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Novel pressure-impedance parameters for evaluating esophageal function in pediatric achalasia

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Abstract

Objective: In achalasia, absent peristalsis and reduced esophagogastric junction (EGJ) relaxation and compliance underlie dysphagia symptoms. Novel high-resolution impedance manometry (HRIM) variables, i.e. bolus presence time (BPT) and trans-EGJ-bolus flow time (BFT) have been developed to estimate the duration of EGJ opening and trans-EGJ bolus flow. The aim of this study was to evaluate esophageal motor function and bolus flow in children diagnosed with achalasia using these variables.

Methods: HRIM recordings from 20 children who fulfilled the Chicago Classification (V3) criteria for achalasia were compared with recordings of 15 children with normal esophageal HRM findings and no other evidence suggestive of achalasia. Matlab-based analysis software was used to calculate BPT and BFT.

Results: Both BPT and BFT were significantly reduced in achalasia patients compared to children with normal esophageal motility (BPT 3.3s vs 5.1s $p<0.01$; BFT 1.4s vs 4.3s $p<0.001$). BFT was significantly lower than BPT (achalasia difference 1.9s±1.3s, $p=0.001$ and normal difference 0.9±0.3s, $p=0.001$). Overall, there was a significant correlation between BPT and BFT ($r=0.825$, $p<0.001$). We observed a two-way differentiation of achalasia patients; those in whom the BPT and BFT were proportional, but significantly lower than in patients with normal peristalsis, and those in whom BFT was disproportionately lower than BPT.

Conclusions: Calculation of BPT and BFT may help determine whether esophageal bolus transport to the EGJ and/or esophageal emptying through the EGJ are aberrant. For achalasia this may detect flow resistance at the EGJ, potentially improving both diagnosis and objective assessment of therapeutic effects.

Key words: High-Resolution Impedance Manometry – Pressure-Flow Analysis – Chicago Classification

What is known:

- The diagnosis of achalasia is based on the combination of clinical history, radiography and high-resolution esophageal manometry (HRM).
- By integrating impedance to HRM (HRIM), a new approach has been developed to estimate the duration of bolus presence time (BPT) and trans-EGJ bolus flow time (BFT).
- In adults, BPT and BFT have shown to be discriminative in equivocal achalasia cases.

What is new:

- In this pediatric study, BPT and BFT were significantly reduced in achalasia patients compared to children with normal esophageal motility.
- Integrated pressure-flow analysis may aid in pediatric achalasia management, particularly given the frequent discordance between symptoms and esophageal function testing.

List of abbreviations

BFT: trans-EGJ bolus flow time; BPT: bolus presence time; CC: Chicago Classification; EGJ: Esophageal gastric junction; EGJOO: Esophageal gastric junction outflow obstruction; HRIM: High-resolution impedance manometry; HRM: High-resolution manometry; ICC: Intraclass correlation coefficient; LES: Lower esophageal sphincter; IRP4s: Integrated relaxation pressure; UES: Upper esophageal sphincter.

Introduction

Achalasia is an uncommon esophageal motility disorder, with an estimated annual incidence of 0.01-0.11 per 100.000 children.[1 2] It is characterized by failure of relaxation of the lower esophageal sphincter (LES) and absence of peristalsis in the distal esophagus both of which lead to slow or absent bolus transit which results in symptoms of dysphagia, obstruction, chest pain, regurgitation, respiratory symptoms (chronic and nocturnal cough, aspiration) and weight loss.[2-4]

In children and adults, the diagnosis of achalasia is based on the combination of the clinical picture, radiographic findings and the results of high-resolution esophageal manometry (HRM). The latter is currently considered the gold standard for diagnosing and subtyping achalasia.[5] According to the recently published Chicago Classification (CC; version 3.0), three subtypes are defined, all requiring a mean integrated relaxation pressure (IRP4s) > 15mmHg.(4) This heavy reliance is potentially problematic. The IRP4s is a complex metric, not only depending on the adequacy of lower esophageal

sphincter relaxation, crural diaphragm contraction and EGJ opening, but also on the pattern and timing of distal esophageal contractility. In clinical practice, instances of clinically evident achalasia with IRP4s < 15mmHg do exist, especially in type I achalasia patients with low intraesophageal pressures and type II achalasia patients with short periods of panesophageal pressurizations.[4 6]

