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Increased Risk for Persistent Intestinal Metaplasia in Patients with Barrett's Esophagus and Uncontrolled Reflux Exposure before Radiofrequency Ablation

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Abstract

Background & Aims—Radiofrequency ablation (RFA) is a safe alternative to esophagectomy for patients with dysplastic Barrett's esophagus (BE). Although some studies have indicated that RFA is effective at eradicating dysplasia, most have found that RFA is not as effective in eradicating intestinal metaplasia. We investigated whether uncontrolled reflux is associated with persistent intestinal metaplasia after RFA.

Methods—Thirty-seven patients with BE underwent RFA, high resolution manometry, and 24 hour impedance-pH testing; they received proton pump inhibitors twice daily. Patients returned every 2 months for repeat treatment or standard surveillance. Patients were classified as complete responders (CRs) if all intestinal metaplasia was eradicated in fewer than 3 ablation sessions. We analyzed clinical parameters to identify factors associated with a CR or incomplete response (ICR).

Results—Among the 37 patients, 22 had a CR and 15 had an ICR. Mann-Whitney U tests revealed that length of BE, size of hiatal hernia, and frequency of reflux, but not acid reflux,

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differed between CRs and ICRs. CRs had fewer weakly acidic than ICRs (29.5 vs 52; $P<.05$) and total reflux events (33.5 vs 60; $P<.05$), and a trend towards fewer weakly alkaline events (1.0 vs 5.0; $P=.06$). No other clinical or manometric features differed between groups.

Conclusion—Uncontrolled, predominantly weakly acidic reflux despite twice daily proton pump inhibitor therapy before RFA increases the incidence of persistent intestinal metaplasia after ablation in patients with BE. Length of BE and size of a hiatal hernia were also associated with persistent intestinal metaplasia after RFA.

Keywords

esophagus; esophageal cancer; risk factor; prognosis

Introduction

Barrett's esophagus (BE) carries an increased risk of adenocarcinoma compared to the general population[1]. This observation has led to considerable interest in ablative therapies for dysplastic BE, with the goal of decreasing the risk of adenocarcinoma. Recent investigations have focused on radiofrequency ablation (RFA) using the HALO (BARRX Medical Inc., Sunnyvale Ca) ablative system. A randomized controlled trial demonstrated that the rate of complete eradication of low grade dysplasia (LGD) and high grade dysplasia (HGD) was 90% and 81% respectively.[2] However, the efficacy of RFA for eradication of intestinal metaplasia (IM) varies widely in the reported literature with complete response for IM (CR-IM) rates ranging between 46 and 98%[2–12]. The largest randomized controlled trial to date[2] reported only a 70% eradication rate for IM and eradication rates for dysplasia are consistently reported to be greater than eradication rates for IM. The recent 5-year ablation durability study reported that when CR-IM was achieved, the response seemed to be durable for 3 years after ablation[13]. However, that study also revealed that many patients required at least 4 ablations in the first year to achieve this response and 25% of patients had recurrent IM during follow-up. A recent investigation by Vacarro et al reported that 25% of patients had recurrent IM within one year of 'successful' ablation [14]. It is unclear why some patients have a durable, complete eradication of IM while others have recurrent or persistent IM after RFA. The presence of IM after ablative therapy is concerning as it implies ongoing malignant potential.

In vitro studies have shown that both acid and other gastric constituents (i.e. bile salts) are toxic to the esophagus, and lead to early changes in the pathogenesis of BE [15,16] . Patients with BE have been shown to carry the highest reflux exposure of any patient population.[17] Previously, the clinical relevance of this reflux exposure was dismissed, as most patients are asymptomatic with once daily PPI therapy. However, given the role of reflux in the pathogenesis of BE, it is conceivable that differences in ongoing reflux exposure may be critical in the persistence of IM after RFA therapy. Indeed, some studies suggest that aggressive reflux management may decrease the recurrence of IM after ablation [18]. Furthermore, a recent pilot investigation reported that when RFA was combined with antireflux surgery, 80% of patients achieved complete eradication of IM with only one ablation.[19] These data suggest that ongoing reflux may contribute to the persistence of IM after ablative therapy. As such, we sought to investigate whether ongoing reflux exposure (both acidic and non-acidic) was associated with persistent IM after RFA.

