Reflux Mechanisms in Gerd : Analysis of the role of transient lower esophageal sphincter relaxations

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ESOPHAGEAL BODY MOTILITY DURING ACID REFLUX EPISODES IN PATIENTS WITH REFLUX DISEASE

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ABSTRACT

Background: Esophageal body motility contributes to clearance of acid. Little is known about esophageal motility within acid reflux episodes during 24 hour ambulatory recording in patients with gastroesophageal reflux disease (GERD).
Methods: We studied esophageal motility during reflux episodes (ambulatory 24 hour esophageal pH- and manometry) in 89 patients with GERD and 15 healthy controls. Subjects were divided into subgroups based on acid exposure time.
Results: Amplitude and duration of esophageal contractions were not significantly different between the groups with normal, mild, moderate and severe reflux. The number of distal esophageal contractions required to raise esophageal pH above 4 was identical in the reflux subgroups during upright reflux, but was significantly ($p<0.05$) different during supine reflux. The frequency of peristaltic waves was significantly ($p<0.001$) decreased in subjects with severe acid reflux both upright and supine.
Conclusions: Esophageal body motility is not impaired during reflux episodes in GERD patients. In subjects with severe acid reflux, the clearance of acid is diminished as consequence of a significant reduction in the frequency of peristaltic waves.

INTRODUCTION

Gastroesophageal acid reflux predominantly occurs during transient lower esophageal sphincter (LES) relaxations or when LES pressure is very low.(1) Other factors involved in the pathogenesis of reflux disease are gastric emptying and composition of gastric refluxate.(2) The duration of a reflux episode is determined by the clearance of acid from the esophagus. Acid clearance is dependent on esophageal body motility and salivary buffering.(2,3)

Previous studies using stationary manometry indicate that esophageal body motility is abnormal in patients with gastroesophageal reflux disease (GERD) (4-10). Abnormalities that have been reported include: reduced amplitude of distal esophageal contractions, reduced velocity of peristalsis and higher percentage of uncoordinated contractions. These motor abnormalities are referred to as "ineffective esophageal motility" (IEM) (5,8,10,11).

In order to obtain a better insight into the relation between esophageal peristalsis and reflux, esophageal motility should be investigated more specifically within the time frame of a reflux episode. Ambulatory solid state manometry and pH metry have the advantage over stationary manometry that prolonged, 24 hour recording is feasible and thereby will more closely reflect the (patho)physiology of daily life.

Aim of our study was to evaluate the esophageal body motor events that contribute to esophageal acid clearance in reflux patients with varying severity of reflux disease.

MATERIALS AND METHODS

Subjects

Between 1997 and 2002 eighty nine patients referred to the motility unit of the department of Gastroenterology of the Leiden University Medical Center for 24 hr pH

monitoring agreed to undergo combined ambulatory 24 hr esophageal pH and manometry recording. The study populations consisted of patients with previously documented endoscopic esophagitis, according to the criteria of Savary and Miller12: twenty-nine patients with esophagitis grade I, twenty-five patients with esophagitis grade II, five patients with esophagitis grade III, four patients with esophagitis grade IV; (all patients with esophagitis grade I-IV: mean age 48 yr; range 20-75 yr; 34M; 29F) In twenty-six patients no erosive esophagitis was found: grade 0 (mean age 49 yr; range 20-75 yr; 14M; 12F). The control group consisted of fifteen healthy subjects (mean age 30 yr; range 19-56 yr; 8M; 7F). These subjects were free of reflux symptoms and were not on chronic medication. Informed consent was obtained from each individual. The study had been approved by the Ethics Committee of the Leiden University Medical Center.

Ambulatory 24 hour esophageal pH- and manometry

In all subjects esophageal manometry (water-perfusion system) was performed to determine the position (upper margin) of the LES. Thereafter a catheter containing three solid-state pressure sensors at 5 cm distance from each other and a glass pH electrode catheter were positioned in the esophagus with the distal pressure sensor and the tip of the pH electrode 5 cm above the LES. Esophageal pressure was recorded at 5, 10, 15 cm above the upper margin of the LES. Both catheters were connected to a portable digital recorder (Microdigitrapper, Medtronic, Denmark).

All studies were performed under ambulatory conditions on outpatient basis and each person was encouraged to follow her/his daily routine during registration. Intake of food and drinks with pH below 4 was restricted. During the study, periods of retrosternal pain or heartburn, eating and drinking, and supine position were registered in a diary. Upon completion of the 24-hour monitoring, all recorded data were transferred to a personal computer and stored for later analysis.

