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The Role of Esophageal pH Monitoring in Symptomatic Patients on PPI Therapy

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BACKGROUND: Ambulatory pH monitoring while on therapy is often recommended in gastroesophageal reflux disease (GERD) patients with continued symptoms. However, to date, little data exist to justify this indication.

AIM: To assess the role of pH monitoring in symptomatic patients despite aggressive therapy with typical or extra esophageal GERD.

METHODS: Retrospective review of 2,291 ambulatory pH tracings (1999–2003) identified subgroup of studies performed on proton pump inhibitor (PPI) therapy. Patients with prior fundoplication or Barrett's esophagus were excluded. Patients grouped on predominant presenting GERD symptoms: typical (heartburn and regurgitation) or extra esophageal (chest pain, cough, hoarseness, sore throat, shortness of breath, asthma). The distribution of abnormal pH parameters in each group calculated and univariate analyses assessed the probability of abnormal pH in each group. Abnormal cutoff values traditionally used in clinical practice and more stringent cutoff values used to determine distribution of abnormality as a function of cutoff values.

RESULTS: A total of 250 patients (mean age 54.3 yrs, 59% female) underwent pH monitoring on either daily (b.i.d.) or twice daily (q.d.) on PPI therapy: 115 (46%) with extra esophageal and 135 (54%) with typical GERD symptoms. Extra esophageal GERD patients were more likely to undergo pH monitoring on b.i.d. PPIs (OR = 2.7; 95% CI = 1.6–4.4; $p < 0.01$). 52 (93%) of typical and 74 (99%) of extra esophageal GERD patients on b.i.d. PPIs tested normal. The odds of a *normal* pH values were 11 times higher for patients on b.i.d. PPIs (OR = 11.4; 95% CI = 4.3–30.1, $p < 0.01$) than those on q.d. PPIs.

CONCLUSIONS: 1) The likelihood of an abnormal esophageal pH for symptomatic GERD patients on b.i.d. PPI is very small. 2) In this group of patients failing b.i.d. PPIs causes other than GERD should be sought.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disorder affecting approximately 35–40% of the adult population in the western world (1–3). Ambulatory pH monitoring is still considered by some to be the gold standard in GERD diagnosis and quantifying degree of esophageal acid exposure (4–6). The current indications for this test include evaluation of patients with either normal (or equivocal) endoscopic findings who are refractory to therapy, documenting abnormal esophageal acid exposure in endoscopy negative patients prior to surgical antireflux repair, and evaluating competence of the antireflux procedure in those with return of symptoms (7–9). Additionally, pH monitoring may also be useful to assess association between esophageal acid and persistent extra esophageal symptoms post therapy such as noncardiac chest pain, asthma, chronic cough, or laryngeal symptoms suspected GERD-related (9, 10).

Proton pump inhibitors (PPIs) are the most potent agents for the medical management of GERD; they act by selective noncompetitive inhibition of H/K ATPase in parietal cells (11). Although, many patients respond to empiric therapy with PPIs, a subgroup of patients initially suspected of having GERD do not improve on either conventional or higher doses of PPIs (12, 13). This may be due to lack of compliance, poor esophageal acid exposure control, or because the symptoms are not due to GERD. The latter may be true especially in patients with persistent extra esophageal symptoms on aggressive acid suppression (14). The pH monitoring while on PPI twice daily (b.i.d.) is currently recommended for such patients in order to assess the degree of acid suppression and determine if continued symptoms are due to poor acid control (14). However, to date no sufficient data exist to justify this indication. Thus, the aim of this study was to evaluate the clinical utility of pH monitoring in a group of patients with typical and extraesophageal symptoms suspected

to be GERD-related and who remain symptomatic despite PPI therapy and to determine if persistent symptoms indicate either the need for more aggressive therapy or the likelihood of another etiology.

