INTRODUCTION

Gastroesophageal reflux disease (GERD) is the most common malady of the esophagus. In the United States it has been estimated that 7% of the general population experience symptoms of GERD on a daily basis whereas 14% have symptoms at least once a week (1,2). An extensive body of information pertaining to the pathophysiology, diagnosis and treatment of GERD in general exists in the medical literature, however the evaluation of nocturnal reflux has been relatively limited (3–6). In 2001, Farup, et al reported an exceptionally high prevalence of nocturnal heartburn among 74% of individuals suffering from chronic reflux symptoms (3). It was also revealed that nocturnal heartburn has a more significantly negative impact on quality of life compared to those individuals with diurnal symptoms. Furthermore, a more recent survey (7) established that 75% of those who experienced heartburn at night had symptoms that affected their sleep, 63% believed that heartburn negatively affected their ability to sleep well, and 40% believed that heartburn negatively affected their ability to function the following day. Interestingly, 71% reported taking over-the-counter medicine but only 29% of these rated this approach extremely satisfactory. Forty-one percent reported trying prescription medicines and only 49% of these rated this approach extremely satisfactory. Hence nocturnal heartburn is prevalent in adults with gastroesophageal reflux disease and the poorer than expected response to implemented therapies carries significant management implications (7).

Nocturnal reflux has been associated with more severe injuries to the esophagus including esophagitis, stricture (8–10) and more importantly adenocarcinoma of the esophagus (11). Hence, a better understanding of the prevalence and the impact of nocturnal heartburn as an indicator of nocturnal acid reflux can have significant potential management implications.

In this chapter we will examine the prevalence of nocturnal reflux, its impact on quality of life in those affected and the consequences of nocturnal reflux in terms of esophageal diseases and their progression. We will appraise the most recent and clinically important publications and central investigatory works performed in this under-studied area of esophagology.

NOCTURNAL HEARTBURN

A large amount of information exists regarding the prevalence of gastroesophageal reflux disease in general, however data specifically addressing nocturnal reflux is sparse (3–6). Only recently has nocturnal heartburn, the cardinal symptom of reflux disease among individuals suffering from chronic heartburn, been established as being unexpectedly prevalent (3). Recent reports reveal a 10% prevalence of nocturnal GERD symptoms in the U.S. population. Nocturnal heartburn was reported by 74% of individuals suffering from chronic heartburn and quality of life was significantly more negatively impacted upon in nocturnal heartburn sufferers compared to those with diurnal symptoms. Two thirds of individuals older than 60 years of age with GERD symptoms had nocturnal symptoms. Elderly patients with GERD tend to have
more nocturnal/supine reflux episodes than their younger counterparts (12) and the pathophysiological changes of aging, together with the weakening of mechanisms that defend against reflux related esophageal injury during sleep, can cause accentuated deleterious consequences in this subset of the population.

In 2002 The Gallup Organization, on behalf of the American Gastroenterological Association, conducted a national population-based telephone interview survey of 1000 adults, who reported experiencing heartburn at least once a week for a minimum of three months. Approximately one quarter reported experiencing heartburn once or more daily, 43% experienced heartburn 1-2 times per week, and 20% experienced heartburn 3-6 times per week. While nearly one third of the respondents had experienced heartburn for 10 years or longer, a total of 15% of respondents reported that their heartburn had been present for only a year or less. Frequency of reported nocturnal and daytime heartburn is summarized in Figure 1. As seen in this figure, 13% of the respondents experienced heartburn only during the night and 20% reported heartburn only during the day. Sixty-five percent of respondents experienced heartburn both during the day and at night. Altogether, 79% of the heartburn sufferers reported experiencing heartburn at night. A large percentage of the respondents reported concomitant symptoms potentially attributable to gastroesophageal reflux, including throat clearing which was reported by 39% of the 1000 respondents, and chronic cough, hoarse voice and asthma which were reported by 16%, 18% and 13%, respectively. In addition, 50% reported a burning sensation in the throat.