Data analysis

Selection of subjects by grade of esophagitis may have become less accurate since nowadays many patients have been treated with acid inhibitory drugs when endoscopy is performed. By then, endoscopic signs of esophagitis may have regressed or even disappeared. Therefore we considered it more appropriate to divide reflux patients into subgroups based on results of 24 hour pH-metry.

Analyses were done for upright and supine reflux separately. For upright reflux, the duration of time with esophageal pH<4 of 0-4% was defined as normal acid reflux (n=40, controls and patients); 4-8% pH<4 as mild upright acid reflux (n=21); 8-12% pH<4 as moderate upright acid reflux (n=17) and >12% as severe upright acid reflux (n=26).13 For supine reflux, acid exposure time below 1.2% was defined as supine reflux in the normal range (n=20), from 1.2% to 10% as mild-moderate supine reflux (n=26) and >10% as severe supine reflux (n=26).13Thirty two subjects had no acid reflux in supine position (time pH<4 when supine ≤ 0.1%) and were not included in the calculations on supine reflux.

An acid reflux episode was defined as a sudden fall in esophageal pH to below 4 with a duration of at least five seconds including the last set of peristaltic contractions that raised the pH to above 4. In all subjects the episodes of acid reflux were marked and based on the diary divided in upright or supine periods. The data were processed by automated analysis

(Multigram 6.31, Medtronic, Denmark). The following parameters of acid reflux were measured: total duration of all reflux episodes (min), number of reflux episodes, mean duration of reflux episodes (min), duration of longest reflux episode (min) and number of reflux episodes lasting longer than five minutes.

Esophageal pressure rises with an amplitude of at least 20 mmHg above the baseline and a duration between 1.0 and 5.0 seconds were recognized as a contraction. All other pressure variations were classified as artifacts or regarded as an unclassified activity. In case of multiple-peaked contractions, the amplitude of the second peak has to be at least 50% of the amplitude of the main peak, the trough-to-peak duration had to be at least 0.5 seconds and the trough had to be 15% of the main peak. During reflux episodes we obtained from each pressure channel: total number of contractions, frequency of contractions (contractions/min), amplitude (mmHg) and duration (sec) of esophageal contractions.

The computer program categorized each contraction as either peristaltic, simultaneous or non-transmitted. Contractions were considered peristaltic when the onset at the proximal esophageal recording site is more than 0.3 but less than 5.0 sec before the contraction onset in the consecutive pressure channel. Contractions in consecutive channels were categorized as simultaneous when the peak interval was less than 0.3 seconds. Non-transmitted contractions occurred in one channel only. A peristaltic wave was defined as a group of coordinated contractions. The frequency of peristaltic waves per reflux episode was measured. Esophageal motility was divided into effective and ineffective peristalsis. Effective peristalsis was defined as complete (proximal, mid and distal contractions) peristalsis with adequate contraction amplitude (≥30 mmHg). Ineffective peristalsis was defined as complete peristalsis but inadequate contraction amplitude or incomplete peristalsis or non-peristaltic contractions. Data were analyzed for upright and supine periods separately. For all parameters, a mean value per registration period was calculated. The analyzed data were transferred to a database program for statistical evaluation.

Statistical analysis

Parameters with normal distributions were expressed as mean ± SEM. Other parameters were expressed as median. The Mann-Whitney U test for non-parametric data was used for statistical analysis to compare results between the groups of patients and the controls. Analysis of variance, followed by Student-Newman-Keuls analysis, was used to compare results between the different groups. Correlations were calculated using Spearman's rank correlation coefficient (Rs). The significance level was set at $p<0.05$.

RESULTS

Esophageal pH and motility in upright position

Subjects were divided into subgroups based on acid exposure time. The number of reflux episodes, duration of reflux episodes, duration of the longest reflux episode and number of reflux episodes >5 min increased significantly ($p<0.001$) with the severity of acid reflux (Table 1).