MATERIALS AND METHODS

Patient Population

We retrospectively identified patients who underwent ambulatory esophageal pH monitoring at the Cleveland Clinic Center for Swallowing and Esophageal Disorders between January 1999 and September 2003. Studies performed in symptomatic patients while on PPI therapy were selected. Patients who had prior fundoplication, Barrett's esophagus, or poor compliance with medication were excluded. Patients were grouped on the basis of PPI dose, once daily (q.d.) or b.i.d., and on the nature of the predominant symptom, typical or extra esophageal. Typical symptoms were defined by the predominant presenting complaint of heartburn or regurgitation, while extra esophageal symptoms included chest pain, cough, hoarseness, sore throat, shortness of breath, or asthma.

Esophageal Testing

ESOPHAGEAL MANOMETRY. All subjects underwent esophageal manometry after an overnight fast to locate both the lower and the upper esophageal sphincter. A transnasal multilumen polyvinyl catheter (diameter 4.5 mm; Arndorfer Specialties, Greendale, WI) was continuously perfused with distilled water at a rate of 0.5 mL/min by a low compliance pneumohydraulic capillary infusion system. The station pull-through technique was used to determine the location and length of both upper and lower esophageal sphincters.

AMBULATORY ESOPHAGEAL pH MONITORING. Immediately after manometry, 24 h esophageal pH monitoring was performed in all subjects, using a 2.1 mm monocrystalline pH catheter with either one or two antimony electrodes (Synectics, Irving, TX). The pH electrodes were calibrated at 37°C in pH 7 and 1 buffer solutions (Fisher Scientific, Fairlawn, NJ) before and after each study was completed. After calibration, the distal pH electrode was passed nasally and positioned 5 cm above the proximal border of the lower esophageal sphincter and the proximal probe (when applicable) positioned 20 cm above the LES. The pH electrodes were connected to a portable digital data recorder (Mark 2 Gold, Synectics), which stores pH data every 4 s for up to 24 h. Patients returned home with instructions to keep a diary recording symptoms, meal times, time of lying down for sleep, and the time of rising in the morning. Patients were encouraged to perform their normal daily activities. There were no dietary restrictions. After 18–24 h, the catheter was removed and diaries were reviewed. After each pH study, data were downloaded onto an IBM-compatible computer for analysis using a Gastrosoft computer program (Gastrosoft, Irvin, TX).

The acid pH data (% time pH < 4) from both pH electrodes were analyzed separately for the total upright and supine periods. Abnormal reflux parameters were defined by values exceeding the 95th percentile values for any of the total, upright, or supine reflux parameters determined previously in our laboratory from studies on healthy volunteers (15, 16): distal % time pH < 4: $>5.5\%$ (total), 8.3% (upright), and 3.0% (supine) positions; proximal % time pH < 4: $>1.1\%$ (total), 1.7% (upright), and 0.6% (supine) positions. Individual subjects were subsequently defined as having an abnormal pH study if at least one of the above individual pH parameters was abnormal and/or if they had symptom index (determined by symptom association within 2 min of a reflux event) of greater than 50%. Additionally a more stringent cutoff value of 1.6% for % total time pH < 4 was used on the basis of prior reports of normal subjects on BID PPI (17–19).

Statistical Analysis

Patient demographics were compared between patients with typical and extra esophageal GERD and between those on q.d. or b.i.d. PPI doses. Continuous variables were summarized via means, medians, and standard deviations while categorical variables were described with estimated proportions. Chi-squared or Fisher's exact test was used to compare categorical variables while Wilcoxon rank sum test was used for continuous variables. Dosing therapies were compared by calculating the observed odds ratios and corresponding 95% confidence interval of typical *versus* extra esophageal symptoms as well as for abnormal *versus* normal pH readings.