Inquiry among respondents with nocturnal heartburn regarding the effects of heartburn on sleep, revealed that in 75% the symptom affected their sleep, and 63% believed that heartburn negatively affected their ability to sleep well. Forty percent of respondents with nocturnal heartburn believed that sleep difficulties due to nocturnal heartburn impaired their ability to function the following day. Prevalence of sleep disturbances among respondents increased with the increase in frequency of the nocturnal heartburn episodes during the week (Figure 2). Forty-two percent of the respondents stated that they have accepted the fact that they cannot sleep through the night, 39% reported that they take naps whenever possible, and 34% reported sleeping in a chair or in a seated position. Surprisingly, 27% reported that their heartburn-induced sleep disturbances kept their spouses from having a good night’s sleep.

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In general, heartburn resulted in some degree of limitation or change in lifestyle of the respondents. Over half reported that heartburn caused changes in the time, nature and quantity of their food intake. Tables 1 and 2 represent some of the effects of heartburn on the lifestyles of respondents.

A variety of medical and non-medical approaches to heartburn were reported by the respondents. Surprisingly, of the 791 respondents with nocturnal heartburn, about 30% of respondents did not report taking any kind of medication, 71% reported taking over-the-counter medication for their heartburn, while 41% reported trying prescription medicines. Altogether, the efficiency of remedies for heartburn was variable. Only 29% of those taking over-the-counter, and 42% of those taking prescription medicine rated these approaches completely satisfactory. Other measures taken by respondents and their effectiveness are summarized in Figure 3 (7).

The findings of this survey and those of Farup, et al (3), suggests that the prevalence and the impact of nocturnal heartburn have been underestimated and that the symptom often is not treated adequately. These issues have practical implications for management of GERD in that they highlight several important features of the disease including (a) only a minority of heartburn sufferers seek medical help and are on adequate treatment, (b) only a minority experience nocturnal heartburn exclusively as almost 8 of 10 of those who report frequent heartburn experience nocturnal symptoms and most patients have the symptom both during the day and at night, (c) it appears that the condition impairs sleep and consequently has a substantial negative impact on daily function and lifestyle. These results suggest a need for a more in-depth and specific inquiry about nocturnal reflux from patients and more effort in recognizing and treating the nocturnal manifestations of GERD.

The mechanisms of nocturnal reflux remain for the most part undefined. In normal subjects, gastroesophageal reflux at night occurs only during periods of wakefulness because transient lower esophageal relaxation, the major mechanism of reflux, occurs only during the awake state (13). Freiden, et al have demonstrated that patients with reflux disease showed reflux by transient lower esophageal sphincter relaxations only 40% of

Table 1
Affected by Heartburn

<table>
<thead>
<tr>
<th>Ability to eat or drink what you want</th>
<th>Greatly</th>
<th>Quite a Bit</th>
<th>Moderately</th>
<th>Mildly</th>
<th>Not at All</th>
<th>DK/RF</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to get a good night’s sleep</td>
<td>11</td>
<td>8</td>
<td>21</td>
<td>23</td>
<td>36</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Ability to eat or drink when you want</td>
<td>11</td>
<td>7</td>
<td>19</td>
<td>23</td>
<td>39</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Ability to sleep when you want</td>
<td>9</td>
<td>7</td>
<td>19</td>
<td>21</td>
<td>43</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Your mood or general well-being</td>
<td>8</td>
<td>8</td>
<td>19</td>
<td>22</td>
<td>42</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Social activities</td>
<td>7</td>
<td>4</td>
<td>12</td>
<td>16</td>
<td>59</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Spouse’s ability to get a good night’s sleep</td>
<td>5</td>
<td>2</td>
<td>10</td>
<td>10</td>
<td>55</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>Ability to function day-to-day</td>
<td>4</td>
<td>4</td>
<td>17</td>
<td>23</td>
<td>51</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Ability to function well at work</td>
<td>4</td>
<td>4</td>
<td>15</td>
<td>17</td>
<td>48</td>
<td>12</td>
<td>100</td>
</tr>
</tbody>
</table>

DK: Don’t know
RF: Refused to answer
Experiencing heartburn affected a number of activities of daily living and social functions of the responders. These included their eating, sleeping, social life and work.
The Impact of Nocturnal Symptoms in GERD