ITo overcome these limitations a new approach has been developed utilizing combined pressure and impedance to estimate the duration of trans-EGJ-flow.[10-12] In adult achalasia patients, trans-EGJ-bolus flow time (BFT) was significantly reduced in all achalasia subtypes and correlated with dysphagia severity.[11] We hypothesized that the BFT could also be applied to better diagnose pediatric achalasia, by detecting impaired bolus flow and thereby complementing the IRP4s to discriminate in equivocal cases. Therefore, the aim of this study was to apply novel pressure impedance parameters to a cohort of children diagnosed with achalasia according to the CC V3.0, and to compare them with children referred for diagnostic HRIM, but with normal esophageal motility and no other evidence of achalasia.[4]

Methods

Combined HRIM recordings of 20 consecutive pediatric achalasia patients (clinical diagnosis and fulfilling CC V3.0 criteria on HRM) and 15 patients who fulfilled criteria for normal esophageal motility and had no signs of achalasia during endoscopy and/or timed barium swallow, were extracted from a clinical database at the Boston Children's Hospital (Boston, MA, USA). Studies were performed between September 2010 and June 2016. Studies were only selected if patients were <21 years at time of HRIM

investigation; we did not apply a lower age-limit. All included patients underwent clinical diagnostic HRIM to investigate dysphagia and/or gastroesophageal reflux related symptoms. All patients with achalasia had a non-equivocal diagnosis based on clinical symptoms, radiographic and manometric values. Some achalasia patients were studied after initial therapy (i.e. pneumatic dilation, []thoracoscopic Heller myotomy) because of persistent symptoms. The CC was used to diagnose and classify the subtypes of achalasia patients. Clinical data, including predominant symptom sub-type and medication use were extracted by chart review and are reported for all patients. The study was approved the by the Boston Children's Hospital Institutional Review Board.

High-resolution impedance manometry recording

All subjects fasted for at least 8 hours for solids, and 4 hours for liquids prior to the study and were studied off esophageal motility influencing drugs. Depending on patient' s age and height, a 3.2 or 4.2-mm diameter solid state HRIM catheter was used incorporating respectively 36 1-cm-spaced pressure sensors and 18 adjoining 2 cm impedance segments (Given Imaging, Los Angeles, CA). Patients were studied sitting in the supine or semi-supine position with a standard protocol including 10 swallows of 5 ml saline administered via a syringe at ≥30 s intervals. Studies were considered for inclusion if they met the following criteria: (i) ≥10 saline liquid swallows performed, (ii) adequate catheter position to measure EGJ pressures, and (iii) no technical errors, e.g., pressure or impedance channel failure. Individual swallows were excluded from analysis if bolus passage into the proximal esophagus was not clearly discernible on the impedance recording, or if secondary swallows overlapped and inhibited the propagating pressure wave.

Data analysis

Objective swallow data were evaluated by using purposed designed software (AIM*plot* copyright T Omari; MATLAB v5.0 2015, MathWorks Inc, Natick, Massachusetts) and by pressure topography analysis using the Chicago Classifcation (V3.0) using ManoView 3.0 analysis software. All studies were blindly reviewed. To perform pressure-flow analysis (PFA), raw pressure-impedance data for all swallows were visualized over a 30-second window and exported from the recording system in text (.txt) format. The calculations used to derive PFA metrics have been previously described.[13 14] In brief, pressure impedance recordings are displayed as pressure topography plots with embedded impedance recordings which show bolus flow movements and relaxation and movement of the upper and lower esophageal sphincter pressure zones. On selection of specific landmarks on the pressure topography space-time plot, specific spatial and temporal regions of interest are mapped. Data for three pressure-flow variables are presented, these are *Peak Pressure, defined as the pressure at maximum contraction,* Intra-Bolus *Distension Pressure* defined as the pressure at nadir impedance, and the *Impedance Ratio*, defined by the ratio of nadir impedance to peak pressure impedance. [13] As the algorithm used to derive these variables requires identification of an esophageal pressure peak, they could not be derived for those patients with achalasia Type I. As only one patient had achalasia Type III, only the grouped data for those patients with achalasia Type II (both treated and untreated) and patients with normal esophageal motility are shown. Unless otherwise indicated, these variables are displayed as mean values for the distal esophagus from transition zone to EGJ. In cases

where the transition zone was not visible, the distal two-thirds of the esophageal tracing was used.

