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ORIGINAL ARTICLE

Quantitative Estimates of Motility from Videocapsule Endoscopy Are Useful to Discern Celiac Patients from Controls

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Abstract
Background Prior work has shown that videocapsule endoscopy image features are a useful tool for quantitatively distinguishing the intestinal mucosal surface of untreated celiac patients from that of controls. The use of dynamic estimates of wall motility may further help to improve classification.
Methods Videocapsule endoscopy clips (200 frames each, 2 frames/s, 576 × 576 pixels/frame) were acquired at five small intestinal locations in 11 untreated celiac patients (celiacs) and ten controls. Color images were converted to grayscale and analyzed frame-by-frame. Variations in the position and width of the center of the small intestinal lumen were quantitatively estimated. The darkest grayscale pixels were used as an estimate of the lumen center. Over 200 frames, the standard deviation of the lumen center *xy* position and the mean and standard deviation in lumen center width were used as dynamic estimates of wall motility. These parameters were plotted in three-dimensional space, and the best discriminant function was used to classify celiacs versus controls at each of the following five locations: (1) duodenal bulb, (2) distal duodenum, (3) jejunum, (4) ileum, and (5) distal ileum.
Results The overall sensitivity for the classification of celiacs versus controls at all five locations was 98.2 %, while the specificity was 96.0 %. From location 1 to 5, there was a tendency for the lumen center width to diminish in terms of frame-to-frame variability by 7.6 % in celiacs ($r^2 = 0.4$) and 9.7 % in controls ($r^2 = 0.7$).
Conclusions In addition to examining the mucosal surface, videocapsule endoscopy can assess small bowel intestinal motility and aid in distinguishing celiac patients from controls.

Keywords Celiac disease · Classification · Motility · Small intestine · Videocapsule endoscopy

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Background

Quantitative assessment methods are useful to detect statistically significant differences in endoscopic images obtained from celiac disease patients [1–5]. At the microscopic level and using standard endoscopy images, it is possible to define the level of villous atrophy based on the surface profile of the small intestinal mucosa as measured from intestinal biopsy [1]. Celiac patients with severe small intestinal villous atrophy (Marsh grade IIIc or IIIb) lack villous projections, or the villi have rounded contours. Biopsy with microscopic analysis is slow, invasive, and cannot be completed during endoscopic investigation. At the macroscopic level, images obtained by standard endoscopy can be used to detect fissures in the small intestinal lumen, as evidence of villous atrophy [4]. Unlike standard endoscopy assessment, biopsy cannot be used for the assessment of the presence of villous atrophy using videocapsule endoscopy. Thus, other means must be used to evaluate videocapsule endoscopy (VCE) images for the

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characterization of abnormal regions or patterns, which may be indicative of villous atrophy and celiac disease.

We have previously quantified VCE images to determine statistical differences in image features that are indicative of the presence of villous atrophy [2–5]. However, information on the relationship between abnormal small intestinal motility and celiac disease is scarce at the present time. The results from some studies suggest that gastrointestinal motor abnormalities may explain some of the symptoms [6], but this hypothesis has not been investigated. In celiac patients, reduced intestinal transit delays may occur segmentally due to motor abnormalities [7]. Symptoms of gastroesophageal reflux in celiac patients may resolve after they are started on a gluten-free diet due to clinical resolution and the restoration of normal small intestinal motility [6, 8–10].

In this study we developed a method to detect and quantify differences in the small intestinal motility of celiac disease patients compared to controls using VCE images. Instead of investigating specific image features, as in previous studies, we used dynamic estimates of wall motility for image classification and sought to characterize motility according to frame-to-frame changes in lumen shape. The center of the lumen on VCE images appears as a dark region as it is at a greater depth from the lens than is the bowel wall. This lumen center varies from one image to the next depending on wall motility and both forward and rotational movement of the videocapsule. Our hypothesis was that quantitative estimates of motility can be obtained from a sequence of videocapsule image features and that these estimates would differ in untreated celiac patients versus controls.

