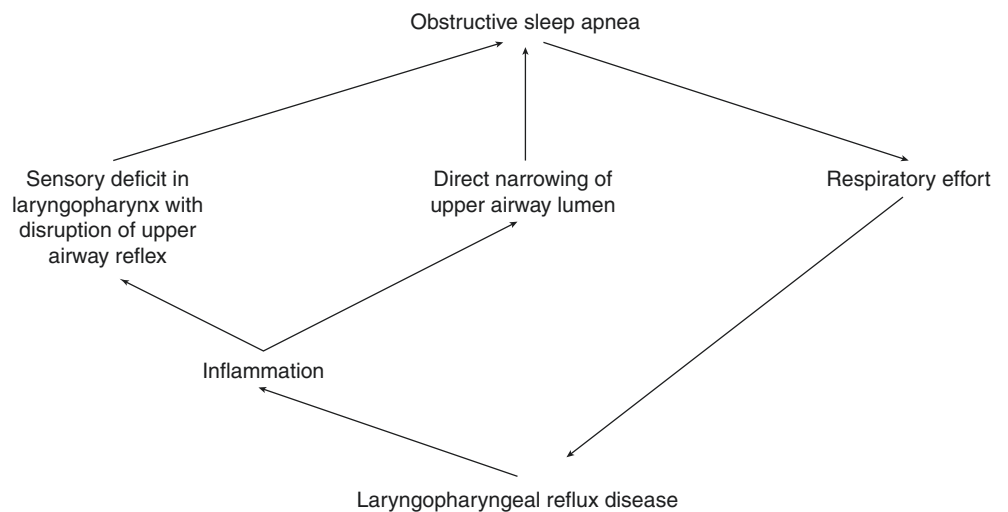
Modulation of Cardiorespiratory Events in Neonates and Infants: Role of Sleep and GER

Protective Airway Reflexes

For better understanding of the interrelationship between GER and cardiorespiratory events in neonates and infants, it is important to recognize two important airway protective reflexes, namely the laryngeal chemoreflex and the esophago-glottal closure reflex. Active glottic closure is involved in both reflexes, and plays an important role in preventing aspiration, but can potentially promote apnea. The laryngeal chemoreflex is elicited by stimulation of laryngeal mucosal receptors by various liquids and the esophago-glottal closure reflux is elicited by distension of the proximal esophagus [38–40].

Apnea of Prematurity (AOP)

The estimated prevalence of GERD is about 10% in sick infants in the Neonatal Intensive Care Unit (NICU) [41]. Pre-term infants are at increased risk for GER partly because of their large fluid intake in addition to the age-specific supine position. A causal relationship between AOP and GER has long been suspected due to the observations that AOP occurs more frequently in the immediate post-prandial period and that the apneic episodes are more likely to occur after episodes of regurgitation, Consequently, the laryngeal chemoreflex has been suggested as the possible mechanism. These observations have been supported by animal studies wherein stimulation of laryngeal chemoreceptors with various liquids, milk formula, and acidic fluids can provoke a prolonged and fatal apnea [42]. The hypothesis on this causative linkage has been also been confirmed in human pre-term infants [38]. Such assumptions led to widespread use of anti-GER medications in the newborn nursery with an expectation that this will reduce the frequency and severity of the apneic episodes. Few earlier studies have shown an association between regurgitation and apnea. Nine pre-term infants and one term infant showed a 14-fold increase in prolonged apnea frequency immediately following regurgitation [43]. However, in a subsequent study, no relationship between the occurrence of GER and apneas was identified in a study of 20 premature infants with a concurrent history of persistent AOP [44]. Furthermore, GER treatment did not reduce the frequency of apnea in 132 premature infants <36 weeks of gestational age [45]. A proposed explanation for the lack of such association between apneas and reflux events was that it was nonacid reflux, undetectable by conventional pH monitoring, that operated as the culprit for AOP causation. This led to implementation of novel diagnostic MII techniques for detection of both acid and non-acid reflux events [46]. However, in a study of 19 preterm infants, using MII technology in conjunction with cardiorespiratory monitoring, Poets et al. concluded that both reflux and apneic events are common, but that no temporal relationships can be identified between cardiorespiratory events and GER [47]. As neonates sleep 80% of the time, it is likely that sleep state might modulate the frequency and severity of these events. To identify the role of sleep in the modulation of GER and to define the spatio-temporal characteristics of GER, respiratory events, and sleep state, Jadcherla et al. have performed concurrent polysomnography with pH impedance study in a group of neonates who are hospitalized in NICU. There were 18 neonates who were hospitalized with apparent life-threatening events, apnea, desaturations, bradycardia, cyanosis, and stridor, with mean post menstrual age of 41 weeks at the time of study. A total of 317 GER events during 16 hours of polysomnography were analyzed. The study concluded that (1) frequency of impedance positive events were significantly less during sleep, (2) proximal migration of refluxate is also significantly less during sleep, and (3) frequency of respiratory symptoms were significantly decreased during sleep [48].