Using the impedance signals, first, potential regions of bolus presence within the EGJ were defined as the intervals during which there was an impedance drop >50% when compared to baseline, as previously described.[10] The duration of bolus presence within the EGJ (BPT) was determined, with the onset of bolus presence defined as the point at which the impedance dropped 90% relative to baseline impedance and the offset as the return to 50%. The trans-EGJ-bolus flow time (BFT) was calculated by summing all periods fulfilling the criteria of BPT, and subtracting time periods of crural contraction.[10] [11] The difference between BFT and BPT was additionally calculated. As previously described, we used the ratio of BFT and BPT (BFT/BPT) to define the effectiveness of trans-EGJ emptying relative to the period of bolus presence (i.e. ratio of 1 means unrestricted trans-EGJ flow, ratio of 0.5 means that flow was estimated to occur during only half the time that bolus was present).[10] [11] The 10th percentile of BFT and BPT in patients with normal esophageal HRM findings were used to define ranges of normality.

Statistical analysis

Distribution of data was evaluated using the Kolmogorov-Smirnov test. Parametric data are expressed as mean ± standard deviation (SD), and nonparametric data as median, interquartile range (IQR). Mann-Whitney U or t-tests and anova or Kruskal–Wallis tests were used to compare mean or median values of continuous outcomes respectively between patients with normal motility and achalasia patients and across achalasia subtypes. Tukey's adjustment for multiple pairwise comparisons was employed to examine pairwise differences (e.g., across patient groups and across achalasia subtypes).

Bivariate associations between continuous variables were evaluated via Pearson's sample correlation coefficients and/or Spearman's sample correlation coefficients in cases of possible violation of relevant statistical assumptions. Statistical tests were performed using IBM SPSS Statistics 23 (SPSS Inc, Chicago, Illinois). Differences were considered statistically significant when $p < 0.05$.

Results

Patient characteristics

Patient characteristics are displayed in Supplemental Digital Content, Table 1, http://links.lww.com/MPG/B17. Fifteen patients were diagnosed with type II achalasia, five with type I and two with type III. Seven of the achalasia patients were studied post-intervention (i.e. balloon dilatation and/or thoracoscopic Heller myotomy), of whom two patients (both type II achalasia) had also been studied prior to treatment. As these patients were included in both the pre- and post-intervention groups, a total number of 22 HRIM tracings was analyzed. All patients that were studied post-intervention, were studied due to persisting dysphagia symptoms. Of these 7 patients, two were type I, four were type II and one was type III. In one patient, prior fundoplication was undone prior to myotomy.

Comparison of EGJ parameters

Comparisons of parameters measured at the EGJ between the three patient groups and amongst achalasia subtypes are presented in Table 1. Integrated relaxation pressure (IRP4s) was significantly lower in the patients with normal motility and treated achalasia patients compared to the untreated achalasia patients (adjusted $p < 0.001$ and $p = 0.014$), but did not differ between treated achalasia patients and patients with normal motility

(Figure 1; adjusted p = 0.892). Patients with normal motility had significantly higher BFT (adjusted p < 0.001 and p = 0.020 respectively) and BPT (adjusted p = 0.001 and p = 0.020) when compared to the untreated and treated achalasia patients. There was no difference in BFT and BPT between treated and untreated achalasia patients (adjusted p = 0.662 and p = 1.000 respectively). None of the three EGJ parameters was found to correlate significantly with patients' age, height or weight (overall and subgroup analysis).

Comparisons of PFA characteristics (Normal motility and achalasia type II only)

Comparisons of PFA characteristics between patients with achalasia Type II and patients with normal motility are presented in Table 2. There were no significant differences in in distension pressures or impedance ratio between the untreated and treated achalasia Type II patients. When compared to patients with normal motility, we found lower peak pressures (adjusted p = 0.001 and p = 0.032 respectively), and higher distension pressures (adjusted p < 0.001 and p = 0.020 respectively) in patients with untreated and treated achalasia. The impedance ratio was higher in patients with untreated achalasia (adjusted p < 0.001) suggesting greater bolus residual..