RESULTS

A total of 2,291 patients had undergone pH monitoring between January 1999 and September 2003. Two-hundred-fifty

Table 1. Patient Demographics

	Total	Typical Symptoms	Extra Esophageal Symptoms	*p*
Number	250	135	115	
Mean age (25th,75th%)	53.5 (42–63)	53 (44–64)	54 (44–61)	0.85
Gender M/F	103/147	53/82	50/65	0.5
PPI q.d.* (%)	119 (47.6%)	79 (58.5%)	40 (34.8%)	$< 0.001^{\#}$
PPI b.i.d.** (%)	131 (52.4%)	56 (41.5%)	75 (65.2%)	

*PPI q.d. = Once daily proton pump inhibitor use.
**PPI b.i.d. = Twice daily proton pump inhibitor use.
#Comparison between typical and extra esophageal symptoms in the use of b.i.d. PPI.

Table 2. Symptom Distribution among Typical and Extra Esophageal GERD Patients Prior to pH Monitoring

	Total	Typical	Extra Esophageal
Number	250	135	115
Heartburn (%)	113 (45.2)	93 (68.9)	20 (17.4)
Regurgitation (%)	100 (40)	70 (51.9)	30 (26.1)
Chest pain (%)	73 (29.2)	22 (16.3)	51 (44.4)
Cough (%)	40 (16)	6 (4.4)	34 (26.9)
Hoarseness (%)	29 (11.6)	4 (3)	25 (21.7)
Sore throat (%)	42 (16.8)	7 (5.2)	35 (30.4)
Asthma (%)	11 (4.4)	1 (0.74)	10 (8.7)

patients were studied while on PPI therapy and constituted our study group (Table 1). The mean age (±SD) was 53.5 (±3.58); 103 (41.2%) males and 147 (58.8%) females. One hundred nineteen (47.6%) patients studied on q.d. and 131 (52.4%) patients on b.i.d. PPIs. One hundred thirty-five (54%) patients complained of typical symptoms, while 115 (46%) patients had extraesophageal symptoms. The age and gender distribution of the patients with typical or extraesophageal symptoms were not significantly different (Table 1). However, there was a higher proportion of patients with extraesophageal symptoms tested on b.i.d. PPIs (65.2%) than those with typical symptoms (41.4%). In fact, the latter group was significantly ($p < 0.001$) more likely to be studied on once daily PPI and the former were more likely to be tested on b.i.d. therapy (OR = 2.7; 95% CI = 1.6–4.4) (Table 1).

The predominant symptoms in the 250 study subjects included: heartburn (45.2%), regurgitation (40%), chest pain (29.2%), cough (16%), hoarseness (11.6%), sore throat (16.8%), and asthma (4%). As expected heartburn and regurgitation were predominant in the group of patients with typical symptoms while chest pain, cough, hoarseness, sore throat, and asthma were the predominant symptoms in the extraesophageal group (Table 2).

Table 3 compares the on therapy median % time pH < 4 in the distal and the proximal esophagus between patients with typical and extraesophageal GERD symptoms. The degree of esophageal acid exposure either in the distal or proximal esophagus was minimal for both groups of patients while on therapy. Additionally, % distal total and upright time pH < 4 were significantly ($p < 0.01$) lower in patients with extraesophageal symptoms than those with typical GERD symptoms (Table 3). Table 4 reveals that as expected, the median distal or proximal esophageal acid exposure were significantly ($p < 0.01$) less in those on b.i.d. than patients on q.d. PPIs. Patients with abnormal proximal pH parameters also had abnormal distal esophageal values.

Table 5 compares the proportion of patients with abnormal pH findings on either q.d. or b.i.d. PPI. The probability of having an abnormal pH finding was much lower in patients on b.i.d. than those on q.d. PPI (3.8% *vs* 31.1%, respectively). In fact, the estimated odds of normal pH are about 11 times higher in patients on b.i.d. PPI (95% CI 4.3–30.1, p-value < 0.01).