Methods

Patient selection

Thirty-seven consecutive patients were recruited from our outpatient GI faculty practice. All patients underwent high resolution esophageal pressure topography (EPT) and 24 hour impedance-pH monitoring prior to ablation therapy. The diagnosis of BE and dysplasia was confirmed by an expert gastrointestinal pathologist at our institution. Barrett's esophagus was defined by the presence of specialized columnar mucosa with goblet cells. Patients with non-dysplastic BE were included if they were deemed high risk (long segment BE with a family history of esophageal adenocarcinoma). Patients with raised or nodular lesions were excluded, as were patients with prior endoscopic therapy for BE. This study was approved by the Northwestern University Institutional Review Board.

High resolution manometry

A solid-state manometric assembly with 36 circumferential sensors spaced at 1 cm intervals was used (Given imaging, Los Angeles, CA). Studies were done after at least a 6-hour fast. The patients underwent transnasal placement of the manometric catheter and positioned to record from the hypopharynx to the stomach. Once in a correct position, the catheter was taped to the nose to maintain it throughout the study. Measurements were collected in both supine and sitting positions to assess esophageal and EGJ function. The manometric protocol included at least ten 5-ml swallows in each posture as well as a 5-minute period to assess basal sphincter pressure.

Impedance-pH testing

The impedance-pH catheter (Medical Measurement Systems Inc., Denmark) was positioned transnasally into the esophagus so that the pH electrode was 5 cm proximal to the EGJ based on landmarks provided by manometry, performed earlier on the same day. Recordings lasted for 24 hours, during which time the impedance-pH data were collected and stored in an external receiver attached to the catheter. Patients were encouraged to engage in their usual daily activities. All patients were taking twice-daily proton pump inhibitors (omeprazole 20 mg bid, esomeprazole 40 mg bid, lansoprazole 30 mg bid, rabeprazole 20 mg bid, or pantoprazole 40 mg bid) for at least two weeks prior to and during impedence-pH testing.

Reflux events were automatically identified and counted. Acid exposure time (AET) was reported as the percentage of the 24-hour study that the pH was less than four. . Each reflux event was correlated with the associated pH of that event and labeled either acidic (AR, pH<4), weakly acidic (WAR, pH 4–7), or weakly alkaline (WalkR, pH≥7) as per consensus guidelines [20]. Impedence-pH data were independently reviewed in a blinded manner to verify the automated findings (Figure 1).

Radiofrequency ablation protocol

The ablation protocol was standardized for all patients and all endoscopy was performed by a single highly experienced endoscopist blinded to the results of the impedance-pH and manometry studies. Initial circumferential ablation was performed with the HALO^{360} catheter (BARRX, Sunnyvale Ca). Patients returned after 2 months, at which time residual BE was focally ablated using the HALO^{90} ablation catheter. All patients received circumferential ablation during the first treatment session and focal ablation with the Halo 90 device on all subsequent ablations. Patients with dysplasia underwent at least two ablations (one circumferential and one focal). In that cohort, we included at least one focal ablation to the newly formed squamocolumnar junction. However, if this was not achieved until the 3rd endoscopy, it was not our protocol to routinely ablate what endoscopically appeared to be a complete response.

Patients then returned in two months for surveillance endoscopy. Surveillance endoscopy was done using high definition endoscopes (Olympus GIF-H180, Olympus corp., Tokyo Japan) with white light and narrow band imaging. At that point, repeat RF treatment was performed if columnar mucosa was noted endoscopically; otherwise surveillance was performed with a standard biopsy protocol (see below). Patients with complete eradication of all dysplasia and IM at the third endoscopy were considered complete responders (CR) and those with residual dysplasia or IM were considered incomplete responders (ICR). Complete responders underwent surveillance again at one year from the initiation of therapy. If IM was found on subsequent biopsy in a patient labeled CR, they were re-categorized as ICR. Incomplete responders underwent repeat treatment every two months until eradication of IM/dysplasia was achieved. Patients were followed in this protocol for one year after the initial ablation therapy. All patients were placed on twice-daily proton pump inhibitor therapy consistent with their prior usage and were provided viscous lidocaine, sucralfate, and acetaminophen with codeine for short-term symptom relief.