Brief Resolved Unexplained Event (BRUE) (Apparent Life-Threatening Event: ALTE)

Apparent Life-Threatening Events are frightening episodes in infants characterized by a combination of apnea, color change, abnormal muscle tone, choking, and gagging that require an intervention by the observer [49]. In 2016, the American Academy of Pediatrics (AAP) released a clinical guideline for practitioners recommending that the term ALTE be replaced by Brief Resolved Unexplained Event (BRUE) [50]. The aim was to allay the anxiety to the caregivers brought about by the use of the term ALTE, as well as to give practitioners clear management guidance by stratifying such infants into high- and low-risk groups. In patients with ALTE, apnea is the most frequently reported symptom, and 60–70% of patients with ALTE will also manifest the presence of recurrent regurgitation or emesis. Thus, GER has been suspected as a causative factor for ALTE. Indeed, up to 40–80% of patients with ALTE have abnormal pH monitoring studies. However, despite such associations, efforts to document a temporal relationship between ALTE and GER by simultaneous polysomnographic and pH probe studies have failed to convincingly demonstrate the occurrence of this process. Indeed, 14 infants with abnormal GER scores and a history of apnea did not show a temporal relationship between reflux and apneic events, the latter being considered
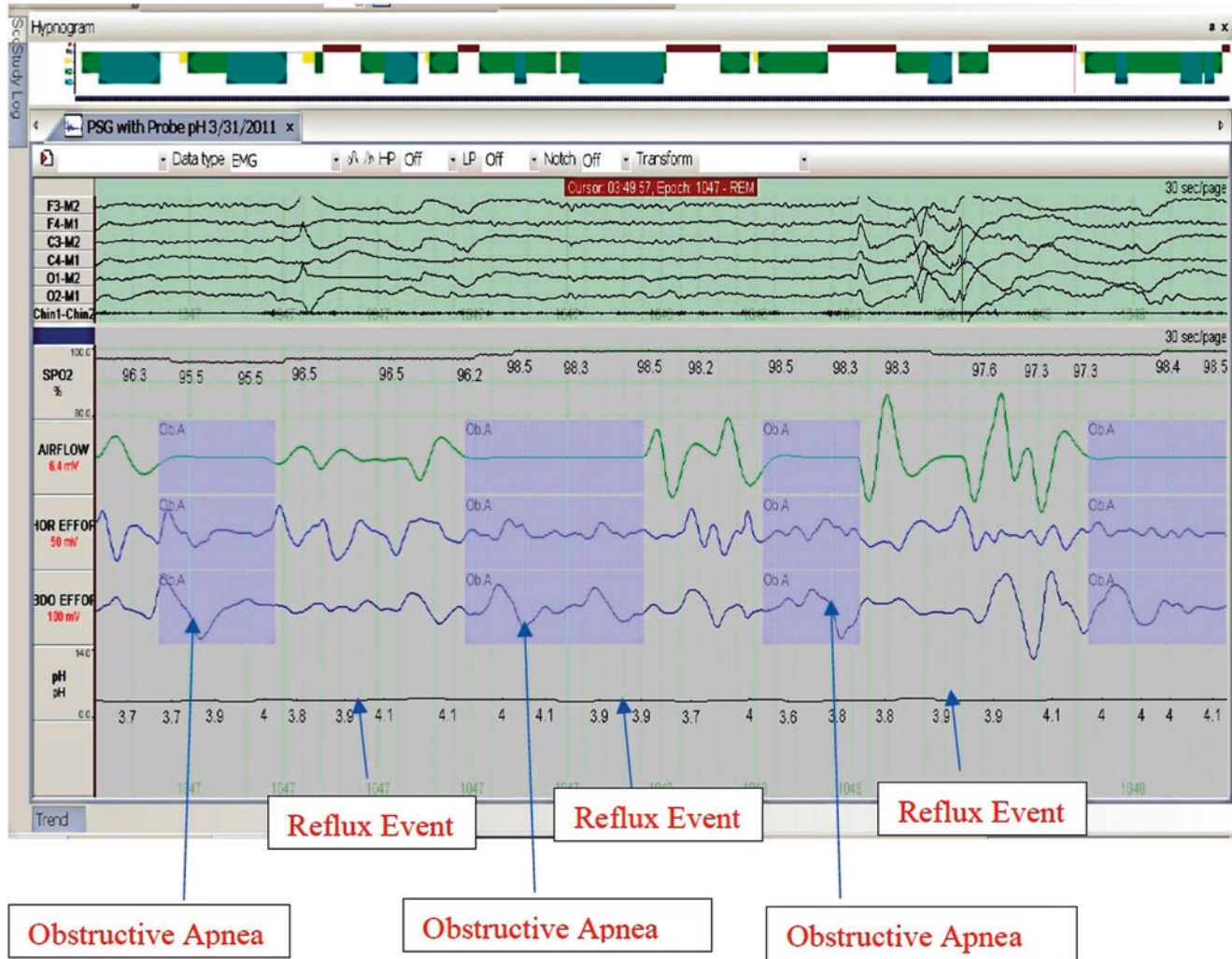
Fig. 8.3 Temporal relationship between obstructive events and reflux events

