The timed barium swallow and its relationship to symptoms in achalasia: analysis of surface area and emptying rate

Short Title: Timed barium swallow in achalasia

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Abstract

Background

Timed barium swallow (TBS) is used to objectively measure response following achalasia therapy; however, findings can be discordant with symptoms. We hypothesized that measurement of surface area of the residual barium column would improve its utility in measuring outcome.

Methods

In a single-center cohort, achalasia patients undergoing therapy between September 2015-2016 who had TBS were included. Four metrics of emptying were studied: Post-therapy residual barium 1) absolute height and 2) surface area as well as percentage reduction of 3) residual height (%H) and 4) surface area (%SA) compared to pre-therapy. Metrics were evaluated against symptom response (Eckardt score).

Results

Twenty-four achalasics (median age 43y; 13 males) were included; 14 received pneumatic dilatation and 10 had peroral endoscopic myotomy. Treatment resulted in significant reduction in median Eckardt score (7 to 1; P=0.03), mean residual barium column height (14.7±8.7cm to 7.9±6.0cm; P=0.01) and surface area (52.7±43.5cm^2 to 24.5±23.6cm^2; P=0.02). There were 4 (17%) initial non-responders (Eckardt>3). %SA was best at discriminating between responders and non-responders (area under curve 0.85±0.08; sensitivity 100%, specificity 80%). Concordance with symptomatic response following therapy was 83% when using 45% as the cut-off for surface area reduction compared to pre-therapy. 8 patients whose static barium height was discordant with symptoms became concordant when % SA was used as a measure of response.

Conclusions

Change in barium surface area is a superior measure of esophageal emptying and better correlates with treatment response than the conventional 5-minute barium height in defining objective response to achalasia therapy.

Keywords

Timed barium swallow; achalasia; surface area; esophageal emptying; therapy

Background

Achalasia is a motility disorder of the esophagus with hallmark features of failed lower esophageal sphincter (LES) relaxation and absence of normal peristalsis in the esophageal body. The former leads to esophageal stasis which is responsible for most of the symptoms in achalasia. All therapies for achalasia aim to disrupt the non-relaxing LES in order to facilitate esophageal emptying.

Although achalasia response to therapy is primarily measured subjectively through various symptom scoring systems, objective measures can be sought to validate symptoms. The timed barium swallow (TBS; also termed timed barium esophagogram); a quick, easy and safe technique undertaken in the outpatient setting. The TBS was first described in 1997 and incorporates a simple radiological algorithm that objectively evaluates the efficiency of oesophageal emptying.[1] After ingestion of a fixed quantity of barium, images are acquired from the esophagus at specified intervals to determine the quantity of retained barium over a set period of time.[1, 2] Being a two-dimensional image, the column height is traditionally used as a de facto measurement of residual barium quantity, and in turn, the degree of esophageal emptying, with emphasis on the five-minute value in most studies. Although there is often good concordance between emptying on TBS and symptom response, this correlation is imperfect, with discordance in 31-50%.[3, 4] It was proposed that such discordance can prognosticate the likelihood of relapse and the need for early therapy.[4, 5] Yet the reason why such a significant proportion of patients with little objective improvement in esophageal emptying following therapy should receive even short-term improvement in their symptom response remains obscure. After all, it is accepted that symptoms in achalasia predominantly arise from poor esophageal emptying and stasis.

In our own practice, we have also encountered a number of patients where there is discordance between TBS findings and symptom relief following achalasia therapy. In some of these cases, after viewing the radiographic images, we observed that the height of the barium column at 5 minutes was often not accurately reflective of improvement in esophageal emptying for various reasons (Figure 1).

Based on these observations we hypothesized that measurement of surface area of the residual barium column would be a more accurate marker of esophageal emptying during TBS than column height (Figure 2). We also aimed to explore whether measurement of the reduction in amount of residual barium with therapy (whether assessed by height or surface area), and/or the *rate* of emptying of barium during TBS would be of additional clinical value to the simple measurement of its absolute value at a fixed time point.