Biopsy Protocol

After ablative therapy patients underwent surveillance. Biopsies were taken using jumbo forceps (RJ4, Boston Scientific, Natick, MA) in four quadrants, starting in the gastric cardia and continuing proximally at 2 cm increments until the proximal margin of the BE segment was sampled. Biopsies were evaluated for the presence of dysplasia and IM. Biopsies were interpreted by one of two expert gastrointestinal pathologists at our institution who were blinded to patient status.

Outcome

The primary aim of the study was to determine whether the severity of ongoing reflux exposure prior to treatment was associated with persistent IM after RFA therapy. Patients with durable, complete eradication of all dysplasia and IM after two ablations were labeled CR, whereas those patients with persistent IM after two ablations were labeled ICR. While reflux exposure was our primary variable of interest between CR and ICR, we also considered the potential impact of manometric and clinical factors on persistent IM after RFA. The manometric properties evaluated included esophagogastric junction (EGJ) pressure, percent failed peristalsis and the distal contractile integral (length × amplitude × duration of the distal esophageal contraction in mmHg-s-cm ^{21}). The clinical factors analyzed were hiatal hernia size, baseline histology, length of BE, age, body mass index (BMI) and smoking history.

Statistical Analysis

Data were entered and analyzed in SPSS v.20. Measurement of central tendency revealed that the data were not normally distributed and violated the assumption of homogeneity of variances. Medians are reported in place of means. To estimate effect sizes for future studies powered to examine *predictors of response* with logistic regression, we performed independent sample non-parametric tests to determine differences between ICR and CR with respect to several factors likely to influence response. Alpha was set at .05. Actual statistical power for these analyses was 82%. Reflux parameters (WAlkR, WAR, TR, percent acid exposure) clinical and manometric factors including hiatal hernia length, maximum length of BE as determined by the Prague classification, baseline histology, smoking history (current, past, never), age and BMI were compared between groups using Mann Whitney U and Fisher's Exact tests.

Results

Pre-treatment, clinical and manometric variables by responder status

Thirty-seven consecutive patients (median age 64.0; range 30–79) underwent ablative therapy; all but 3 had a hiatal hernia. Among the 37 patients entered, 22 patients achieved eradication of all IM in less than three ablation sessions (CR- complete responders) while 15 patients required three or more ablations due to persistent IM or dysplasia (ICR- incomplete responders). After a third ablation 24 patients were CR and 13 ICR. In total 35 of 37 patients achieved CR-IM at the end of the 12-month study follow up period, with two patients being persistent non responders and subsequently referred for cryoablation. The median number of ablations in the total cohort was 2 (range 2–6). and in the ICR group, 4 (range 3–6). All of the CR group underwent two ablations. The median number of endoscopies in the CR group was 4 (range 3–4) and in the ICR group, 5 (range 4–7.) Only one patient who was initially labeled CR was re-categorized as ICR on follow-up; this did not change the analysis.

There were no manometric features distinguishing CRs from ICRs. One patient in the CR group had distal esophageal spasm. Median basal EGJ pressure in the CRs was 7.5 mmHg compared to 6.0 mmHg in the ICRs (ns). The median DCI was 648 mmHg-s-cm in the CRs compared to 566 mmHg-s-cm in the ICRs (ns). Weak and failed peristalsis was equally common in the CRs and ICRs (CR 47% weak, 10% failed; ICR 53% weak, 9% failed; ns).

There were significant differences between CR and ICR with respect to length of BE (4.0 vs. 6.0 cm, $z = 3.1$, $p < .01$, [95% CI = −5.0,0.1] and size of hiatal hernia (2.3 vs. 3.0 cm, $z = 3.2$, $p < .01$ [95% CI = −3.0, −0.5). There were no significant differences between groups with respect to the other clinical parameters—age, BMI, smoking history or histology (Table 1).

