Symptom severity and oesophageal chemosensitivity to acid in older and young patients with gastro-oesophageal reflux

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Abstract

Introduction: elderly patients appear to have a more aggressive form of gastro-oesophageal reflux disease than younger patients. Reduced pain perception with age is a possible underlying mechanism.
Aims: to compare the extent of oesophageal mucosal injury, acid exposure, symptom severity and perception thresholds for acid infusion in older (aged 60 or older) and younger patients with gastro-oesophageal reflux.
Methods: twenty-five younger and 23 older patients completed the study. We determined acid exposure and oesophageal mucosal injury by ambulatory 24-h oesophageal pH monitoring and upper endoscopy, respectively. We determined chemosensitivity by infusing 0.1 N hydrochloric acid into the mid-oesophagus for 10 min at 10 ml/min after a 2-min infusion of normal saline at a similar rate. We quantified acid perception thresholds by the lag time to initial typical symptom perception, intensity rating at the end of acid infusion and an acid perfusion sensitivity score, calculated from the fractional duration of symptom perception and intensity rating.
Results: mean percentage of total time with pH <4 was higher in the older (15.8 ± 2.4) than in the younger patients (11.9 ± 1.8; P=0.18). Of the older group, 74% had erosive oesophagitis versus 64% in the younger group. Frequency of symptoms (heartburn, acid regurgitation and dysphagia) was lower in the elderly group. Older patients perceived heartburn and acid regurgitation as much less severe than younger patients (P<0.05). Younger patients had a significantly shorter lag time to initial symptom perception (P<0.05) and a higher sensory intensity rating (P<0.08). The acid perfusion sensitivity score was significantly lower in the older group (P<0.05).
Conclusions: older patients with gastro-oesophageal reflux disease have reduced symptom severity for heartburn despite a tendency towards increased severity of oesophageal mucosal injury and acid exposure. Age-related reduction in chemosensitivity to acid is a possible underlying mechanism.

Keywords: elderly patients, gastro-oesophageal reflux disease, oesophageal chemosensitivity, symptom severity

Introduction

Gastro-oesophageal reflux disease may have different characteristics in elderly people and may require more aggressive treatment. Little is known about the pathophysiological effect of ageing on gastro-oesophageal reflux disease and the underlying mechanism responsible for the more severe form of the disease. The term ‘presby-oesophagus’ was coined by Soergel et al. to describe motility abnormalities of the ageing oesophagus [1]. However, the reported oesophageal motor function abnormalities were described in elderly patients with several underlying co-morbidities, such as diabetes mellitus and neurological disorders [2]. There are no age-related differences in 24-h oesophageal pH monitoring parameters of normal subjects [3, 4]. Although previous studies suggested that basal and maximal gastric acid output decline with ageing, recent studies have documented a lack of age effect on basal gastric acid secretion in both normal subjects and patients with peptic ulcer disease [5, 6]. Epidemiological data have demonstrated that gastro-oesophageal reflux disease and Barrett’s oesophagus peak during the seventh decade [7, 8]. Only 54% of elderly patients with documented gastro-oesophageal reflux disease complained of heartburn,
suggesting altered visceral pain perception [9]. Other studies have also noted alteration in oesophageal pain perception to acid in elderly patients with gastro-oesophageal reflux disease. Raiha et al. found that regurgitation, dysphagia, respiratory symptoms and vomiting were more common than heartburn in elderly patients with gastro-oesophageal reflux disease [10]. Elderly patients had more severe disease, as manifested by the extent of mucosal injury and the frequency of complications of gastro-oesophageal reflux disease and Barrett’s oesophagus, regardless of underlying comorbidity. There were no differences in severity of symptoms when compared with younger patients. Recently, Grade et al. suggested that reduced chemoreceptor sensitivity to acid observed in patients with Barrett’s oesophagus may be related to age and not just to the presence of Barrett’s epithelium [11].

Although altered oesophageal pain perception to acid has been suggested as the possible underlying mechanism, no study has compared perception thresholds in elderly and younger patients with gastro-oesophageal reflux disease. The aims of our study were to determine symptom severity and perception thresholds for acid perfusion in elderly and young subjects with gastro-oesophageal reflux disease, and to determine the extent of oesophageal mucosal injury and acid exposure in both groups. Our hypothesis was that elderly patients have a significantly higher perception threshold for acid perfusion when compared with younger patients with gastro-oesophageal reflux disease.