Parameters of distal esophageal body motility during reflux episodes are shown in Table 2. The total number of contractions per reflux episode, that is the number of contractions needed to raise esophageal pH to level above 4, was not significantly different between the four groups (Figure 1). Subjects with severe acid reflux had a significantly ($p<0.001$) lower frequency of distal esophageal contractions in the reflux episode (1.4 ± 0.1 contractions/min) than subjects with acid reflux in the normal range (2.1±0.1 contractions/min) and mild acid reflux (1.9 ± 0.2 contractions/min). The amplitude of contractions in the distal esophagus was slightly but significantly ($p<0.05$) lower in subjects with severe acid reflux (47 ± 2 mmHg) compared to normal acid reflux (56 ± 2 mmHg) but are considered in all groups to be adequate (amplitude ≥30 mmHg). The frequency of contractions (n/min) per reflux episode correlated inversely with the severity of acid reflux ($Rs = -0.40$; $p<0.0001$).

The efficacy of esophageal motility during reflux episodes in the upright period is shown in Table 3. The frequency of peristaltic waves during a reflux episode was significantly ($p<0.001$) lower in the subjects with severe acid reflux (1.4 ± 0.1 contractions/min) compared to subjects with acid reflux in the normal range (2.2 ± 0.1 contractions/min) and mild acid reflux (1.9 ± 0.2 contractions/min). Effective peristalsis during reflux episodes in the subjects with severe acid reflux (33 ± 3%) was significantly ($p<0.001$) lower compared to subjects with acid reflux in the normal range (46 ± 3%). An increasing esophageal acid exposure time correlated inversely ($Rs = -0.27$; $p=0.005$) with the percentage effective peristalsis.

Table 1. *Characteristics of esophageal pH-metry during upright position (mean ± SEM). Patients with gastroesophageal reflux disease and controls are divided in subgroups based on acid exposure time in the upright position during the 24 hour period. ^ denote significant (p<0.001) differences versus the normal group; # denote significant (p<0.001) differences versus the mild group; * denote significant (p<0.001) differences versus the moderate group.*

Subgroup (subjects)	Normal (n=40)	Mild (n=21)	Moderate (n=17)	Severe (n=26)
Time esophageal pH<4 (%), upright	0-4%	4-8%	8-12%	>12%
Reflux time (min)	26 ± 3	62 ± 7	88 ± 14	128 ± 13
Number of reflux episodes	19 ± 3	44 ± 9^	59 ± 18^	49 ± 6^
Duration of reflux episode (min)	1.7 ± 0.3	1.7 ± 0.2	1.9 ± 0.2	3.1 ± 0.4^#*
Duration of longest reflux episode (min)	3.7 ± 0.5	8.5 ± 1.6	16.4 ± 6.3^#	16.8 ± 2.7^#
Number of reflux episodes >5 min	0.3 ± 0.1	2.0 ± 0.7^	2.6 ± 0.7^	4.4 ± 0.7^#*

Table 2. *Characteristics of esophageal motility during reflux episodes in upright position. ^ denotes a significant (p<0.001) difference versus the normal group, # denotes a significant (p<0.001) difference versus the mild group, * denotes a significant (p<0.05) difference versus the normal group.*

Time esophageal pH<4, upright	Normal (0-4%)	Mild (4-8%)	Moderate (8-12%)	Severe (>12%)
Number of distal contractions / reflux episode	3.6 ± 0.7	3.0 ± 0.3	3.3 ± 0.5	3.6 ± 0.5
Frequency of distal contractions (N/min)	2.1 ± 0.1	1.9 ± 0.2	1.7 ± 0.2	1.4 ± 0.1^#
Amplitude of distal contractions (mmHg)	56 ± 2	51 ± 3	50 ± 3	47 ± 2*
Duration of distal contractions (sec)	2.3 ± 0.1	2.3 ± 0.1	2.1 ± 0.1	2.0 ± 0.1

Table 3. *Efficacy of esophageal motility during reflux episodes in upright position. Effective peristalsis is described as complete peristaltic waves with adequate contraction amplitude(>30 mmHg). Ineffective peristalsis is incomplete peristalsis or non-peristaltic contractions or contractions with inadequate amplitude. ^ denote significant (p<0.001) differences versus the normal group, # denotes a significant(p<0.001) difference versus the mild group.*

Time esophageal pH<4, upright	Normal (0-4%)	Mild (4-8%)	Moderate (8-12%)	Severe (>12%)
Frequency of peristaltic waves per reflux episode (N/min)	2.2 ± 0.1	1.9 ± 0.2	1.8 ± 0.1	1.4 ± 0.1^#
Effective peristalsis (%)	46 ± 3	45 ± 3	41 ± 4	33 ± 3^
Ineffective peristalsis (%)	54 ± 4	55 ± 3	59 ± 4	67 ± 3

Esophageal pH and motility in supine position

The results of supine esophageal pH-metry and motility during all supine reflux episodes are shown in Tables 4-6. The duration of reflux episodes, duration of longest reflux episodes and number of reflux episodes lasting more than 5 min increased significantly ($p<0.001$) with the severity of supine acid reflux (Table 4).