Comparison of reflux exposure between CR and ICR

As hypothesized,reflux exposure was most strongly asso ciated with response status. The AET varied greatly, but was on average less than 5%, the upper limit of normal in both groups (median 2.0% range 0–22%). Seven of the 37 patients (20%) with BE had abnormal distal esophageal acid exposure despite twice daily PPI therapy. Weakly acid reflux events were significantly more common in ICR *vs.* CR (52 vs. 29.5, $z = 2.2$, $p = .03$ [95%CI = −65.0,2.0), and TR (60.0 vs. 35.5, $z = 2.1$, $p = .03$ [95%CI = −67.0,−4.0). Weakly alkaline reflux events were rare but there was a trend for them to be more common in ICR (5.0 vs. 1.0, $z = 1.9$, $p = .06$ [95%CI = −8.0,0). Acid reflux events did not differ between groups.

In order to evaluate whether our findings were the result of insufficient ablation treatments, we re-evaluated the data classifying patients as CR or ICR on the basis of at least 3 ablation sessions. This resulted in two patients in the ICR group being re-categorized to CR but it did not change the overall analysis as we continued to find significantly more WAR, WAlkR and TR events in ICR compared to CR. These results are illustrated in Figure 2.

Finally, we performed Pearson correlations to determine the extent of overlap between variables.) Length of BE was positively correlated with size of hiatal hernia ($r = 0.54$, $p < .01$). Length of BE and hiatal hernia were also positively correlated with age ($r = 0.34$, $p < .05$; $r = 0.54$, $p < .01$, respectively) and negatively correlated with WAlkR ($r = −0.59$, $p < .05$).

Body mass index was positively correlated with WAlkR ($r = 0.39$, $p < .05$) and length of BE (0.34, $p < .05$). Acid reflux was positively correlated with EGJ pressure (.37, $p < .05$) and BMI (.34, $p < .05$). Weakly acidic reflux and TR were positively correlated with size of hiatal hernia ($r = 0.35$, $p < .05$; $r = 0.40$, $p < .05$).

Discussion

The major finding from this study was that the severity of ongoing reflux exposure despite twice daily PPI therapy was associated with persistent IM in BE patients after RFA. In particular, WAR events, which comprise a majority of reflux events in patients taking PPIs were most strongly associated with persistent IM after RFA. Additional factors associated with an incomplete response to RFA were hiatal hernia size and length of BE. Baseline histology, manometric variables, age, smoking history and BMI were not associated with persistent. These data suggest that uncontrolled reflux, irrespective of acidity, predisposes BE patients to an incomplete RFA response.

A multitude of studies have reported on the efficacy of RFA for BE ablation and it is clear that RFA is a safe and effective therapy for BE-associated dysplasia. [2,3,5–10,22–24] The current report suggests that RFA is less effective at eradicating IM. A plausible explanation for this is that RFA does not address the underlying pathophysiology of BE, which is abnormal reflux. [25,26] In fact, patients with BE are known to have more reflux than patients with peptic strictures and severe erosive esophagitis, regardless of concomitant symptoms. [27] Although there are favorable mucosal changes after RFA therapy, these patients likely continue to have uncontrolled reflux as demonstrated with impedance-pH reflux monitoring prior to treatment. Proton pump inhibitors are usually effective at decreasing the acidity of this refluxate, but several studies have shown that even this is not uniformly achieved. [28–30] In our dataset, 20% of patients had continued abnormal esophageal acid exposure despite twice daily PPI therapy. Furthermore, considerable in-vitro and ex-vivo data suggest that bile salts are equally caustic to the esophageal epithelium and are by themselves sufficient to cause BE and BE related cancer. [16,26,31–34] Consistent with these observations, we found that patients with a greater number of WAR and WAlkR events were less likely to achieve eradication of IM. We also noted an association between size of hiatal hernia and response to RFA. This is potentially attributable to the anatomic deformity imparted by the hernia itself or to its pathophysiological significance in both facilitating reflux events and impairing refluxate clearance. [35–38] With respect to anatomy, the hernia may compromise the ability to achieve adequate tissue apposition with the ablation catheter. This limitation was addressed in a study of intraoperative RFA at the time of fundoplication in patients with large hiatal hernias. Laparoscopy assisted RFA was performed to facilitate increased mucosa contact time and CR-IM was achieved in 80% of patients after only one ablation.[19] However, it is uncertain as to whether that excellent response rate was the result of the intraoperative ablation or the correction of reflux with fundoplication.