Methods

Patients with symptomatic gastro-oesophageal reflux disease with at least three episodes per week of heartburn or acid regurgitation in the last 3 months were recruited from gastro-intestinal and internal medicine clinics at the Tucson Veterans Affairs Medical Center. Exclusion criteria included oesophageal peptic stricture, Barrett’s oesophagus, previous gastrointestinal surgery, peptic ulcer, autonomic and peripheral neuropathy, myopathy, diabetes mellitus, functional bowel disorder, treatment with a proton pump inhibitor or any other underlying disease or medication that may affect symptom perception, lower oesophageal sphincter pressure or increase acid clearance time. Patients discontinued H2 receptor antagonists at least 10 days before the beginning of the study. We excluded patients with both normal upper endoscopy and ambulatory 24-h oesophageal pH monitoring, and those who were unable to complete all study components.

This study was approved by the human subject committee of the University of Arizona.

Study protocol

All subjects agreeing to participate signed an informed consent form. Patients under 60 were enrolled in the younger group and those aged 60 and older into the elderly group. We assessed symptom severity using an ordinal scale for heartburn, acid regurgitation, dysphagia and chest pain. We quantified acid reflux by ambulatory 24-h oesophageal pH monitoring, and determined the presence and extent of oesophageal mucosal injury by an upper endoscopy. Patients also had a modified acid perfusion test to determine oesophageal chemosensitivity to acid.

We evaluated symptoms such as heartburn, acid regurgitation, chest pain and dysphagia. Patients ranked the severity of each symptom on the following scale [12]: mild, can be ignored if I do not think about it; moderate, cannot be ignored, but does not affect my lifestyle; severe, affects my lifestyle; very severe, markedly affects my lifestyle.

After an overnight fast, we inserted a pH probe with lower oesophageal sphincter identifier (Synectics Medical, Digitrapper Mark III) via the nose into the oesophagus. The pH probe was then placed 5 cm above the upper margin of the lower oesophageal sphincter and was connected to a digital portable recorder. We attached a reference electrode to the upper chest. We instructed patients to keep a diary recording meal times, position changes and the time and type of their symptoms. At the beginning and the end of the study the electrode and the system were calibrated in standard solutions of pH 1 and pH 7. Reflux was defined as pH < 4 and reflux time as the interval until pH is > 4. The presence of gastro-oesophageal reflux disease was established when the percentage of total time with pH < 4 was < 4.2% [13]. We analysed the recorded data by using standard commercially available computer software (Synectics).

We carefully evaluated the distal portion of the oesophagus during standard upper endoscopy to determine the presence of mucosal injury. The extent of mucosal damage was assessed using the Hetzel-Dent grading system [14]: grades 2–4 were considered diagnostic of erosive oesophagitis. Patients with grade 5 were excluded from the study.

We placed a manometry catheter with a central lumen 10 cm above the upper border of the lower oesophageal sphincter. By using a Harvard apparatus, we infused saline initially into the oesophagus at a rate of 10 ml/min for 2 min. Without the patient’s knowledge, 0.1 N hydrochloric acid was infused for about 10 min at a similar rate. We instructed patients to report whenever typical heartburn was reproduced.

We quantified stimulus–response functions to acid by three measures: lag time, sensory intensity rating and an acid perfusion sensory score. We defined lag time as the time (in s) to initial typical symptom perception and sensory intensity rating as the intensity of typical symptom perception at the end of acid perfusion, using a previously validated verbal descriptor scale, ranging from no sensation (0) to extremely
intense (20). The acid perfusion sensitivity score was calculated by multiplying the duration of typical symptom perception (expressed in s) and the sensory intensity rating at the end of acid perfusion. For convenience this was divided by 100 to give an acid perfusion sensitivity score in cm·s.

Results are presented as mean values ± SEM. An independent two-sample t-test was used to investigate differences between the continuous variables and the two age groups. We used log transformation since the data were not normally distributed. We used Mann–Whitney tests to investigate differences between the interval-scaled data and the two age groups.

Results

From January until December 1996, we recruited 30 consecutive patients to the younger group and 33 to the older group. Six patients (three from each group) who had normal upper endoscopy and 24-h oesophageal pH monitoring—despite reports of heartburn symptoms—were excluded. In addition, eight patients (six in the older group and two in the younger group) were found to have Barrett’s epithelium. We excluded these patients, as well as one older patient with adenocarcinoma of the oesophagus, from further evaluation.