Method

Clinical Procedure and Data Acquisition

Retrospective VCE data was obtained from 11 celiac patients and ten control patients. The celiac patients were on a gluten-free diet, except for one patient with hemophilia and positive anti-endomysial antibody who had not yet started the diet. These patients had a diagnostic biopsy with Marsh grade II-IIIC lesions and positive serology for celiac disease upon diagnosis. The single celiac patient with hemophilia did not have a biopsy but was positive for anti-tissue transglutaminase immunoglobulin A (IgA) antibody and anti-endomysial antibody. For the VCE study, informed consent was obtained. Indications for the procedure included suspected celiac disease or Crohn's disease (CD), iron deficiency anemia, obscure bleeding, chronic diarrhea, and/or abdominal pain unexplained by previous evaluation. Patients were excluded from the study if they were under 18 years of age, had a history of or suspected small bowel obstruction, dysphagia, presence of pacemaker or other electromedical implants, previous gastric or bowel surgery, pregnancy, or nonsteroidal anti-inflammatory drug (NSAID) use during the previous month. For analysis, only complete VCE studies that reached the colon were used. The study was approved by the Internal Review Board at Columbia University Medical Center, with all patients being evaluated between 1 May 2008 to 31 July 31 2009.

To obtain the small bowel images the PillCam videocapsule was used (ver. SB2, 2007; Given Imaging, Yoqneam, Israel) [11]. The device includes a recorder unit, battery pack, wireless interface, and real-time viewer. The capsule acquires two digital image frames per second, with a resolution of 576 × 576 pixels, and is a single-use pill-sized device [11]. For each patient undergoing the procedure, abdominal leads were placed on the upper, mid, and lower abdomen, and a belt containing the data recorder was strapped about the waist. All subjects swallowed the videocapsule with radio transmitter in the early morning with approximately 200 cc of water and 80 mg simethicone after an overnight fast without bowel preparation. Subjects were allowed to drink water 2 h after capsule ingestion and to eat a light meal after 4 h after capsule ingestion. The recorder was then removed and the data downloaded to a HIPAA-compliant PC-based computer console equipped with RAPID software (ver. 5, 2008; Given Imaging). The RAPID software was used for review and clinical report generation during the VCE studies. Videos were reviewed and interpreted by three experienced gastroenterologists. Selected de-identified videoclips, 200 frames in length, were exported to external media without patient identifiers for further quantitative analysis. Images were acquired immediately distal to the pylorus, corresponding to the proximal duodenum and immediately proximal to the colon, corresponding to the distal ileum (locations 1 and 5, respectively). The total small bowel transit time of the videocapsule was divided into tertiles. Video clips were also acquired from each of the three tertiles for each patient (locations 2, 3, and 4, respectively).

Quantitative Analysis

From each color videoclip, 200 grayscale images (256 brightness levels, 0 = black, 255 = white, and 576 × 576 pixels in dimension) were extracted using Matlab ver. 7.7, 2008 (The MathWorks, Natick, MA). The image data were ported into software created by the authors which was coded using the Intel Visual Fortran Compiler (ver. 9.0, 2005; Intel Corp, Santa Clara, CA). As a first approximation, in each image, 10,000 of 331,776 pixels with lowest grayscale level were detected and used to estimate the lumen center. The maximum width (w) of the lumen center was defined as the longest continuous segment of pixels in the x direction,

with all pixels being within the lowest 10,000 in grayscale level. The center of this segment was defined as the x position of the lumen center, and the row number in pixels along the y axis was defined as the y position.

Celiac and control videoclips were classified using two different sets of parameters. The parameters for classification system 1 were the standard deviation (SD) in the lumen x position, and the mean and SD in lumen width. The parameters for classification system 2 were the SD in $(x + y)/2$, and the mean and SD in lumen width. Each set of parameters was separately plotted using the map3d computer software program (Scientific Computing and Imaging Institute, University of Utah, Salt Lake City, UT) [12]. This program allows computer-generated scatterplots to be rotated on the computer screen. For each small intestinal location, the best rotation to separate celiacs from controls was determined manually, and a discriminant function was drawn for classification. The sensitivity and specificity of the technique were calculated. The unpaired t test was used to determine significant differences between the means at each location (SigmaPlot 2004 for Windows ver. 9.01, Systat Software, San Jose, CA; MedCalc 2008, ver. 9.5, MedCalc Software, Mariakerke, Belgium).