The largest existing follow-up study for RFA (AIM dysplasia) reported that in patients who achieved CR-IM at two years, 25 percent had recurrent IM at year five. Furthermore, many patients required more than four ablation sessions to achieve a complete response. [24] These findings highlight two important issues regarding RFA: 1) that patients often require multiple ablation sessions over a period of a year to eradicate all dysplasia and IM and 2) that despite complete eradication of all dysplasia and IM, recurrence of IM is frequently observed during subsequent surveillance. The current investigation identified ongoing reflux as a potential risk factor for persistent IM after two ablation sessions. Although our follow-up period was insufficient to address the second phenomenon, it is possible that ongoing reflux may also be contributing to recurrent IM as well.

In this investigation, we categorized patients as CRs if they achieved complete eradication of all dysplasia and IM after two ablations sessions. Those with persistent IM/dysplasia at that time point were labeled ICR. Other investigations have reported that the median number of ablations to achieve CR-IM was three. However, there is currently no consensus on the

number of treatments needed to define a non-responder. A common investigational approach is of ablation every two months until visible IM is gone. We have found that approximately 60% of patients achieve CR-IM after two ablation sessions, whereas the remainder required additional treatments. That observation led us to adopt the two treatment criterion for defining CRs. In fact, in our patient population, the median number of ablations needed for CR was two. To explore the importance of the threshold selected, we also evaluated differences in WAR among patients with at least three treatments. Using that definition, an additional two patients achieved CR-IM, but that did not change the overall results of our analysis. Two patients were complete non-responders (persistent IM or dysplasia) at the end of the study follow-up. As such, 95% of patients in our cohort eventually achieved CR with RFA therapy.

There are a few limitations of this study. Our sample consisted of only 37 subjects, unequal sample sizes, and a non-equal distribution of means and variance. An analysis using logistic regression would have required a minimum sample size of 138 (69 per group) based on the preliminary data we acquired in this study. Hence, the study was underpowered to address the question of which factors *predict* response to RFA in BE, and instead can only report on factors that differ between CR and ICR. The study was, however, sufficiently powered for the analysis performed ($\beta = .82$), thereby providing the most comprehensive data yet available on reflux and esophageal physiology in patients undergoing RFA therapy. Lastly, as we only had two persistent non-responders, we cannot comment on the role of reflux exposure on that outcome. In addition, this was a single center study and assumes the inherent bias of that.

In conclusion, we found that the severity of ongoing reflux exposure, hiatal hernia size, and length of BE were associated with persistent IM after RFA therapy. While we are unable to speak to the unique contribution of reflux exposure on response to RFA because of significant autocorrelation between hiatal hernia and reflux, that correlation was quite modest.. These data suggest that post-ablation reflux exposure, specifically WAR, in BE patients is an important determinant of persistent IM and hence, may imply a persistent risk of adenocarcinoma after RFA. Further investigation with larger cohorts and long term follow-up will be needed to determine whether physiologic testing and operative management of reflux should be considered in patients who undergo RFA.