Materials and methods

A retrospective cohort study at a single tertiary referral center in London was performed comprising consecutive patients diagnosed with achalasia who fulfilled entry criteria during a twelve-month period from September 2015 to August 2016 inclusive. In all patients, a diagnosis of achalasia was reached using a 36-channel, solid state high-resolution manometry system (Manoscan Eso Z, Medtronic, Hertfordshire, UK).[6] Patients were eligible for inclusion if they received therapy for achalasia and if a TBS and Eckardt symptom score were performed at baseline and at a minimum of 3 months post-therapy.

Recent randomized controlled trials have shown that there is no difference in outcome following either graded pneumatic dilatation, surgical myotomy or per-oral endoscopic myotomy (POEM).[7, 8] Choice of achalasia therapy was at the discretion of the patient and the treating physician following an unbiased discussion; however, patients who underwent surgery were not included, as these patients were a more heterogenous group and often had their investigations performed at other institutions. Short (three months) and long-term (> 1 year) durability of therapeutic response was measured.

Timed barium swallow technique

The protocol used was based on that originally described by de Oliveira et al.[1] Two hundred milliliters (or maximal amount tolerated) of low density barium sulfate suspension was ingested by the standing patient followed by images of the esophagus at 1, 2 and 5 minutes.

The dimensions of any residual barium column above the LES were measured. Height was measured as the distance between the LES and the superior extent of the barium column (at the barium-foam interface where foam was present). Width reflected the widest point of the column; both height and width were measured using electronic calipers on a radiology Picture Archiving and Communications System (PACS; Impax 6.0, AGFA healthcare, Mortsel, Belgium). For surface area calculation, manual definition of column boundaries was performed using a freehand polygon tool from the same PACS, which automatically calculates the surface area within these specified boundaries (Figure 2). All measurements were undertaken by two of the coauthors (AP and JM), a senior radiologist experienced in esophageal radiology and a radiology fellow who underwent training in TBS interpretation.

Outcomes and statistical analysis

We compared various barium column metrics of esophageal emptying on TBS, namely: i) post-therapy column height at 5 minutes following ingestion (cm) ii) post-therapy column surface area (cm^2), (iii) percentage reduction in column height post-therapy compared to prior to therapy, and iv) percentage reduction in column surface area post-therapy compared to prior to therapy. T-test was used to compare means between groups. We constructed receiver operating characteristic (ROC) curves and calculated the area under the curve (AUC) to evaluate the relationship between these barium stasis metrics and resolution of symptoms. By convention, and in the absence of another gold standard, an Eckardt score of ≤3 defined adequate symptom relief following therapy for the purpose of assessing diagnostic accuracy of the TBS parameters.[9] The Youden index was used to determine the optimal threshold for each parameter. The concordance of each TBS emptying metric with symptomatic relief was then evaluated using a 2x2 Fisher exact test.

The rate of emptying during the TBS study was also calculated. Emptying rate was measured by calculation of the difference between five-minute and one-minute barium column height (and surface area), divided by number of minutes (four). Correlation of emptying rate with symptomatic outcomes was performed by comparing the change in emptying rate from baseline to post-therapy in responders and non-responders to achalasia therapy. Analyses were performed using IBM SPSS Statistics for Mac, version 23.0 (IBM Corp, Armonk, NY, USA).

Results

Twenty-four patients (13 male) fulfilled the criteria for inclusion into the study and completed all pre- and post-therapy required tests. The median age of the cohort was 43 years (interquartile range (IQR) 33-55). Patients were subclassified into Type I (*N*=10), Type II (*N*=12) and Type III (*N*=2) achalasia based on high-resolution manometric classification.[6] Achalasia therapy was performed by pneumatic dilatation in 14 and per-oral endoscopic myotomy (POEM) in 10.

Among the cohort, regardless of treatment modality, there was a significant reduction in median Eckardt score from baseline (7; IQR 5-8.25) to three months post-therapy (0.5; IQR 0-1; *P*=0.03). There was no difference in outcome following therapy between patients who had sequential graded dilatation and POEM (median Eckardt score 0.5 and 1 respectively; *P*=0.74).