Results

Videocapsule images were successfully obtained from all five small intestinal levels in all patients. Clinical parameters for these patients are provided in Table 1. The celiac and control patients were approximately evenly matched for age and gender. The celiac patients undergoing standard endoscopy with biopsy were found to have a Marsh score ranging from II to IIIc, indicating villous atrophy of the small intestinal mucosa in the majority of cases. An example of images obtained from the duodenal bulb region (location 1) in an untreated celiac patient is shown in Fig. 1. This patient had villous atrophy classified as Marsh IIIc, and the endoscopic image demonstrates fissuring and scalloping of folds. Figure 1a is an original image taken at time 1:03:16; in Fig. 1b, the darkest 10,000 pixels out of the total of $576 \times 576 = 331{,}776$ pixels are shown in light gray. The maximum continuous width dimension of this light-gray region was determined automatically by computer software and is denoted by the horizontal red line. Its parameters are shown at the right ($y = 509$ pixels, $x = 301$ pixels, $w = 113$ pixels), with the 0,0 coordinate being at the top left. The results for the image that was obtained 1 s later (i.e., 2 frames later in the sequence) are shown in Fig. 1c, d, with Fig. 1c showing the original grayscale image and Fig. 1d giving the result of the quantitative analysis. The luminal center is again denoted by the uniform light-gray region, and it encompasses a similar area and location as in Fig. 1c. The maximum width of the region is toward the bottom of the image. The parameter values ($y = 542$ pixels, $x = 337$ pixels, $w = 107$ pixels) are still similar to those of Fig. 1b.

Table 1 Clinical parameters

Parameter	Celiac	Controls
Gender		
Male	5	4
Female	6	6
Diabetes	0	1
Age (years)	47.5 ± 15.9	50.6 ± 23.8
Men	44.0 ± 20.7	51.5 ± 26.2
Women	50.5 ± 11.7	50.0 ± 24.6
Marsh score		
II	2	–
IIIa	4	–
IIIb	1	–
IIIc	3	–

Data are presented as a number, or as the mean ± standard deviation (SD)

One celiac patient had hemophilia and could not undergo biopsy for the Marsh score analysis

For comparison, sets of images taken later in the same videoclip for the same celiac patient are also shown (Fig. 2). The darker region at the upper left in the image is the center of the lumen. The detected darkest pixels are noted by a uniform light-gray region in Fig. 2b. In this case it is mostly the edges of the central region that are outlined, with the widest region shown by a horizontal red bar; its parameters are given at the right. Two seconds (four frames) later, there is an evident difference in the size and shape of the luminal center (Fig. 2c). Although it appears to be in the same general location as in Fig. 2a, it also appears to have widened. Indeed, the region of darkest pixels, as noted in Fig. 2d, differ from those in Fig. 2b. The widest region is now a sliver toward the middle of the image in Fig. 2d, with parameters given at the right. Although the differences in width parameters from Fig. 2b to Fig. 2d are significant, this is partially due to a wider disparity in frames between the images Fig. 2a–b versus c–d (4 frames in Fig. 2 compared with only 2 frames in Fig. 1).

Classification system 1 (see Methods) for the five small intestinal locations are shown in Fig. 3. In each of the five scatterplots, celiac parameters are shown in red ($n = 11$ patients), and control parameters are shown in blue ($n = 10$ patients). Due to overlap, occasionally a scatterpoint will not be visible in each scatterplot. The discriminant functions are given as black curved lines. All projections have the same orientation, with the coordinate axes given at the right in Fig. 3. The axes for the standard