The total number of distal esophageal contractions per reflux episode in subjects with severe supine reflux (7.7 ± 2.5 contractions) was significantly ($p<0.05$) higher compared to subjects with normal supine reflux (3.6 ± 1.2 contractions; Table 5 and Figure 1). The frequency of distal esophageal contractions was significantly ($p<0.05$) lower in subjects with mild-moderate supine reflux (1.2 ± 0.2 contractions/min) or severe supine reflux (1.1 ± 0.4 contractions/min) compared to subjects with normal supine reflux (2.7 ± 0.5 contractions/min). The severity of supine reflux correlated significantly both with the number of distal esophageal contractions ($Rs = 0.60$; $p<0.05$) and the frequency of distal contractions during reflux episodes ($Rs = -0.43$; $p<0.001$). Amplitude and duration of distal contractions in the reflux episodes were not significantly different between the three subgroups (Table 5). This was true not only for distal esophageal motility but also for mid and proximal esophageal motility (data not shown). Thus, subject with severe supine acid reflux did not have a lower amplitude of distal esophageal contractions but needed more contractions to clear the acid while the contraction frequency also was significantly lower.

The frequency of peristaltic waves was significantly ($p<0.01$)lower in subjects with severe supine reflux (1.1 ± 0.4 waves/min) and mild-moderate supine reflux (1.2 ± 0.2 waves/min) compared to normal supine reflux (2.7 ± 0.5 waves/min). The percentage of effective peristalsis was not significantly different between subgroups of supine acid reflux (Table 6).

Table 4. *Characteristics of esophageal pH-metry during supine position (mean ± SEM). Only subjects with supine acid reflux were included. ^ denote significant (p<0.001) differences versus the normal group.*

Time esophageal pH<4, supine	Normal (n=20)(<1.2%)	Mild-moderate (n=26) (1.2-10%)	Severe (n=26)(> 10%)
Reflux time (min)	6.5 ± 3.0	24 ± 3.3	91.9 ± 13.9
Number of reflux episodes	9 ± 4	8 ± 2	22 ± 12
Duration per reflux episode (min)	1.6 ± 0.5	4.9 ± 0.9	12.8 ± 3.0^
Duration longest reflux episode (min)	2.0 ± 0.8	11.2 ± 2.1	50.0 ± 13.1^
Number of reflux episodes >5 min	0.3 ± 0.3	0.9 ± 0.1	3.0 ± 1.1^

Table 5. *Characteristics of esophageal motility during reflux episodes in supine position. (mean ± SEM). ^ denote significant (p<0.05) differences versus the normal group*

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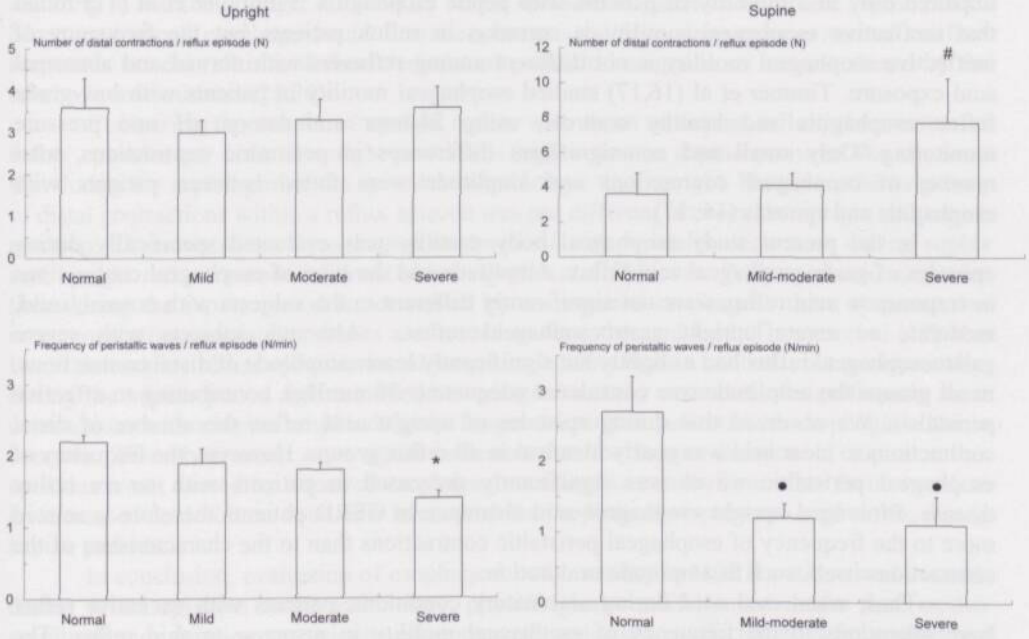
Time esophageal pH<4	Normal (<1.2%)	Mild-moderate (1.2-10%)	Severe (>10%)
Number of distal contractions/reflux episode	3.6 ± 1.2	4.1 ± 0.7	7.7 ± 2.5^
Frequency of distal contractions (N/min)	2.7 ± 0.5	1.2 ± 0.2^	1.1 ± 0.4^
Amplitude of distal contractions (mmHg)	56 ± 8	50 ± 3	51 ± 3
Duration of distal contractions (sec)	2.3 ± 0.2	2.3 ± 0.2	2.7 ± 0.1