Defined by post-therapy Eckardt score of ≤3, twenty patients (83%) were deemed to have responded to treatment ("responders"), whereas 4 (17%) were judged to have not responded ("non-responders"). All four non-responders had Type I achalasia.

Mean duration of long-term follow-up post-therapy was 3.02 ± 0.99 years. Therapeutic response was durable with median Eckardt score at long-term follow up of 1 (IQR 0-1). Of those with initial treatment response, only 1 patient suffered a relapse of symptoms. This patient had inadequate emptying of barium on TBS at three months following therapy (9.7cm column at 5 minutes).

At assessment three months following therapy, there were significant reductions in both mean barium column height at 5 minutes (14.7 ± 8.7 cm to 7.9 ± 6.0cm; P=0.01) and surface area (52.7 ± 43.5 cm^2 to 24.5 ± 23.6 cm^2; P=0.02). The mean reduction in height was 7.0 ± 7.1cm and the mean reduction in surface area was 27.0 ± 23.4cm^2. The change in residual barium quantity in responders and non-responders is illustrated in Figure 3. In responders, there was a significant reduction in the residual barium column height following therapy (15.5cm to 7.3cm; P<0.001) that was not seen in non-responders (9.3cm to 10.5cm; P=0.60). Similarly, in responders, there was a significant decrease in barium column surface area following therapy (52.0cm^2 to 19.5cm^2; P<0.001) that was not evident in non-responders (42.9cm^2 to 33.6cm^2; P=0.14).

Comparison of metrics to assess adequacy of esophageal emptying

The test characteristics were assessed using ROC curves. Quantified by AUC, the diagnostic accuracy of the four TBS metrics differed, with surface area metrics outperforming height metrics, and the metrics measuring percent *reduction* in residual barium following therapy outperforming those measuring absolute static images of residue (Table 1). Specifically, the AUCs for post-therapy barium column height, post-therapy surface area, percentage reduction in barium column height from baseline, and percentage reduction in barium column surface area from prior to therapy were 0.69, 0.71, 0.82 and 0.85, respectively; however only the latter two metrics were found to be accurate discriminators between responders and non-responders (P values of 0.04 and 0.03 respectively; Table 1).

Using optimal cutoffs determined for each metric by Youden's J statistic, the sensitivity, specificity and concordance of each metric was assessed (Tables 1 and 2). Overall, we found that of all the metrics assessed, a 45% surface area reduction from baseline correlated most closely with symptomatic response following therapy (Table 2). Assessing esophageal emptying using this criterion, concordance with symptomatic outcome (success or failure; Eckardt score ≤3 or >3 respectively) occurred in 20/24 (83%) of patients (Fisher exact test $P<0.01$). Concordance was lower using all three other metrics (Table 2). There were 8 patients (7 responders and 1 non-responder) where the TBS findings were discordant with symptomatic outcome when assessed by static column height but became concordant when assessed by percentage surface area reduction (Table 3).

The sensitivity of all metrics was very high; almost all non-responders had an abnormal TBS post therapy with significant barium stasis identified whatever the metric used However, there was marked variation in the specificity between the four metrics in question, with the most accurate being percentage reduction of barium column surface area, with a specificity of 0.80 at a cutoff of 45% reduction in surface area (Table 2).

When analyzing by achalasia subtype, poorer concordance for all TBS parameters was found in Type I achalasia; however, percentage surface area reduction performed best in all subtypes.

Rate of emptying

Mean rate of barium emptying changed from 3.5cm^2 per minute at baseline to 2.2cm2/min following therapy (P=0.34). Twenty responders emptied barium at a mean rate of 3.8cm2 barium per minute at baseline, and 2.4cm2/min post-therapy; however, this difference did not reach statistical significance (*P*=0.42; Figure 4). In the 4 patients with treatment failure, emptying rate was 2.4cm2/min at baseline compared to 1.2cm2/min following therapy (*P*=0.42). The change in emptying rate post-therapy was -1.3cm2/min and -1.2cm2/min in treatment successes and failures respectively (*P*=0.97).