Concordance between IRP4s, BFT and BPT

Overall, there was a significant correlation between IRP4s and BFT, IRP4s and BPT and between BFT and BPT (Figure 1; Spearman's r = -0.638, p < 0.001; r = -0.358, p = 0.030 and r = 0.825, p < 0.001). There was a significant correlation between BPT and BFT for children with normal motility (Spearman's r = 0.961, p < 0.001) and for treated achalasia patients (Spearman's r = 0.811, p = 0.027). Only a weak trend was noted for untreated achalasia patients (r = 0.468, p = 0.078).

As shown in Figure 1, patients with normal motility showed a linear relationship between BPT and BFT and had a BFT/BPT ratio ≥ 0.5, estimating trans-EGJ-flow to occur during at least half the time that the bolus was present. In contrast, achalasia patients appeared to separate into two groups; 1. those in whom the BPT and BFT were proportional, but significantly lower than patients with normal peristalsis (i.e. BFT/BPT ratio ≥ 0.5 and BPT OR BPT < 10^{th} percentile of patients with normal motility), and 2. those in whom BFT was disproportionately lower than BPT (BFT/BPT ratio < 0.5). Patients in Group 2 appeared to have evidence of greater distal flow resistance as indicated by a significantly higher IRP4s and higher PFI compared to patients in Group 1 ($p = 0.028$ and $p < 0.001$ respectively). Untreated Type 2 achalasia patients were more often in Group 2 (64%) compared to Group 1 (36%) however this was not a statistically significant proportion (Fisher exact test statistic 0.395). One of the treated achalasia Type II patients that underwent HRIM study twice due to persisting dysphagia symptoms was initially in Group 2 and shifted to Group 1 at repeat analysis post-intervention, suggesting that therapy had been ineffective, even though the IRP4s had normalized (40.2mmHg to 6.6mmHg). The other treated patient, that was first in Group 1, showed similar BFT and BPT characteristics at repeat analysis post-intervention as patients with normal motility, although dysphagia symptoms persisted in this patient.

Esophageal emptying, pressurization and trans EGJ-flow

Overall, there was a significant negative correlation between impedance ratio and BPT and BFT (Spearman's r = -0.603, p < 0.001 and r = -0.760, p < 0.001 respectively). There was also a significant overall negative correlation between distension pressure and BPT / BFT (r = -0.326 / -6.616, p = 0.049 / <0.001). Patients in Group 2 had significantly higher

distension pressures when compared to patients with normal peristalsis (20.2 (17.2 – 23.4) mmHg vs 7.4 (4.6 – 11.1) mmHg; adjusted $p < 0.001$). There were no significant differences in between patients in Group 1 (11. 6 (7.9 – 17.1) mmHg) and patients in Group 2 ($p = 0.105$) or patients with normal motility ($p = 0.083$ and $p = 0.128$ respectively). The impedance ratio was significantly lower in patients with normal motility (0.29 (0.19 – 0.39)) when compared to patients in Group 1 (0.79 (0.45 – 0.90); $p = 0.001$) and Group 2 (0.80 (0.62 – 0.87); $p < 0.001$)), but did not differ significantly between Groups 1 and 2 ($p = 1.000$)

Discussion

The aim of this study was to evaluate esophageal motor function in children diagnosed with achalasia using novel esophageal pressure-flow variables. Our findings support that in children, some metrics measured at the EGJ, BFT in particular, provide added information on EGJ outflow obstruction, as was previously shown in adults.[10 11] BFT integrates measures of EGJ opening (impedance) and pressure to predict when trans-EGJ bolus flow is occurring, thereby providing a more comprehensive evaluation of EGJ function than the (pressure only) IRP4s.