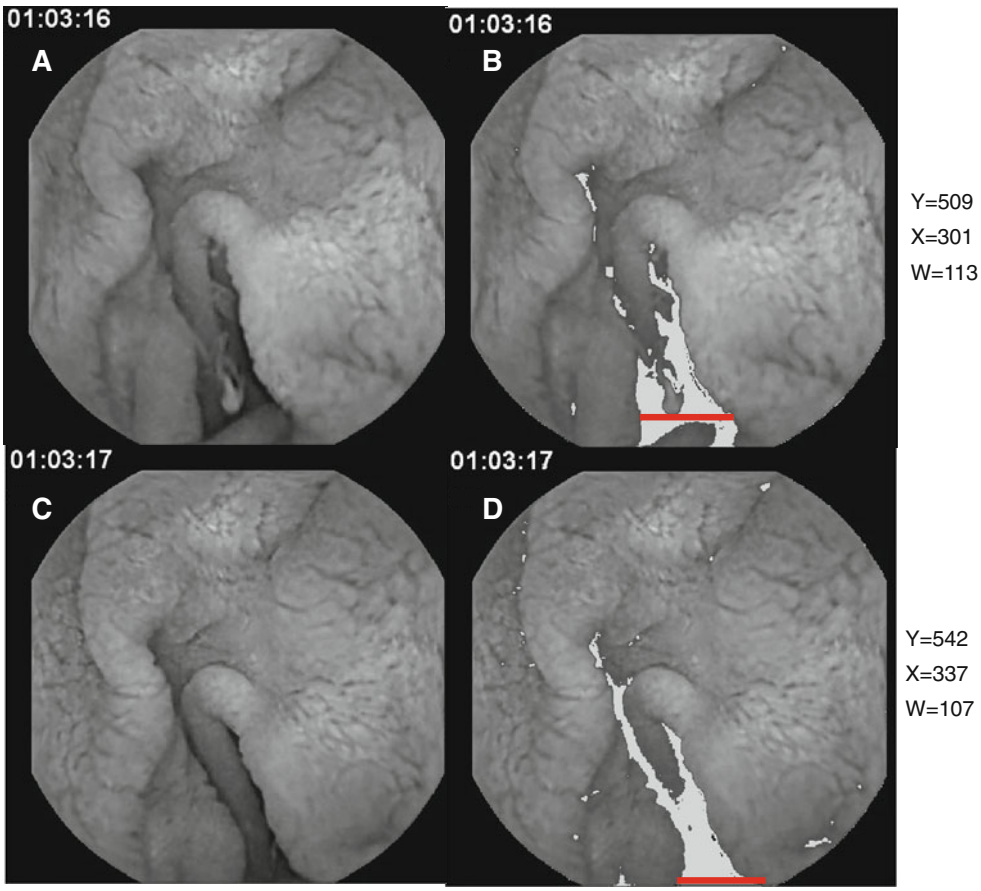

Fig. 1 Videocapsule endoscopy images from the duodenal bulb of an untreated celiac disease patient. **a**, **c** Untouched images, **b**, **d** images with lowest 10,000 pixel grayscale level noted by uniform *light-gray color*. Maximum width in these regions is denoted by the *red line*. Images in **a** and **b** were taken only 1 s prior to the images in **c** and **d**, and there is only a small difference in estimated lumen center location and width between the two sets of images

deviation in the x position and the mean and standard deviation in width project into the plane; thus, the discriminant functions depend on all three parameters. These functions are drawn approximately the same in each scatterplot; thus, similar classification can be used at each small intestinal location. Most of the scatterpoints are correctly classified based on the discriminant function, as given in Table 2 (classification system 1). Similarly, results for classification system 2 for five small intestinal locations are shown in Fig. 4. The orientation is the same as in Fig. 3. Celiac and control scatterpoints tend to be separated by a discriminant function that runs roughly diagonally from the upper left to lower right in each scatterplot, as given in Fig. 3. Most of the scatterpoints are correctly classified, with actual values for sensitivity and specificity shown in Table 2 (Scheme II).

The statistics for all classification parameters are noted in Fig. 5 (red = celiac, blue = control). Fig. 5a–d show graphs for the x position of the standard deviation, xy position of the standard deviation, width mean, and width standard deviation, respectively. The small intestinal location is denoted on the abscissa of each graph. There are no significant differences in parameters for any particular location; however, several significant trends are noted (defined as $p \leq 0.2$). There are several significant trends from location 1 through 5 as determined by linear regression ($r^2 > 0.35$). The width parameter mean and standard deviation trend lower for celiacs, and the width parameter standard deviation trends lower for controls, as noted by dotted lines. These results suggest an overall decrease in motility, as defined by changes in the maximal width of the lumen center, distally along the small intestine of celiacs.

Discussion

In our study, we sought to develop an automated and quantitative technique to directly characterize motility according to frame-to-frame changes in lumen shape. These dynamic estimates measure motility over 200 image frames, thus incorporating information beyond methodology that analyzes static features in a single frame. The overall sensitivity for classification of celiacs versus controls at all five locations was 98.2 %, while the specificity was 96.0 %. Small intestinal motility remains an understudied area, particularly for celiac disease patients [13].