The individual and group pH parameters (total, upright, and supine) for all patients tested on PPI therapy is illustrated in Figure 1 and shows that the majority of patients tested had normal pH parameters. The distribution of pH abnormality based on presenting symptoms and dose of PPIs is shown in Figure 2. When tested on q.d. PPI, the observed proportion of abnormal pH monitoring was 31% and 30% in patients with typical and extra esophageal GERD symptoms, respectively. However, this proportion was much less for those tested on b.i.d. dosing especially for patients with extraesophageal GERD symptoms (1%) (Fig. 2). Including patients with normal pH parameters who had abnormal symptom index resulted in minimal change in these findings (Fig. 3). Similar trends were observed using a more stringent cutoff of normality for patients on PPI therapy (% time pH < 4 less than 1.6%) (Fig. 4). Only 9% of patients with continued extraesophageal symptoms on b.i.d. PPIs therapy had abnormal values (Fig. 3).

DISCUSSION

We found that ambulatory pH monitoring in symptomatic patients on b.i.d. PPIs is most likely to be normal, especially in the group of patients with extraesophageal symptoms. This holds true by different definition of abnormality. Using the commonly employed and less stringent cutoff for abnormality of % total time pH < 4 of 5.5% revealed that only 1% of the symptomatic patients with extraesophageal symptoms on PPI b.i.d. had abnormal esophageal pH values (Fig. 2). The inclusion of symptom index only increased this value to 2% of patients (Fig. 3) and using the least stringent (and less

Table 3. Median (25th, 75th Percentile) % Time pH < 4 by Presenting Symptoms

	Symptoms				
	Typical		Extra Esophageal		
% Time pH < 4	N	Median (25th, 75th%)	N	Median (25th, 75th%)	p-Value
Distal: Total	135	1.0 (0.2, 3.8)	114	0.3 (0.1, 1.2)	< 0.01
Upright	135	1.5 (0.3, 4.4)	114	0.5 (0.1, 1.3)	< 0.01
Supine	135	0.0 (0.0, 0.8)	114	0.0 (0.0, 0.4)	0.11
Proximal: Total	57	0.2 (0.0, 0.5)	69	0.1 (0.0, 0.3)	0.16
Upright	57	0.3 (0.0, 0.7)	69	0.2 (0.0, 0.4)	0.07
Supine	57	0.0 (0.0, 0.0)	69	0.0 (0.0, 0.0)	0.4

Table 4. Median (25th, 75th Percentile) % Time pH < 4 Based on PPI Dose

	Meds				
	q.d.		b.i.d.		
% Time pH < 4	N	Median (25th, 75th%)	N	Median (25th, 75th%)	*p*-Value
Distal: Total	118	1.2 (0.3, 4.9)	131	0.3 (0.1, 1.2)	<0.01
Upright	118	1.7 (0.4, 4.9)	131	0.4 (0.1, 1.5)	<0.01
Supine	118	0.0 (0.0, 2.7)	131	0.0 (0.0, 0.1)	<0.01
Proximal: Total	54	0.2 (0.1, 0.9)	72	0.1 (0.0, 0.3)	<0.01
Upright	54	0.3 (0.1, 1.3)	72	0.2 (0.0, 0.4)	0.01
Supine	54	0.0 (0.0, 0.0)	72	0.0 (0.0, 0.0)	0.09

commonly used) criteria the abnormal value was only 9% (Fig. 4).

We also found that the majority of the patients with typical symptoms (58.5%) were tested on q.d. PPI while the patients with extraesophageal symptoms (65.2%) were more likely to be tested on b.i.d. dosing. This finding may be due to differences in management. Indeed, patients with typical symptoms are often initially treated with a daily dose of PPI while those with extraesophageal symptoms usually receive a b.i.d. dose from the start. In our study, 31% of the patients with typical symptoms and 30% of those with extraesophageal symptoms had abnormal pH monitoring when treated with daily PPI, while this was the case in only 7% and 1% of patients on b.i.d. PPI (Fig. 2). Our results are consistent with those from other studies showing that increasing the PPI dose from q.d. to b.i.d. will normalize the pH parameters in the majority of patients with either typical or extraesophageal symptoms (13, 17, 20). This suggests that the control of esophageal acid exposure is a dose-dependant phenomenon. Thus, given the fact that nearly one-third of symptomatic patients on single daily PPI may have abnormal esophageal acid exposure, it may be more prudent to double the dose of PPI before performing a pH study.