In our cohort, both BFT and BPT were significantly lower in achalasia patients compared to patients with normal esophageal motility. Consistent with the known effect of dilation therapy, the IRP4s was significantly lower in patients post-intervention (Figure 1).[15] However, unlike IRP4s, BFT and BPT were not significantly different in the treated group when compared to the untreated group. This is consistent with the fact that the treated achalasia patients were presenting with persistent symptoms. While this suggests

that the BFT may actually correspond with the clinical impact of therapy, our study did not include patients who responded to therapy and therefore cannot fully address this question. A recent study prospectively followed a cohort of 75 achalasia patients after pneumotic dilatation or Heller myotomy and found that BFT correlated better with clinical and radiographic treatment outcome as compared to IRP4s.[16]

The CC and its metrics have been developed to characterize specific features of deglutitive esophageal function and classify motility disorders in a hierarchical fashion, based upon data from healthy adults.[4] Because of the lack of established age-appropriate reference ranges for the metrics which drive the CC, corroboratory evidence in support of a CC diagnosis is particularly important in children. In a previous study, we found younger age to correlate significantly with higher IRP4s, potentially leading to the over-diagnosis of achalasia and other IRP4s driven CC diagnoses, when a fixed cut-off values are applied. Parameters such as the impedance ratio, and the esophageal impedance integral ratio (not investigated here), may have additive value by defining the degree and extent of bolus retention over multiple swallows.[17] In addition, distension pressures were higher amongst achalasia patients and were negatively correlated with BFT, consistent with flow resistance during esophageal emptying [15]

Overall, we found significant correlation between BFT and BPT and observed a two-way differentiation of achalasia patients; those in whom the BPT and BFT were proportional, but significantly lower than in patients with normal peristalsis (Group 1), and those in whom BFT was disproportionately lower than BPT (Group 2). Patients in both Group 1 and 2 showed significantly higher impedance ratio when compared to patients with normal motility and patients in Group 2 also showed significantly higher distension

pressures. These data suggest, conceptually, that the BFT to BPT relationship may help stratify patients with a disproportionately reduced BFT as a marker of outflow resistance and patients with the ability to generate sufficient intra-esophageal pressure to establish a flow-permissive gradient across the EGJ. However, further studies are needed to explore the effect of therapy on individual patients characterized in this way.

To our knowledge, no other study has specifically investigated pressure-impedance characteristics in a cohort of pediatric achalasia patients. This work has limitations as it requires both HRIM recordings and MATLAB programming thereby making it not widely available. The analysis technique still requires identification of appropriate landmarks and will be subject to the expertise of the interpreter in localizing these landmarks. However, its automation and objectivity in the derivation of additional functional measures of bolus movement in relation to esophageal and EGJ pressurization may complement a pressure-only derived diagnosis of achalasia and its subtypes. We recognize the limitations of a retrospective cohort study with sometimes incomplete clinical data, particularly in relation to symptom severity. As age of included patients ranged from 8-21 years old at time of HRIM investigation, it is not sure whether results could be extrapolated to a younger achalasia population. Further, our patients with normal motility are not equivalent to healthy controls, the achalasia cohort was heterogeneous and specific pediatric validation studies of the parameters used to characterize EGJ outflow resistance have not been performed. Additionally, our cohort only included two patients that were studied both pre- and post-intervention due to persisting symptoms. As a result, we were unable to evaluate parameters in relation to treatment success.

In summary, in pediatric achalasia patients, novel integrated pressure-flow variables may have additional value for diagnostic assessment and monitoring of therapeutic efficacy. Of the variables assessed in this study, the BFT parameter and its relationship with bolus presence within the EGJ may have clinical value by stratifying patients with a disproportionately reduced BFT as a marker of outflow resistance. Our study suggests that an improved HRIM evaluation using integrated pressure-flow criteria would better aid in pediatric achalasia management decisions, particularly given the frequent discordance between symptomatic and objective measures of esophageal function. However, further studies are needed to correlate these parameters with symptom severity before and after therapy.