Twenty-five consecutive younger and 23 older patients with symptomatic gastro-oesophageal reflux disease were therefore included in the study. The age and sex distributions of the two groups are shown in Table 1. There was a significant age difference between the older and younger group (P < 0.001). On symptom assessment, 24 (96%) of the younger and 21 (91.3%) of the older patients experienced heartburn, 24 (96%) and 20 (87%) acid regurgitation, 13 (52%) and nine (39.1%) dysphagia, and 14 (56%) and 13 (59.1%) chest pain. When we assessed severity of symptoms, younger patients reported significantly more severe heartburn than older patients (P < 0.02). Eleven (44%) younger and 17 (74%) older patients reported mild to moderate heartburn while 13 (52%) younger and four (17.6%) older patients experienced severe to very severe heartburn (Figure 1). Reported severity of acid regurgitation was also significantly higher in the younger group (P = 0.03). There was no statistical difference in the reported severity of dysphagia (P = 0.3) and chest pain (P = 0.6).

Table 1 shows the patient characteristics of the two groups. One patient from each group had normal 24-h oesophageal pH monitoring, despite erosive oesophagitis on upper endoscopy. The mean percentage of total time with pH < 4 was arithmetically higher in the older group than in the younger patients (Table 1; P = 0.18). The mean percentage of total time in both the supine and upright position with pH < 4 was arithmetically higher as well in the older patients (P = 0.48 and P = 0.2, respectively). Of the older group, 74% had erosive oesophagitis on upper endoscopy versus 64% of the younger group.

Table 2 summarizes the results of the stimulus–response functions to acid during the acid perfusion test in the two groups. All of the younger patients had a significantly shorter lag time to initial symptom perception (P < 0.05) and a higher sensory intensity rating that almost reached statistical significance (P = 0.08). The acid perfusion sensitivity score was significantly lower in the older patients (P < 0.05). Even when patients with erosive oesophagitis only (grades 2–4) were compared, younger patients had significantly shorter lag time to initial symptom perception and a higher acid perfusion sensitivity

| Table 1. Characteristics of younger (<60 years) and older (≥60 years) patients |
|-------------------------------------|-------------------|-------------------|
| Age (years)                         | Older (n = 25)    | Younger (n = 25)  |
| Mean                                | 70 ± 1            | 46 ± 1            |
| Range                               | 60–81             | 30–57             |
| Gender (male/female)                | 22/1              | 23/2              |
| Upper endoscopy grade               |                   |                   |
| 0–1                                 | 6 (26%)           | 9 (36%)           |
| 2–4                                 | 17 (74%)          | 16 (64%)          |
| Ambulatory 24-h oesophageal pH monitoringa |                   |                   |
| Mean                                | 16 ± 2            | 12 ± 2            |
| Range                               | 1–54              | 3–41              |
| Supine                              | 13 ± 3            | 10 ± 2            |
| Upright                             | 17 ± 2            | 14 ± 2            |

a% of mean time with pH < 4.
score ($P < 0.05$). Sensory intensity rating was higher in the younger patients with erosive oesophagitis and was close to reaching statistical significance ($P = 0.08$).

When we used regression analysis, there was a significant correlation between age and lag time to initial symptom perception ($P = 0.01$), sensory intensity ($P = 0.007$) and acid perfusion sensitivity score ($P = 0.015$). In addition, with each additional year of age there was an increase of 5.7 s in lag time to initial symptom perception, a 0.17 drop in sensory intensity rating and a 0.9 drop in acid perfusion sensitivity score.

### Discussion

This study demonstrates that older patients with gastro-oesophageal reflux disease appear to perceive heartburn and acid regurgitation less severely than younger patients, despite a trend toward increased acid exposure and oesophageal mucosal injury. Evaluating a large cohort of elderly patients with documented gastro-oesophageal reflux disease, Raiha et al. suggested that heartburn might not be considered a typical symptom of acid reflux in these patients [10].

Several other studies comparing symptom assessment in elderly and younger patients with gastro-oesophageal reflux disease did not separate frequency and severity of symptoms—two factors that contribute independently to a patient’s perception of disease severity. Collen et al. were unable to demonstrate difference in symptom severity between elderly and younger patients [15]. A “pyrosis symptom score” was used that solely assessed various responses of an individual’s heartburn to antacid treatment rather than the patient’s self-perception of the effect of gastro-oesophageal reflux disease symptoms on lifestyle. Similarly, when Triadafilopoulos et al. compared symptom severity between younger and older patients with gastro-oesophageal reflux disease, they found no difference between the two groups [16]. Although they investigated a patient population similar to that in our study (mainly men), an overall symptom severity score was calculated by adding the individual scores for six different symptoms. Symptoms such as dysphagia and chest pain, which were equally perceived in our study, were also included and integrated into the cumulative symptom score.