Some advocate the use of a more stringent cutoff of <1.6% for normality in the distal esophagus for patients on b.i.d. PPIs (17–19). Kuo and Castell studied 19 normal subjects after a 7-day course of b.i.d. omeprazole and reported that the 95% upper limit of normal total % time of distal esophageal acid exposure was 1.6% (17). Using this criterion for normality, Katzka *et al*. (18) evaluated the importance of pH monitoring in 36 patients with extraesophageal symptoms resistant to b.i.d. omeprazole. They found that 72% of patients had normalized their esophageal pH parameters while 28% continued to have abnormal acid reflux. These results are similar to ours with abnormalities in 30% of patients with continued *typical* symptoms on b.i.d. PPIs; but differ from the 9% abnormality in those with *extraesophageal* symptoms (Fig. 4). Our population is twice as large as the one studied by Katzka *et al*. (18) improving the power of our observation and reducing variability often seen in small sampled populations. More importantly, the use of the more stringent cutoff of 1.6% is not universally accepted in practice, and its clinical relevance is uncertain.

The current recommendation for patients with extra esophageal symptoms unresponsive to PPI b.i.d. therapy is to perform pH monitoring on therapy in order to ensure adequate acid suppression (14). On the basis of our data, the probability of a normal result is 91–99%, casting doubt on the clinical utility and cost-effectiveness of such a recommendation. There are, however, certain circumstances where one may feel compelled to perform pH monitoring in such patients. This includes if there is a suspicion that the patient may not be compliant with taking the medication or more importantly in order to objectively document that esophageal exposure to acid reflux is not responsible for the continued symptoms in patients on b.i.d. PPIs. Clinically, the latter is the most likely reason this test may be performed. For example, when there is persistence from other subspecialties (such as ENT, pulmonary, or cardiology) on the role of GERD in patients with extraesophageal symptoms who often do not complain of heartburn or regurgitation (14) but are unresponsive to aggressive acid suppression. The use of pH monitoring in such cases is often not to look for continued acid reflux, as current recommendations suggest, but it is to prove that this entity is not the cause for patients' residual and/or persistent symptoms. Thus, are we performing the test for the sake of the patients or to show our colleagues in other subspecialty that our pretest suspicion is correct? Given the low, cost-effectiveness of such an approach, not to mention the physical discomfort for the patients undergoing the tests, perhaps we should shift our attention to better educating our colleagues and initiating a search for other potential causes for patients' extraesophageal symptoms. This will result in multidisciplinary care for our patients who may also benefit from finding the cause and appropriately treating their symptoms. For example, alcohol, tobacco, allergies, asthma, post

Table 5. Distribution of pH Test Results and the Odds Ratio of Normality.

PPI dose	Patients with Abnormal pH (%)	Patients with Normal pH (%)	Estimated Odds Ratio (95% CI)	*p*-Value
q.d. (n = 119)	37 (31.1)	82 (68.9)		
b.i.d. (n = 131)	5 (3.8)	126 (96.2)	11.11(4.1, 25.0)	<0.01