Figure 1: EGJ parameters in achalasia patients (all subtypes) and patients with normal motility. In symptomatic treated achalasia patients, IRP4s normalized to the level seen in patients with normal motility, reflecting the effect of dilation therapy on the LES. BFT and BPT were significantly reduced in both symptomatic treated and untreated achalasia patients when compared to patients with normal motility, but not between treated and untreated achalasia patients. This may potentially reflect that the treated achalasia patients were presenting with refractory symptoms, suggesting that BFT and BPT may actually correspond with the clinical impact of therapy,
[a,b,c]indicates pairwise significance between Groups using Tukey's adjustment for multiple pairwise comparisons.
[a]vs.Normal, [b]vs.Untreated Achalasia, [c]vs. Treated Achalasia ([a,b,c]$p<0.05$, [aa,bb,cc]$p<0.01$, [aaa,bbb,ccc]$p<0.001$

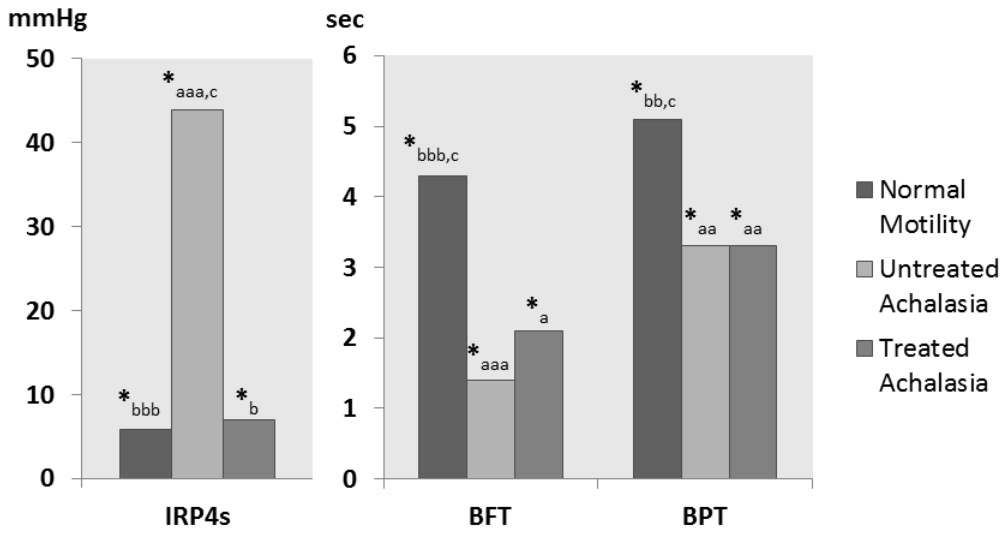

Figure 2: Concordance of trans-EGJ-bolus flow time (BFT) and bolus presence time (BPT) amongst patients with normal esophageal motility and achalasia subtypes pre- and post-intervention. The dots indicate patients naïve to treatment, the squares indicate treated achalasia patients. Colors represent the different achalasia subtypes. * and # represent the same patient before (circle) and after (square) intervention. Circles demarcate separation of achalasia patient into two groups: Group 1 (undashed circle) - reduced esophagogastric junction (EGJ) outflow proportionate to transport (BFT/BPT ratio ≥ 0.5 and BPT OR BPT < 10th percentile of patients with normal motility) and Group 2 (dashed circle) - reduced EGJ outflow disproportionate to transport (BFT/BPT ratio < 0.5).

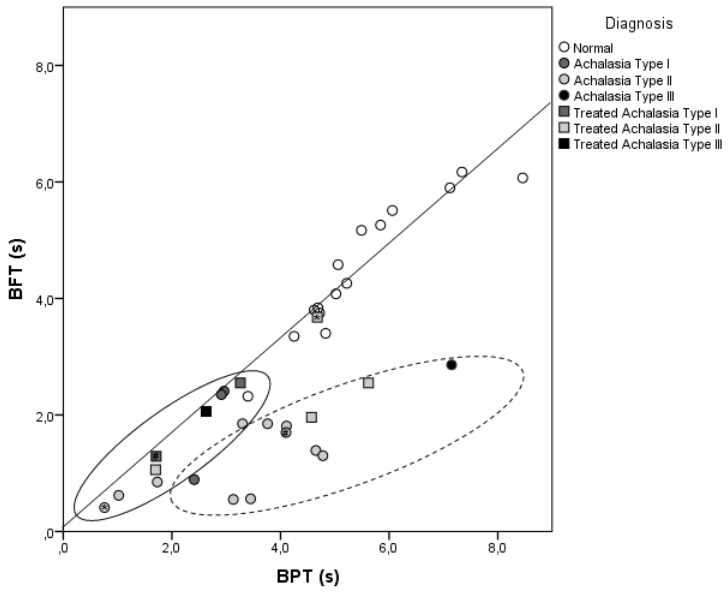

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Table 1 – Comparison of EGJ Parameters