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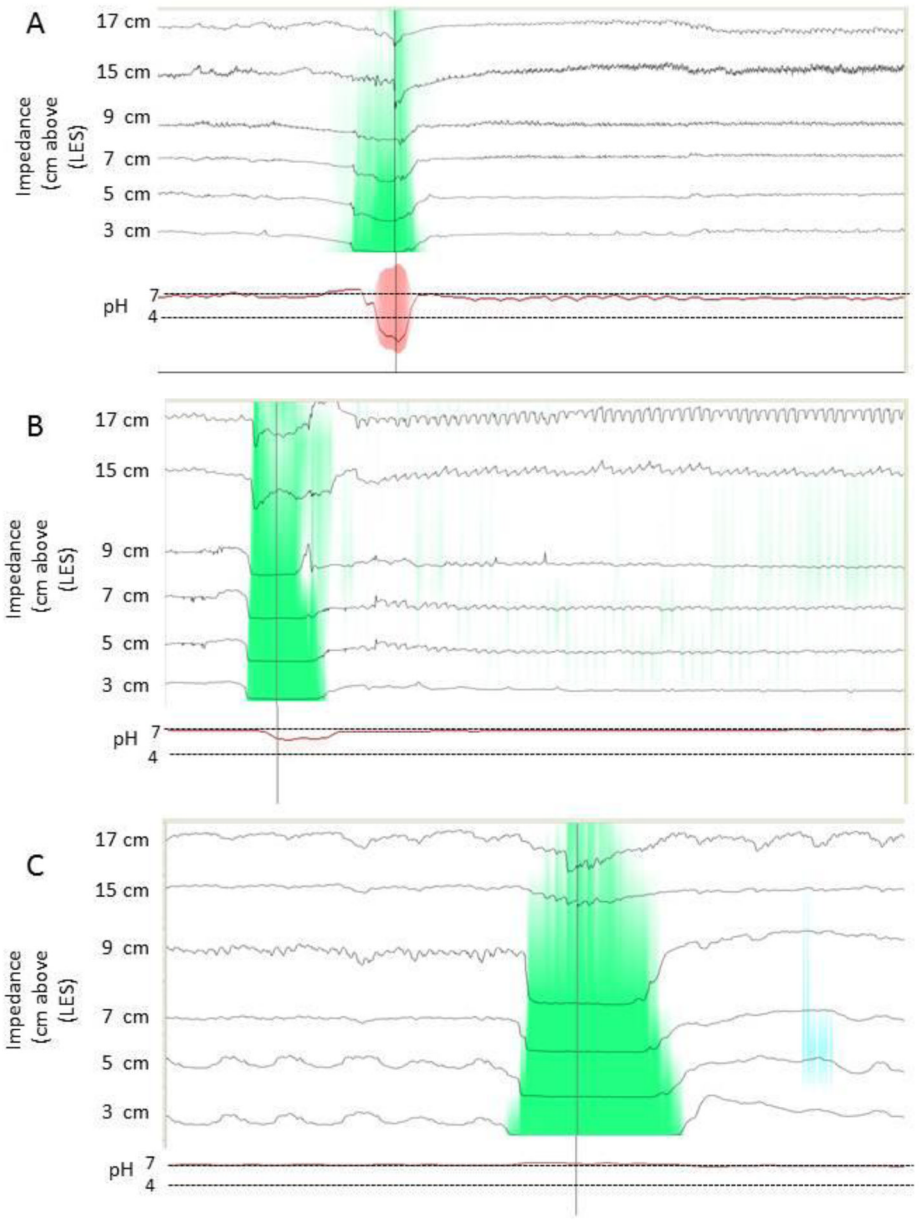

Figure 1.
Impedance-pH recordings demonstrating acid reflux (A), WAR (B), and WAlkR (C). The green colorization on the impedance tracings illustrates the retrograde flow of refluxate to the most proximal recording site (17 cm). The corresponding pH tracing in red at the bottom demonstrates the nadir pH to be 2.3 in A, 5.8 in B, and 7.2 in C.