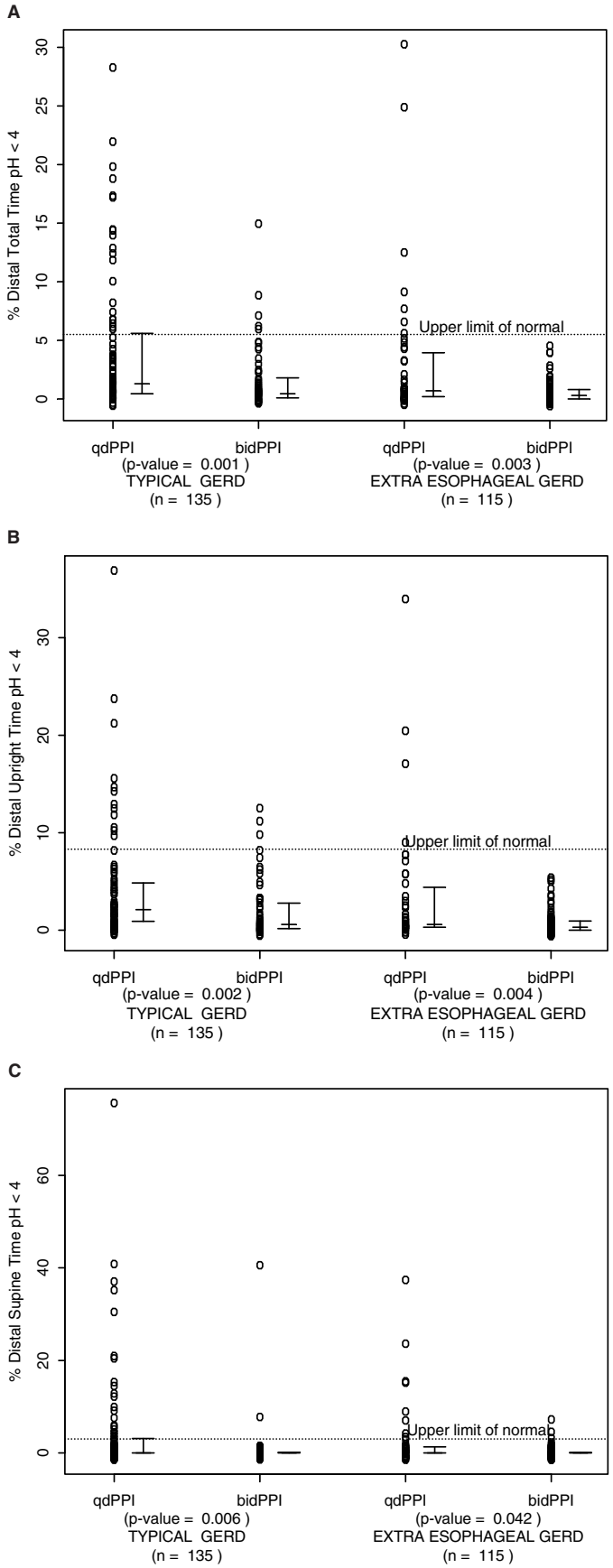

Figure 1. Individual and group distal esophageal % pH < 4 parameters for patients with typical and extra esophageal symptoms as a function of PPI dose: (*A*) Total, (*B*) Upright, (*C*) Supine. Dash line indicates the upper limit of normality.

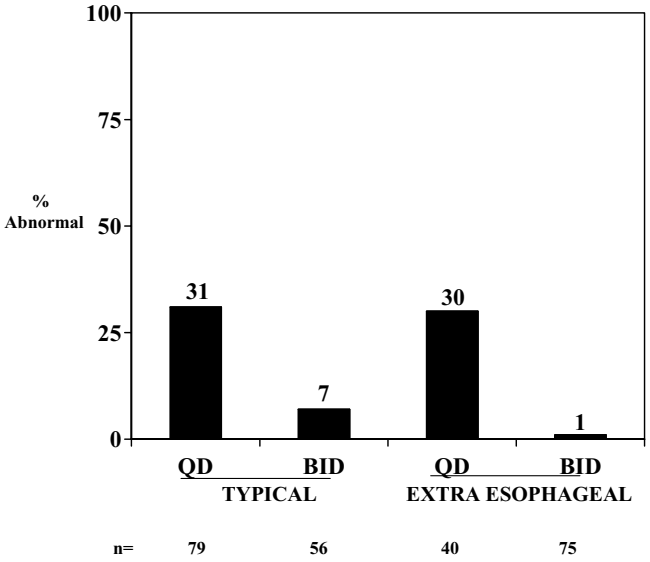

Figure 2. Percentage of typical and extra esophageal GERD patients with abnormal pH paramerters. Abnormality defined by % time pH < 4 greater than 5.5% (total), 8.3% (upright), and 3.0 (supine) (ref. 15).