Table 6. *Efficacy of esophageal motility during reflux episodes in supine position. Effective peristalsis is described as complete peristaltic waves with adequate contraction amplitude (>30 mmHg). Ineffective peristalsis is incomplete peristalsis or non-peristaltic contractions or contractions with inadequate amplitude. ^ denote significant (p<0.01) differences versus the normal group.*

Time esophageal pH<4	Normal (0-1.2%)	Mild-moderate (1.2-10%)	Severe (>10%)
Frequency of peristaltic waves per reflux episode (N/min)	2.7 ± 0.5	1.2 ± 0.2^	1.1 ± 0.4^
Effective peristalsis (%)	37 ± 8	30 ± 4	37 ± 3
Ineffective peristalsis (%)	63 ± 8	70 ± 4	63 ± 3

Figure 1. *Number of distal esophageal contractions required to raise pH to a level above 4 in subjects with varying severity of reflux for upright reflux (left upper panel) and supine reflux (right upper panel). Frequency of peristaltic waves (n/min) during a reflux episode in subjects with varying severity of reflux for upright reflux (left lower panel) and supine reflux (right lower panel).*
*upright * $p<0.01$ severe vs mild and normal*
supine # $p<0.05$ severe vs normal and mild-moderate
supine • $p<0.01$ severe and mild-moderate vs normal



DISCUSSION

Esophageal motor dysfunction consisting of failed or hypotensive peristalsis may lead to impaired volume clearance of acid refluxate.(14) The severity of reflux esophagitis is related not only to the frequency but also to the duration of gastroesophageal reflux episodes (6,7). Previous studies indeed have shown that in patients with gastroesophageal reflux disease esophageal motility is impaired (4-11) Esophageal dysmotility is associated with more severe reflux symptoms and failure of medical treatment. On the other hand, reflux parameters or grade of esophagitis do not significantly differ between patients with or without dysmotility (15) Kahrilas et al (4) demonstrated that esophageal peristaltic function is impaired only in a minority of patients with peptic esophagitis. Vinjirayer et al (11) found that ineffective esophageal motility is common in reflux patients but the frequency of ineffective esophageal motility is not different among refluxers with normal and abnormal acid exposure. Timmer et al (16,17) studied esophageal motility in patients with low-grade reflux esophagitis and healthy controls, using 24-hour ambulatory pH and pressure monitoring. Only small and non-significant differences in peristaltic contractions, total number of esophageal contractions and amplitude were found between patients with esophagitis and controls (16, 17).

In the present study esophageal body motility was evaluated specifically during episodes of gastroesophageal acid reflux. Amplitude and duration of esophageal contractions in response to acid reflux were not significantly different in the subjects with normal, mild, moderate or severe upright gastroesophageal reflux. Although subjects with severe gastroesophageal reflux had a slightly but significantly lower amplitude of distal contractions, in all groups the amplitude was considered adequate (>30 mmHg), contributing to effective peristalsis. We observed that during episodes of upright acid reflux the number of distal contractions to clear acid was nearly identical in all reflux groups. However, the frequency of esophageal peristaltic waves was significantly decreased in patients with severe reflux disease. Prolonged upright esophageal acid clearance in GERD patients therefore is related more to the frequency of esophageal peristaltic contractions than to the characteristics of the contractions itself, such as amplitude or duration.