Elderly subjects appear to have a more severe disease than younger subjects with gastro-oesophageal reflux disease [15–17]. The underlying mechanism for this perplexing phenomenon has been a source of speculation. Increased susceptibility to acid and long duration of acid reflux exposure are hypotheses which have never been substantiated [15, 18]. Oesophageal

### Table 2. Comparison of stimulus–response functions to acid during acid perfusion test between younger (< 60 years) and older (≥ 60 years) patients with gastro-oesophageal reflux disease (mean value ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Younger</th>
<th></th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erosive oesophagitis</td>
<td>All</td>
<td>Erosive oesophagitis</td>
</tr>
<tr>
<td></td>
<td>($n = 16$)</td>
<td>($n = 25$)</td>
<td>($n = 17$)</td>
</tr>
<tr>
<td>Lag time to initial typical symptom perception (s)</td>
<td>$127 \pm 32$</td>
<td>$136 \pm 39$</td>
<td>$266 \pm 49^c$</td>
</tr>
<tr>
<td>Sensory intensity rating$^a$</td>
<td>$12 \pm 1$</td>
<td>$12 \pm 1$</td>
<td>$9 \pm 1^d$</td>
</tr>
<tr>
<td>Acid perfusion sensory score (cm-s)$^b$</td>
<td>$63 \pm 6$</td>
<td>$60 \pm 8$</td>
<td>$41 \pm 7^c$</td>
</tr>
</tbody>
</table>

$^a$Validated verbal descriptor scale, ranging from no sensation (0) to extremely intense (20).

$^b$Duration of typical symptom perception multiplied by sensory intensity rating at the end of acid perfusion and divided by 100.

$^cP < 0.05$, $^dP = 0.08$.  

Figure 1. Comparison of reported symptom severity for heartburn of younger (¶, < 60 years) and older (¶, ≥ 60 years) patients with gastro-oesophageal reflux disease. Younger patients had more severe heartburn than older patients ($P < 0.05$). None = no symptoms of heartburn.
motility changes that occur with age have long been disputed [2]. Age-related alteration in oesophageal pain perception might be an important contributing factor. As we have demonstrated, oesophageal afferent chemosensitivity to acid was significantly diminished in elderly patients with gastro-oesophageal reflux disease, despite increased acid exposure and oesophageal mucosal inflammation. Heartburn and acid regurgitation were perceived as less severe by the elderly patients. Similar results were obtained by Raiha et al. in their assessment of 195 consecutive elderly subjects [10].

Other studies have supported the concept of altered pain perception in elderly people. Lasch et al. detected diminished visceral pain perception with ageing, using graded oesophageal balloon distensions and comparing normal elderly people with normal younger subjects [19]. This important observation indicates that altered oesophageal pain perception in elderly people is the result of an ageing process rather than an acquired phenomenon that results from disease. Patel et al. have demonstrated reduced visceral pain perception in the proximal and mid oesophagus of normal elderly subjects compared with normal younger subjects, using the technique of impedance planimetry [20]. There is reduced sensitivity to intravesophageal acid in patients with reflux-induced strictures compared with patients with uncomplicated erosive oesophagitis [21]. These patients were much older and 11% had no preceding reflux symptoms.

Altered oesophageal pain perception may adversely affect the medical care-seeking behaviour of an individual, delaying presentation until progression to more severe disease and possible complications [22] (as demonstrated by the patient excluded by the recognition of adenocarcinoma). Symptoms that are perceived as less severe will probably be approached less aggressively.

Our patient population included mainly US veterans, explaining the male predominance. The lack of women in our study may compromise its ability to be generalized; however gastro-oesophageal reflux disease is far more common in men than in women (a ratio of 2–3:1).

Other factors may contribute to increased severity of gastro-oesophageal reflux disease in the elderly patient. For example, decrease in salivary secretion with age may contribute to increase in the amount of acid exposure and oesophageal mucosal injury that elderly patients experience [23]. Reduced chemosensitivity to acid is another important factor that should be recognized: it may mean that the clinical severity of gastro-oesophageal reflux disease of many elderly patients is underestimated and thus under-treated.

### Key points
- Elderly patients appear to have a more aggressive form of gastro-oesophageal reflux disease than younger patients.
- While the frequency of typical symptoms of gastro-oesophageal reflux disease is similar in older and younger patients, perception of severity is significantly higher in younger patients.
- There is increased oesophageal acid exposure and mucosal injury in older patients.
- Elderly patients have reduced chemoreceptor sensitivity to acid.
- Altered oesophageal pain perception to acid may be the mechanism responsible for the increased severity of gastro-oesophageal reflux disease in elderly people.

### References

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