Discussion

Consistent with previous studies.[3, 4] we found that TBS static barium column height was discordant with symptomatic response in up to 50% of patients (Table 2). This study demonstrated that measuring the change in surface area of the barium column at 5 minutes on TBS correlated more closely with symptomatic outcome following therapy than the static barium column height, static barium surface area or the change in column height from baseline. There were 8 patients where esophageal emptying based on static barium column height was discordant with symptomatic outcome; however, these became concordant when esophageal emptying was assessed by change in surface area (7 responders and 1 non-responder; Table 3). This suggests that in many cases, discordance between TBS and symptomatic outcome may be reflective of (i) barium column height being an imprecise measure of esophageal emptying compared to surface area, and/or (ii) magnitude of reduction in barium stasis following therapy having closer correlation with symptom relief than the absolute measurements of residual barium post-therapy.

Other studies have also assessed the performance of TBS surface area,[1, 10, 11] but often using a gross estimate (height times width) rather than precise calculation, and to our knowledge none have compared the correlation of surface area and height metrics with symptomatic outcomes in achalasia. We found that the main reason for the 5-minute surface area being a truer measure of emptying was its more accurate reflection of changes in esophageal width and longitudinal esophageal contraction occurring during an image capture (Figure 2). Further, in some cases, measurement of the barium column height might have been inaccurate, as coating of the oesophageal mucosa by barium is not uncommon when associated with aperistalsis (Figure 1b) whereas surface area measurement is not confounded by this. Still, these cannot be the sole explanations for discordance between barium column height and symptomatic outcome, as we nevertheless found another 4 patients (Table 2a) where *both* surface area and height measurements were discordant with symptomatic outcome. Sometimes, the anatomy of the esophagus may explain this discordance as a dilated, sigmoid esophagus measures both the height and surface area of retained barium inaccurately compared to an esophagus that has not yet decompensated. For example, a dilated esophagus can produce a "sump" effect, whereby barium pools at the distal end of a sigmoid shaped anatomy regardless of LES disruption (Figure 1a).

On the other hand, there were other cases whereby a true column of barium above the OGJ persisted despite adequate symptomatic relief. Others have described such cases as being more likely to need future therapy, with relapse rates of 64-90% over 12 to 48 months follow-up in treatment responders with poor TBS emptying.[4, 5] However, longevity studies of our cohort did not find this to be the case. We observed a much lower rate of relapse, with only 1 of 20 initial responders (5%) relapsing over a mean 3 year follow up period. The lone relapse was a patient who had poor emptying as assessed by both surface area and height at both initial post therapy and three year follow up assessment.

We found that following endoscopic therapy, the percentage reduction of residual barium correlated more closely with symptomatic response than absolute, “snapshot” measures of residual barium volume at five minutes. This is analogous to findings of other studies that compare symptom response and TBS emptying in achalasia following treatment. Vaezi et al. assessed the percentage reduction in barium column height and found concordance with symptoms in 69%;[3] whereas when using the absolute measure of residual barium height post-therapy as a marker of response, Rohof et al. described a symptom correlation of only 50%.[4] It appears that patients who begin with severe stasis of the barium column prior to therapy can appreciate symptomatic relief when esophageal emptying post-therapy is improved, despite still being incomplete.

While percentage reduction of both height and surface area post-therapy were found to be accurate diagnostic discriminators on ROC analysis, the latter seemingly has more clinical relevance. Firstly, this metric had better concordance with symptom response than percentage reduction in height (83% vs. 71%). Further, using surface area has inherent logic as the oesophagus in achalasia is commonly not a simple linear tube, such that measurements of height might not be accurate if dynamic variations in girth are not taken into account. Moreover, surface area is likely to be more analogous to measuring volume without the expense and time of 3-D imaging.