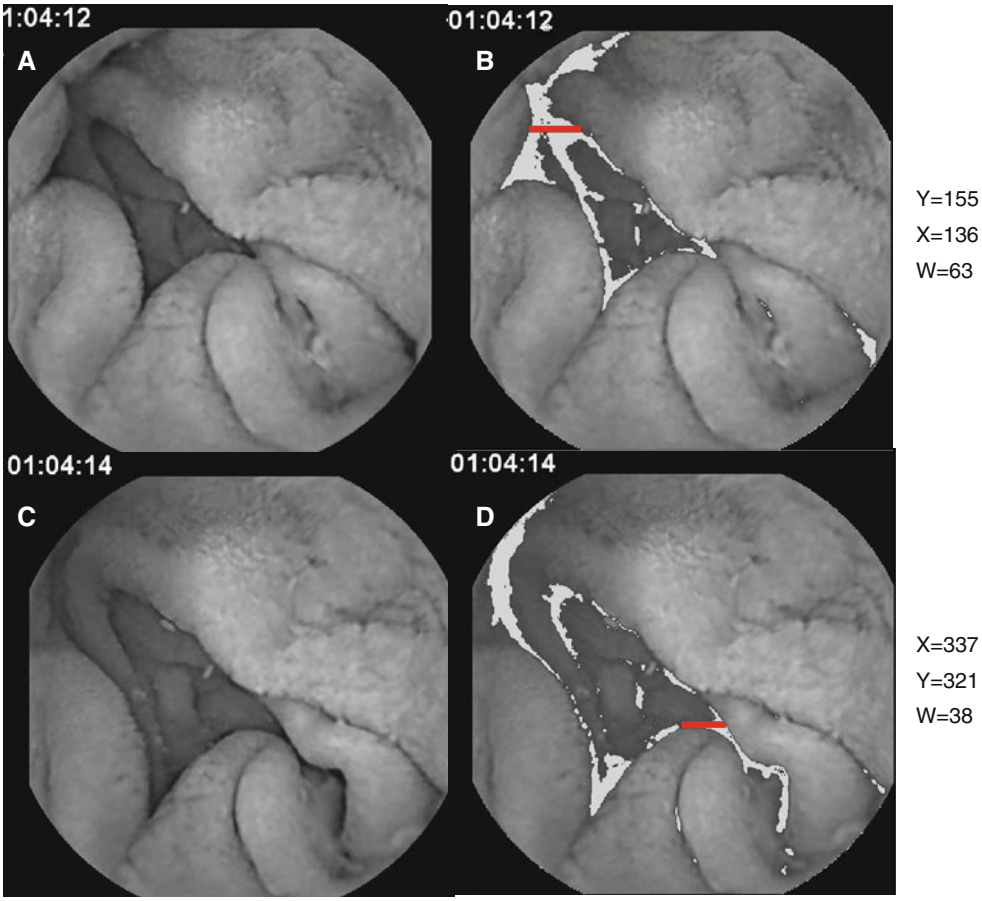

Fig. 2 Videocapsule endoscopy images from the duodenal bulb of the same untreated celiac disease patient as in Fig. 1. Images in **a** and **b** were taken 2 s prior to the images in **c** and **d**. In comparison to **a** and **b**, **c** and **d** show marked difference in estimated lumen center location and width