as a manifestation of more general developmental delay [51] (Figs. 8.3 and 8.4). In another study of 20 infants with ALTE with no clinical symptoms of emesis, no correlations between duration, lowest value of esophageal pH, and the number of apneas or duration of apneas could be found [52]. Even in patients with proven GER and ALTE, no relationship between GER and obstructive episodes in terms of frequency, duration, or temporal occurrence was detected [53]. Although it is often stated that gastroesophageal reflux is the most common cause of a brief resolved unexplained event or apparent life-threatening event, a recent literature search of multiple cross-sectional observational studies concluded that there are very few data to support the hypothesis of cause and effect [54]. Thus, based on the current evidence, in the major-

ity of infants, GER is not related to ALTE, although a clear temporal relation based on history, observation or testing may occur in individual infants.

Thus, both GER and apneic episodes (central/obstructive) are common in vulnerable infants in specific age groups, but there is an apparent lack of temporal relationships between the apneic events and GER. Several plausible reasons for the lack of such relationship could include (1) methodological issues such as small cohort size, selection bias, different methods for the diagnosis of apnea and GER, (2) the two conditions may share a common causative mechanism, and (3) different mechanisms for airway obstruction other than laryngeal closure with regurgitation may be operational.

Fig. 8.4 Possible mechanisms for the relationship between obstructive sleep apnea syndrome (OSAS) and gastroesophageal reflux disease (GERD). The mechanisms of the specific linkage between OSAS and GER are not fully elucidated, but possible explanations include the generation of large negative intrathoracic pressures, insufficient lower esophageal sphincter (LES) function, increased arousals, autonomic neural unbalance, and obesity predisposing to both conditions. TLESR transient lower esophageal sphincter relaxations. (From: Mizuta et al. [55])
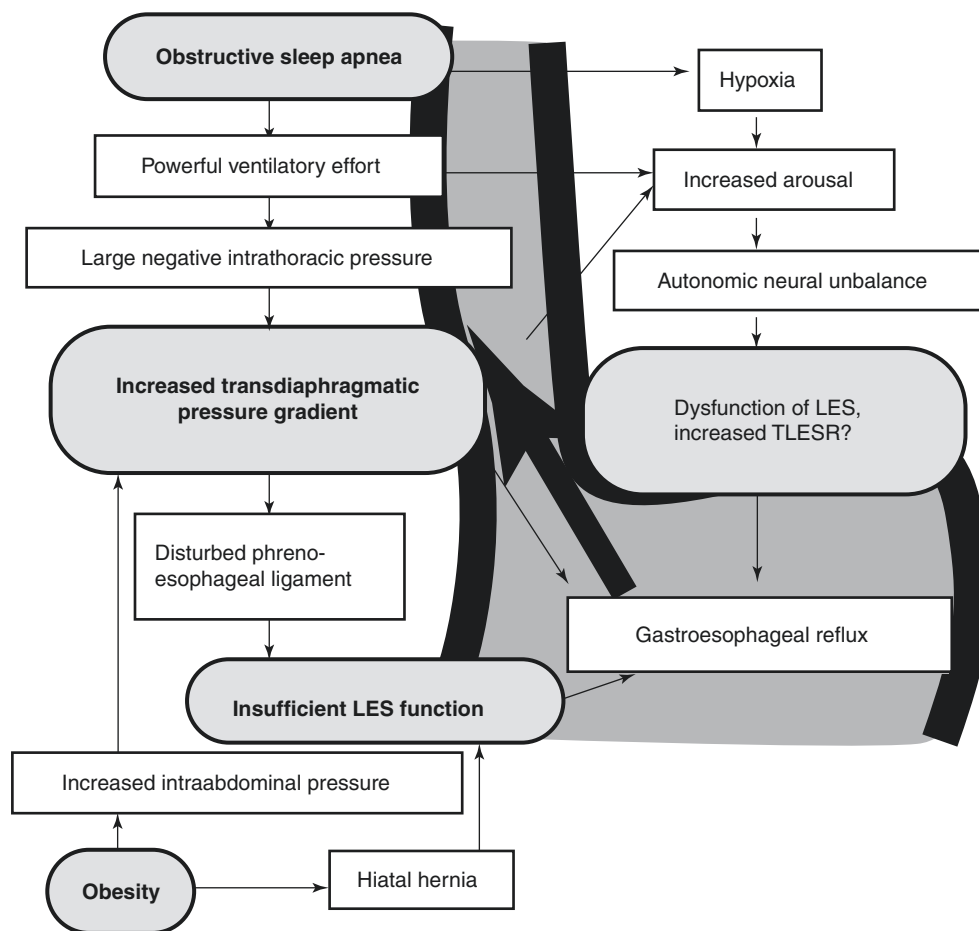
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