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Table 2
How Treated

<table>
<thead>
<tr>
<th></th>
<th>All with Hearthburn</th>
<th>Prescription Medication</th>
<th>Over-the-Counter Medication</th>
<th>No Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed foods eaten</td>
<td>56</td>
<td>63</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>Eating smaller meals</td>
<td>50</td>
<td>56</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>Propped up head for</td>
<td>48</td>
<td>58</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>Reducing stress</td>
<td>43</td>
<td>47</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>Accepted that can’t</td>
<td>42</td>
<td>43</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>Sleep in chair or</td>
<td>39</td>
<td>41</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td>Reduced or quit</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Changed frequency of</td>
<td>25</td>
<td>29</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Quit smoking</td>
<td>14</td>
<td>14</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Number of interviews</td>
<td>(1000)</td>
<td>(386)</td>
<td>(340)</td>
<td>(274)</td>
</tr>
</tbody>
</table>

Lifestyle changes made due to heartburn symptoms among all respondents, those taking prescription medicine, those taking over-the-counter medicine and those who did not report taking any medicine. As seen across the board, except for changes in frequency of exercise and smoking, one third to one half of respondents from all groups reported that they have made various changes in their activities of daily living and lifestyle due to heartburn.

the time. The remaining 60% of reflux episodes were divided between free reflux, stress reflux, and unclear mechanisms and even these mechanisms of reflux are operative only in the awake state (14). As with swallowing, the transient lower esophageal sphincter relaxation frequency is also correlated to sleep stages, with the highest frequency in the awake state. There are a number of similarities in the swallow induced and transient lower sphincter relaxation, as both are mediated by the vagus nerve (15-17), wakefulness is essential to both of them, and both have been speculated to occur through the stimulation of pharyngeal mechanoreceptors (18,19). Transient lower esophageal sphincter relaxation triggered by pharyngeal stimulation is in addition to the main mechanism of this relaxation, namely proximal gastric distention.

Esophageal acid clearance is a two-step process involving (a) volume clear-

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nce and (b) acid neutralization (20,21). In this process, the majority of refluxate is cleared from the esophagus by either primary or secondary peristalsis, while the residual acid that remains in the esophagus is neutralized by salivary bicarbonate and to a lesser extent, by bicarbonate secreted from the esophageal submucosal glands (22). Acid clearance is curtailed during sleep. Swallowing virtually ceases during sleep and consequently primary peristalsis is not stimulated. Esophageal volume clearance during sleep is almost totally a function of secondary peristalsis that may not be stimulated by the reflux of small amounts of gastric content. Experimental data suggests that a threshold volume ranging between 5 and 30 mL is required to stimulate secondary peristalsis in healthy individuals (23). Furthermore the triggering mechanism of secondary peristalsis among healthy elderly individuals and among patients with reflux esophagitis is deteriorated (24–26). Therefore, volume clearance of refluxed gastric acid during sleep may not be as reliable as in the awake state. In addition, not only does the recumbent position during sleep facilitate reflux, the effect of gravity after the reflux event retards esophageal clearance for individuals in this position.

The cessation of swallowing during sleep also impairs acid clearance because there is no salivary bicarbonate available to neutralize the hydrochloric acid dissolved in the esophageal mucosal unstirred water layer. Consequently, as a result of the reduction in esophageal volume clearance and acid neutralization during sleep, nocturnal acid reflux might be especially damaging to the esophagus because the acid will have prolonged contact with the mucosa.

Several studies have documented recumbent nocturnal acid exposure among the majority of patients with severe consequences of reflux disease such as Barrett’s esophagus and erosive esophagitis (27–30). Lagergren, et al reported the risk of esophageal adenocarcinoma to be eight times higher among persons in whom heartburn, regurgitation or both occurred at least once a week as among persons without these symptoms. Symptoms of reflux at night were associated with a risk nearly 11 times higher (11). In addition, the reduced esophageal peristaltic activity may predispose to proximal migration of the acid refluxate (31), thereby increasing the likelihood of damage to the oropharynx and airway.

Evidence suggests that sleep-related gastroesophageal reflux is an important element in the development of the complications of GERD, including esophagitis (8), exacerbation of bronchial asthma (32), and other respiratory complications (33). The strong relationship between the number of supine and/or sleep-related episodes of prolonged acid clearance and the development of severe complications associated with GERD has been documented (34–37). The number of reflux events greater than 5 minutes in duration during the nocturnal interval best distinguishes patients with erosive lesions from symptomatic GERD patients without mucosal damage (38). Previous studies have shown that reflux events are usually preceded by a brief arousal response, and this would suggest that fragmented and disturbed sleep might induce or enhance reflux in individuals with a tendency for gastroesophageal reflux (14).