Thus, when evaluated during ambulatory conditions, patients with excessive reflux have alterations in the frequency of esophageal motility in response to acid reflux. The mechanism underlying the impaired distal motor response to reflux is not clear. Altered esophageal sensitivity may be a mechanism underlying the reduced peristalsis. Subjects with frequent heartburn but without esophageal erosions have a lower threshold for esophageal sensation and pain (18). Sensory thresholds of patients with excessive reflux or Barrett esophagus however are significantly higher compared to patients with non-erosive GERD (19,20). Visceral sensitivity is affected by age. Older GERD patients have reduced sensations to chemical or mechanical stimuli despite increased acid exposure (21,22). In our study the age of patients with severe reflux was not different from that of patients with less pronounced reflux.

Disordered peristaltic activity does not improve after healing of esophagitis (23,24). It has been suggested that impaired esophageal motility in reflux esophagitis is a consequence of esophageal inflammation but others have also pointed to impaired motility as a pre-existing factor in the pathogenesis of reflux. Our observations provide additional information because we focused on effective esophageal motility. We have clearly shown that under

physiological conditions peristaltic function in subjects with mild to severe upright acid reflux is not different from the group with normal reflux. The frequency of esophageal contractions was significantly decreased in subjects with severe acid reflux, but the amplitude of contractions was not significantly affected.

During the supine reflux periods no differences in amplitude or duration of esophageal contractions were shown between the groups with different acid exposure time. However, in patients with severe supine reflux the number of distal contractions required to clear the esophagus from acid was significantly higher compared to those with normal and mild-moderate reflux. Apart form that, the frequency of peristaltic waves was also reduced, resulting in markedly longer duration of reflux episodes in patient with severe supine reflux. Sleep may impair esophageal acid clearance, but arousal from sleep ensures normal swallow responses to acid reflux and characteristics of peristaltic contractions are not altered by the level of consciousness (25,26).

Comparing the results of upright reflux with those of supine reflux, the number of reflux episodes per hour in upright position is higher than in supine position. We observed that during the supine period the episodes lasted longer than upright. However, the frequency of distal contractions within a reflux episode was not different between the upright and supine position. Characteristics of esophageal contractions and peristaltic sequences during supine and upright reflux episodes did not show significant differences. Prolonged acid clearance time during the supine period is not caused by an impaired esophageal motor response, but more contractions/peristaltic waves are needed to clear the acid load. Timmer et al (17) also found that supine reflux episodes lasted longer in patients than in controls, but paradoxically, during the supine period reflux induced esophageal activity consisted of significantly more contractions with a higher amplitude and a longer duration in patients with esophagitis than in controls. This observation once again indicates that the longer duration of supine reflux episodes is not caused by impaired esophageal motility but results from other factors such as an increased acid volume load or a latency of the esophageal response to acid reflux during supine periods.

In conclusion, evaluation of esophageal body motility in GERD patients and controls during reflux episodes under ambulatory, physiological conditions has shown that: neither amplitude, nor duration nor velocity of esophageal peristalsis is affected both for upright and supine reflux episodes the frequency of distal esophageal contractions is significantly reduced in patients with severe acid reflux during upright reflux episodes the number of contractions to clear acid is constant among various reflux subgroups whereas during supine reflux episodes the number is significantly higher in patients with severe acid reflux.