The rate of barium emptying during TBS did not correlate well with treatment outcomes; however, the standard TBS protocol captured the first image at one-minute following barium ingestion, thus excluding the data from within the first minute. Following successful therapy, emptying became more analogous to healthy individuals,[11] with a far larger proportion of the barium being cleared within the first minute. Therefore, this lack of 1-minute emptying data is likely to account for our inability to identify any difference in emptying rate between responders and non-responders. A previous study of TBS emptying rate in achalasia patients similarly reported no improvement in emptying rate post-myotomy for similar reasons.[10] In future, amending the TBS protocol to capture a "zero-minute" image immediately after consumption of barium may allow an accurate measurement of emptying rate, although this will also depend on the rate that the barium is imbibed.

Limitations of the study mainly relate to the small sample size and retrospective analysis. In particular, we had a very low rate of treatment failure which warrants some caution in interpreting the results. Measurement of the surface area necessarily adds time to the interpretation of the TBS and requires an experienced radiologist. We used the Eckardt score to assess patients' treatment response, yet it has well recognized limitations for this purpose. Fundamentally, these relate to the fact that dysphagia is the primary symptom targeted with achalasia therapy, yet comprises only one quarter of the total score.[12-14] However, in the absence of another true gold standard to define treatment response in achalasia, we have followed convention in using the Eckardt score.

In conclusion, our study suggests that measurement of the 5-minute barium column height on TBS may be suboptimal in predicting treatment response. Rather, change in barium surface area appears to be a superior measure of esophageal emptying and better correlates with treatment response.

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Table 1: Receiver operating characteristic analysis

TBS parameter	Area under the curve	*P*	Optimal cutoff*
Post-therapy 5-min barium column height	0.69 ± 0.12	0.24	5 cm
Post-therapy 5-min barium column surface area	0.71 ± 0.13	0.18	860 cm^2
% Reduction in 5-minute barium height post-therapy from baseline	0.82 ± 0.09	0.04	38%
% Reduction in surface area of 5-min barium post-therapy from baseline	0.85 ± 0.08	0.03	45%

* Youden's J statistic

Table 2: Comparison of various TBS emptying parameters determined by ROC and their concordance with symptomatic relief post-therapy

TBS criterion for adequate emptying*	Sensitivity	Specificity	Concordance between adequate TBS & symptom relief (based on ES) n/total (%)	*P* (Fisher exact test)
Post-therapy 5-min barium column height of <5cm	75%	45%	12/24 (50%)	0.62
Post-therapy 5-min barium column surface area of <860cm^2	100%	45%	13/24 (54%)	0.26
>38% Reduction in 5-minute barium height post-therapy from baseline	100%	65%	17/24 (71%)	0.03
>45% Reduction in SA of 5-min barium post-therapy from baseline	100%	80%	20/24 (83%)	<0.01

*Optimal cutoff values determined using ROC analysis and Youden Index (see Table 1 also)

Table 3: Comparison of TBS emptying by surface area and height criteria in treatment successes and failures

(a) Treatment success

	Adequate emptying by surface area criterion	**Inadequate emptying by surface area criterion**
Adequate emptying by height criterion	9	0
Inadequate emptying by height criterion	7	4

(b) Treatment failures

	Adequate emptying by surface area criterion	**Inadequate emptying by surface area criterion**
Adequate emptying by height criterion	0	1
Inadequate emptying by height criterion	0	3

Figure 1: Problems with timed barium swallow interpretation. (A) illustrates the "sump" phenomenon whereby barium persistently pools in a decompensated sigmoid-shaped esophagus despite adequate LES disruption. (B) twin problems of barium foam caused by mixture with retained secretions, along with barium residue also coating the esophageal mucosa, may confound interpretation of column height.

Figure 2: This 65-year-old female had a good therapeutic response from pneumatic dilatation for achalasia (post-therapy Eckardt score 1). Nevertheless, the height of the residual barium column (A) worsened due to change in configuration of the esophagus following therapy. Measurement of the surface area (B) however, better captures reduction in barium stasis following therapy.

Figure 3: Comparison of change in (a) height and (b) surface area in responders and non-responders. * $P<0.001$

Figure 4: Emptying rate in responders and non-responders