Patients with severe erosive esophagitis, peptic strictures and Barrett’s metaplasia often have excessive recumbent nocturnal esophageal acid exposure and may not achieve symptomatic or endoscopic remission when proton pump inhibitors are given twice daily, because of an incompetent anti-reflux barrier and delayed esophageal clearance secondary to associated ineffective esophageal body motility (39–42).

Reduction of nocturnal recumbent acid exposure is attempted by elevation of the head of the bed, a maneuver designed to decrease esophageal acid contact time. Several studies have examined the effect of different recumbent positions on the frequency of GER (43–45). Khoury, et al confirmed prior observations that esophageal acid exposure and acid clearance time are prolonged in the right lateral decubitus position (46). A recent report in infants demonstrated that esophageal acid exposure time and clearance were best in the left lateral decubitus position and that elevation of the head of the bed did not contribute to any further improvement (45). The normal left-curved turn of the esophagus into the stomach may be straightened by effects of gravity while lying in the right lateral decubitus position and the esophagogastric junction (EGJ) may be in a dependent position relative to the gastric pool in this position (47). This hypothesis is supported by the observations of Shay, et al who found that the EGJ was either submerged below the air-barium interface or immediately adjacent to it in 74% of the radiographs taken in
the right lateral decubitus position. In contrast, the EGJ was in the air above the air-barium interface when subjects were upright or lying on their left side (43). An increased number of reflux episodes observed either in the supine or right lateral decubitus positions may be explained by transient spontaneous LES relaxations triggered by gastric content at the cardia. This data suggests that patients with GER should be advised to sleep primarily in the left lateral decubitus position. Whether this would decrease nocturnal symptoms, prevent the other sequelae of GER and accelerate healing however requires further study.

Association of suprasophageal and respiratory disorders with gastroesophageal reflux disease has increasingly become the topic of investigation in recent years (48–51). Previous retrospective reviews (48) reported an increased risk for a variety of respiratory and aerodigestive tract diseases such as pharyngitis, sinusitis, laryngitis, chronic bronchitis, and asthma among patients with reflux esophagitis. In some studies, 13%–39% of heartburn sufferers reported suprasophageal symptoms, including asthma, hoarseness, chronic cough, and frequent throat clearing. The role of nocturnal reflux events in causing suprasophageal complications has not been systematically studied. Since asthma, chronic cough, and hoarse voice are common clinical problems, their by-chance concomitant presence with heartburn is a possibility and more serious conditions such as malignancy inducing respiratory symptoms need to be ruled out before these symptoms are attributed to reflux disease.

One of the unexpected findings of the available studies is the percentage of respondents who are dissatisfied with their GERD therapy, including both prescription and over-the-counter medications. In one survey, among 70% of respondents who reported taking any medication, less than half expressed satisfaction. More surprising was the percentage (15%) of those who used over-the-counter medication in addition to prescription drugs, suggesting either inadequate dosage or inappropriate usage or timing of the latter (7).

A troublesome consequence of nocturnal heartburn is sleep disturbances and its negative impact on the next day function. Especially disturbing is the limiting effect that nocturnal heartburn is reported to have on personal and social activities of the studied population (7). The socioeconomic impact of these findings could be important and again raise the question of appropriate treatment strategies for chronic nocturnal heartburn.

CONCLUSION

Nocturnal symptoms occur in the majority of adults with heartburn. Limited available data specifically addressing nocturnal gastroesophageal reflux indicate its association with more severe reflux induced injuries such as esophagitis and stricture (8–10), as well as adenocarcinoma of the esophagus (11), respiratory and otolaryngologic disorders, sleep disturbances, diminished quality of life and undesired changes in activities of daily living. The expected result from the implemented therapy for heartburn is not achieved by a substantial percentage of patients. In view of the reports indicating reasonable specificity of heartburn for diagnosis of gastroesophageal reflux disease (52), a better understanding of the prevalence and impact of nocturnal heartburn can have significant potential diagnostic and management implications. These findings indicate the need for a more directed inquiry when questioning GERD patients regarding nocturnal reflux symptoms including sleep disturbances and morning respiratory symptoms such as cough and hoarseness that improve throughout the day, especially in the elderly and devising a more targeted management strategy addressing this issue.

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