nasal drip, and voice overuse or abuse may be other potential causes of laryngeal signs (21). Gastrointestinal diagnoses such as gastroparesis or hypersensitive esophagus should also not be overlooked.

In conclusion, we found that in patients with continued extraesophageal symptoms on aggressive acid suppressive therapy, pH monitoring is most likely to be normal using conventional and the most stringent criteria of normality. In such patients symptoms are most likely not related to acid

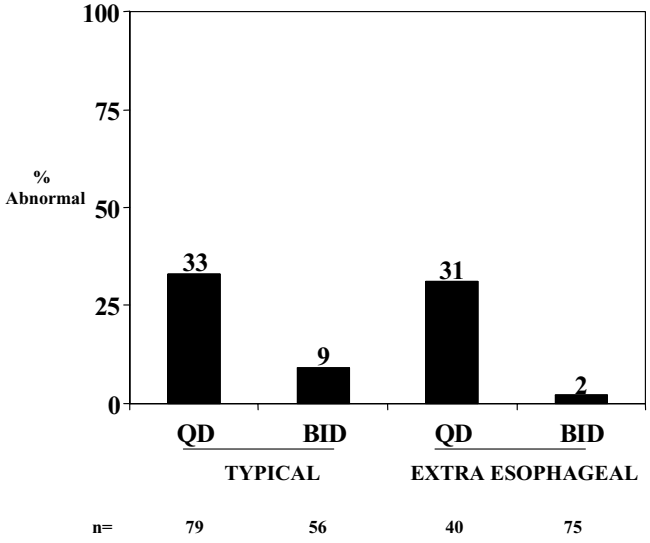

Figure 3. Percentage of typical and extra esophageal GERD patients with abnormal pH paramerters. Abnormality defined by % time pH < 4 greater than 5.5% (total), 8.3% (upright), and 3.0 (supine) (ref. 15) and abnormal symptom index.

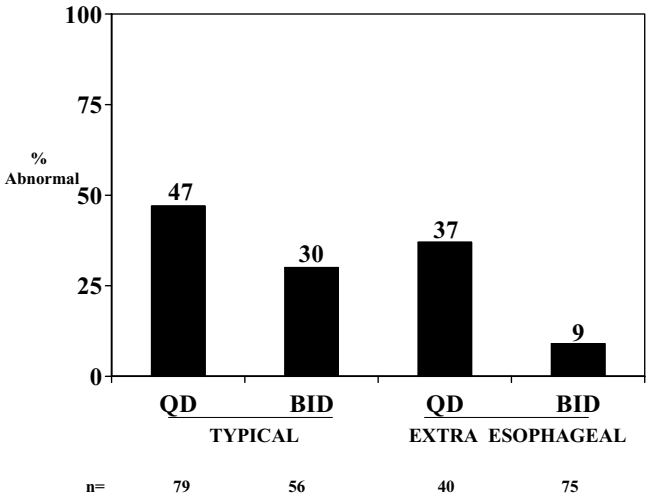

Figure 4. Percentage of typical and extra esophageal GERD patients with abnormal pH paramerters. Abnormality defined by % total time pH < 4 greater than 1.6% (ref. 17).

reflux; however, the role of nonacid reflux in these patients requires further testing. Future studies with impedance monitoring may provide the needed data in this regard. Until then, continued symptoms in such patients should alert us to search for other previously overlooked causes.

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