Group	BFT (s)	BPT (s)	BPT and BFT difference (s)	BFT and BPT ratio (s)	IRP4s (mmHg)
Untreated Achalasia (n=15)					
Type 1 (n=3)*	2.4 (0.9 – 2.4)	2.9 (2.4 – 3.0)	0.56 (0.55 – 1.52)	0.8 (0.4 – 0.8)	43.9 (21.1 – 51.3)
Type 2 (n=11)	1.3 (0.6 – 1.8)	3.5 (1.7 – 4.1)	2.3 (0.9 – 2.9)	0.4 (0.3 – 0.5)	43.2 (33.8 – 51.0)
Type 3 (n=1)#	2.9	7.2	4.3	0.4	48.1
All	**1.4 (0.6 – 1.9)^{aaa}**	**3.3 (2.4 – 4.1)^{aa}**	**1.9 (0.6 – 2.9)**	**0.4 (0.3 – 0.6)^{aaa}**	**43.9 (33.8 – 51.0)^{aaa,c}**
Treated Achalasia (n=7)					
Type 1 (n=2)*	1.9 (1.3 – 2.6)	2.5 (1.7 – 3.3)	0.6 (0.4 – 0.7)	0.8 (0.8 – 0.8)	6.2 (5.4 – 6.9)
Type 2 (n=4)	2.3 (1.3 – 3.4)	4.6 (2.4 – 5.4)	1.8 (0.7 – 3.0)	0.5 (0.4 – 0.7)	11.9 (7.2 – 38.2)
Type 3 (n=1)#	2.1	2.6	0.57	0.8	3.1
All	**2.1 (1.3 – 2.6)^{a}**	**3.3 (1.7 – 4.7)^{a}**	**0.7 (0.6 – 2.6)**	**0.8 (0.5 – 0.8)**	**6.9 (5.4 – 15.1)^{b}**
Normal (n=15)	**4.3 (3.8 – 5.5)$^{bbb, c}$**	**5.1 (4.6 – 6.3)^{bb,c}**	**0.9 (0.6 – 1.2)**	**0.8 (0.8 – 0.9)^{bbb}**	**5.8 (2.2 – 11.6)^{bbb}**
p-value (ANOVA, All Groups)	**< 0.001**	**0.001**	**0.196**	**< 0.001**	**< 0.001**

*Range provided; #Only one patient with type III achalasia.
^{a,b,c} Indicates pairwise significance between Groups using Tukey's adjustment for multiple pairwise comparisons.
^{a}vs.Normal, ^{b}vs.Untreated Achalasia, ^{c}vs. Treated Achalasia (^{a,b,c}p<0.05, ^{aa,bb,cc}p<0.01, ^{aaa,bbb,ccc}p<0.001).

Table 2 – Comparison of PFA Parameters; Type 2 Achalasia vs. Normal Only

	Peak Pressure (mmHg)	Distension Pressure (mmHg)	IR
Untreated Achalasia Type II (n=11)	34.9 (29.8 – 54.8)[aa]	20.7 (16.1 – 27.3)[aaa]	0.8 (0.8 – 0.9)[aaa]
Treated Achalasia Type II (n=4)	35.6 (27.6 – 59.6)[a]	18.2 (25.4 – 16.9)[a]	0.6 (0.5 – 0.8)
Normal (n=15)	78.79 (53.6 – 101.0)[bb,c]	7.4 (4.6 – 11.1)[bbb,c]	0.3 (0.2 – 0.4)[bbb]
p-value (ANOVA, All Groups)	**0.001**	**< 0.001**	**< 0.001**

[a,b,c]indicates pairwise significance between Groups using Tukey's adjustment for multiple pairwise comparisons.
[a]vs.Normal, [b]vs.Untreated Achalasia type II, [c]vs. Treated Achalasia type II ([a,b,c]p<0.05, [aa,bb,cc]p<0.01, [aaa,bbb,ccc]p<0.001