REFERENCES

1. Dent J, Holloway RH, Toouli J, Dodds WJ. Mechanisms of lower esophageal sphincter incompetence in patient with symptomatic gastroesophageal reflux. Gut 1988;29:1020-1028.
2. Castell DO, Murray JA, Tutuian R, Orlando RC. Arnold R. Review article: the pathophysiology of gastro-esophageal reflux disease – oesophageal manifestations. Aliment Pharmacol Ther 2004;20:14-25.
3. Helm JF, Dodds WJ, Pelc LR, Palmer DW, Hogan WJ, Teeter BC. Effect of esophageal emptying and saliva on clearance of acid from the esophagus. N Engl J Med 1984;310:284-288.
4. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology 1986;91:897-904.
5. Leite LP, Johnston BR, Barrett J, Castell JA, Castell DO. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. Dig Dis Sci 1997;42:1859-1865.
6. Kasapidis P, Xynos E, Mantides A, Chrysos E, Demonakou M, Nikolopoulos N, Vassilakis JS. Differences in manometry and 24-H ambulatory pH metry between patients with and without endoscopic or histological esophagitis in gastro oesophageal reflux disease. Am J Gastroenterol 1993;88:1893-1899.
7. Coenraad M, Masclee AAM, Straathof JWA, Ganesh S, Griffioen G, Lamers CBHW. Is Barrett's esophagus characterized by more pronounced acid reflux than severe esophagitis? Am J Gastroenterol 1998;93:1068-1072.
8. Ho S-C, Chang C-S, Wu C-Y, Chen G-H. Ineffective esophageal motility is a primary motility disorder in gastroesophageal reflux disease. Dig Dis Sci 2002;47:652-656.
9. Achem AC, Achem SR, Stark ME, DeVault KR. Failure of esophageal peristalsis in older patients: association with esophageal acid exposure. Am J Gastroenterol 2003;98:35-39.
10. Fouad YM, Katz PO, Hatlebakk JG, et al. Ineffective esophageal motility: the most common motility abnormality in patients with GERD-associated respiratory symptoms. Am J Gastroenterol 1999;94:1464-1467.
11. Vinjirayer E, Gonzalez B, Brensinger C, Bracy N, Obelmejias R, Katzka DA, Metz DC. Ineffective motility is not a marker for gastroesophageal reflux disease. Am J Gastroenterol 2003;98:771-776.
12. Savary M and miller G. The esophagus. Handbook and atlas of endoscopy. Solothurn, Switzerland: Gassmann A.G. 1978:135-139.
13. Masclee AAM, de Best ACAM, de Graaf R, Cluysenaer OJJ, Jansen JBMJ. Ambulatory 24-hour pH-metry in the diagnosis of gastroesophageal reflux disease. Scand J Gastroenterol 1990;25:225-230.
14. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology 1988;94:73-80.
15. Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized , clinical and manometric study. Gastroenterology 2001;121:5-14.
16. Timmer R, Breumelhof R, Nadorp JHSM, Smout AJPM. Esophageal motility in low-grade reflux esophagitis, evaluated by stationary and 24-hour ambulatory manometry. Am J Gastroenterol 1993;88:837-841.
17. Timmer R, Breumelhof R, Nadorp JHSM, Smout AJPM. Oesophageal motor response to reflux is not impaired in reflux oesophagitis. Gut 1993;34:317-320.
18. Rodriguez-Stanley S, Robinson M, Earnest DL, Greenwood-Van Meerveld B, Miner PB. Esophageal hypersensitivity may by a major cause of heartburn. Am J Gastroenterol 1999;94:628-631.

19. Winwood PJ, Mavrogiannis CC, Smith CL. Reduced sensitivity to intraoesophageal acid in patients with reflux induced strictures. Scan J Gastroenterol 1993;28:109-112.
20. Trimble KC, Pryde A, Heading RC. Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD. Gut 1995;37:7-12.
21. Lasch H, Castell DO, Castell JA. Evidence for diminishing visceral pain with aging: studies using graded intraesophageal balloon distention. Am J Physiol 1997;272:G1-G3.
22. Fass R, Pulliam G, Johnson C, Garewal HS, Sampliner RE. Symptom severity and oesphageal chemosensitivity to acid in older and young patients with gastro-oesophageal reflux. Age and aging 2000;29:125-130.
23. McDougall NI, Mooney RB Ferguson WR, Collins JSA, McFarland RJ, Love AHG. The effect of healing oesophagitis on esophageal motor function as determined by oesophageal scintigraphy and ambulatory oesophageal motility/pH monitoring. Aliment Pharmacol Ther 1998;12:899-907.
24. Timmer R Breumelhof R, Nadorp JHSM, Smout AJPM. Oesophageal and gastroesophageal reflux before and after healing of reflux oesophagitis. A study using 24 hour ambulatory pH and pressure monitoring. Gut 1994;35:1519-1522.
25. Orr WC, Robinson MG, Johnson LF. Acid clearance during sleep in the pathogenesis of reflux esophagitis. Dig Dis Sci 1981;26:423-427.
26. Orr WC, Johnson LF, Robinson MG. Effect of sleep on swallowing, esophageal peristalsis and acid clearance. Gastroenterology 1984;86:814-819.