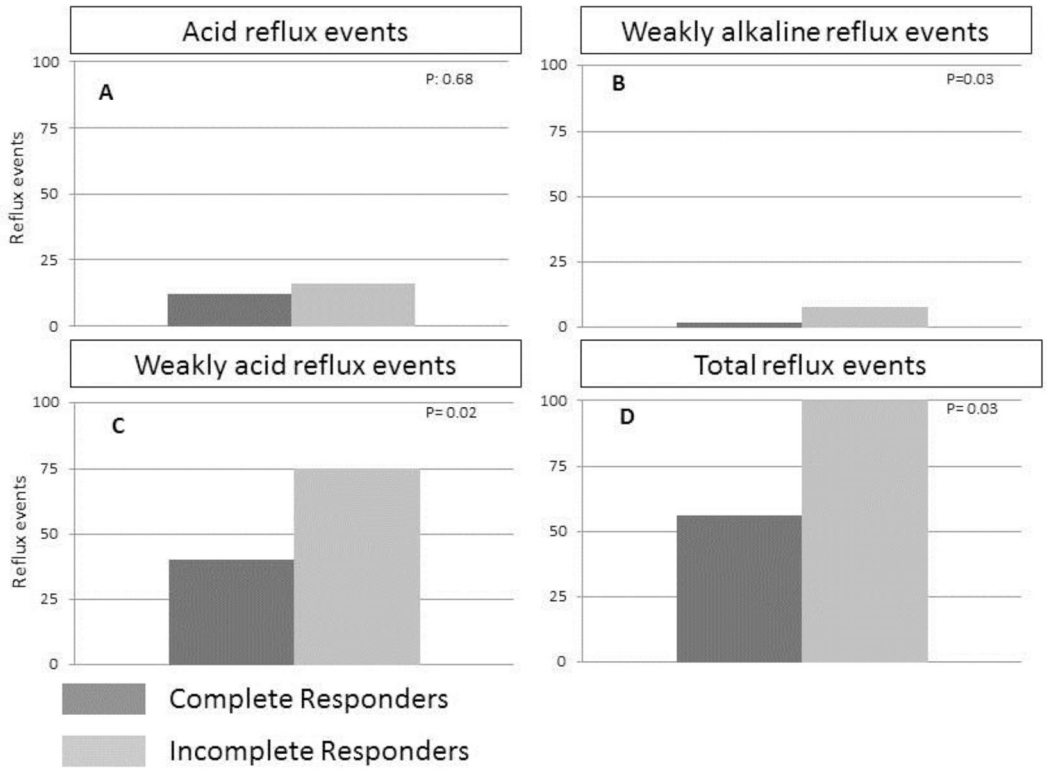

Figure 2.

Reflux exposure was compared between ICR and CR after recalculating the data based on at least 3 ablations**. (A)** AR varied considerably, but there was no significant difference between ICR and CR. **(B**) Weakly alkaline reflux events (pH>7) were uncommon, however, they were significantly more frequent in ICR compared to CR. Weakly acidic reflux (C and D) events accounted for the bulk of total reflux events and were significantly more frequent in ICR compared to CR.

Table 1

Variables by responder group CR vs. ICR (Mann Whitney U test). Four factors were significantly different between groups: BE length, hiatal hernia length, WAR, and TR. While there was a trend for WAlkR, it was not statistically significant.

Variable	**CR (N = 22)**		**ICR (N =15)**		**Test Statistic**		
	Median	**Variance**	**Median**	**Variance**	**z**	**p**	**95% CI**
	Baseline Characteristics						
Age	**63.0**	147	**68.0**	101	1.5	0.14	
BE (cm)	**4.0**	3.9	**6.0**	10.4	3.1	**<.01**	**−5.0,0.1**
Histology NDBE/LGD/HGD	**7/10/5**		**4/7/4**		X2 = 0.14, p =0 .93		
HH (cm)	**2.3**	1.5	**3.0**	9.2	3.2	**<.01**	**−3,−0.5**
BMI	**28.0**	16.0	**30.0**	21.1	1.3	0.19	
Never Smoked	**15** (68%)		**12** (80%)		X^2 = 1.0, p = 0.59		
	High Resolution Manometry						
EGJP (mmHg)	**7.5**	62.8	**6.0**	28.9	−0.82	0.42	
DCI (mmHg-s-cm)	**648**	1501343	**566**	732623	−0.43	0.68	
Peristalsis Weak/ Absent (%)	**35.0**	1140	**30.0**	1174	−0.03	0.99	
Peristalsis present (%)	**50.0**	1023	**60.0**	1167	0.05	0.53	
	pH-Impedance Monitoring						
Acid exposure time (%)	**0.20**	26.6	**0.20**	119	0.26	0.57	
AR	**2.0**	360	**3.0**	1076	0.48	0.64	
WAlkR	**1.0**	25.4	**5.0**	82.1	1.9	0.06	−8.0,0
WAR	**29.5**	695	**52.0**	2762	2.2	**0.03**	**−65.0,− 2.0**
TR	**33.5**	999	**60.0**	2779	2.1	**0.03**	**−67.0,−4.0**

Abbreviations: CR, complete response; ICR, incomplete response; BE, Barrett's Esophagus; NDBE, non-dysplastic Barrett's esophagus; LGD, low grade dysplasia; HGD, high grade dysplasia; HH, hiatal hernia; BMI, body mass index, EGJP, esophagogastric junction pressure; DCI, distal contractile integral; AR, acid reflux; WAlkR, weakly alkaline reflux; WAR, weakly acidic reflux; TR, total reflux