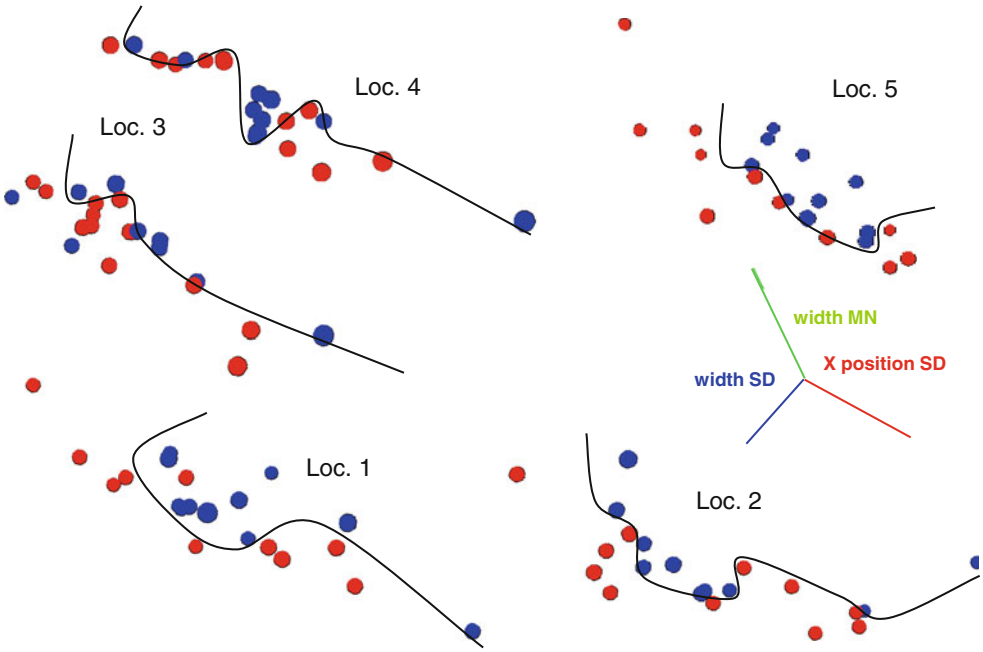

Fig. 3 Projections and discriminant functions using classification system 1. Scatterplots for small intestinal locations 1 through 5 are shown. The discriminant functions are shown as *black curved lines*. Celiac scatterpoints are given in *red* and control scatterpoints are in *blue*. The same projection is used for each scatterplot as noted by the coordinate axes at the *right*. *MN* mean *SD* standard deviation

Table 2 Statistics

Parameter location	Scheme 1		Scheme 2	
	Sensitivity	Specificity	Sensitivity	Specificity
Loc 1	90.9	100.0	90.9	100.0
Loc 2	100.0	100.0	81.8	100.0
Loc 3	100.0	80.0	100.0	100.0
Loc 4	100.0	100.0	90.9	90.0
Loc 5	100.0	100.0	100.0	100.0
Overall	98.2	96.0	92.7	98.0

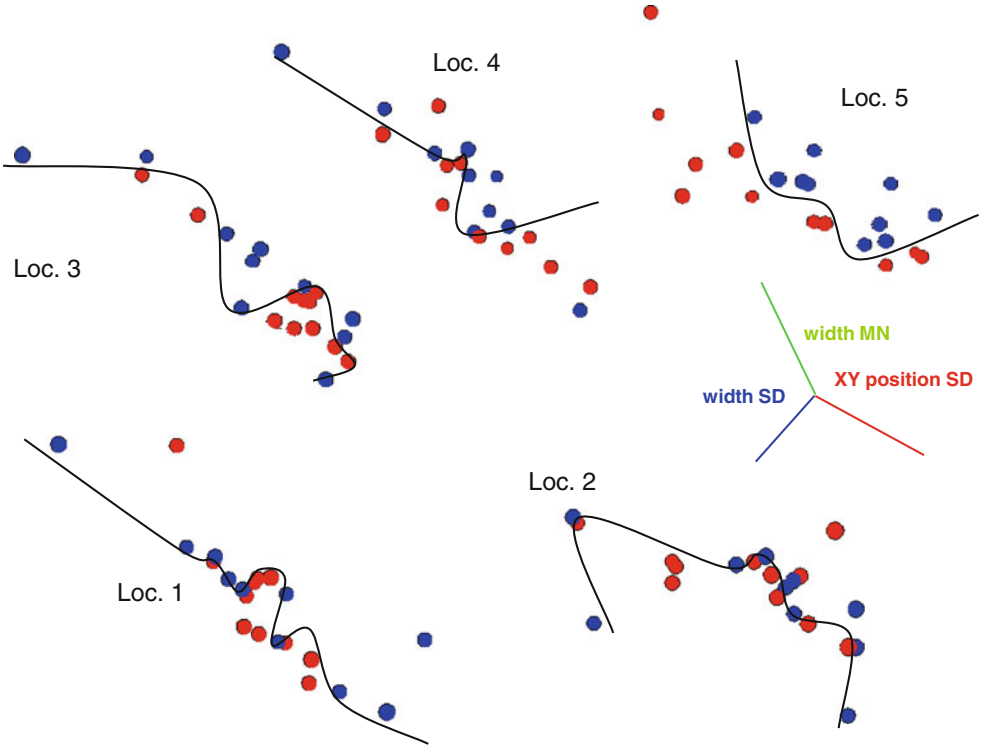

Fig. 4 Projections and discriminant functions using classification system 2. Description is the same as for Fig. 3

Methods of Quantitative Analysis

Analyses to quantitatively estimate small intestinal motility from VCE images have been introduced in the past by several research groups. The magnitude of small intestinal contractions has been estimated from videocapsule image series using location-specific textural and color information [14]. To avoid additional complexity, we did not consider color or textural information in our study, yet this information may further improve the characterization of celiac disease patients. In another study, temporal variations in intestinal contractions were estimated based on frame-to-frame variation of the edges of image features [15]. The spatial orientation of edge pixels in each image feature was used to determine spatial variations in intestinal contractions. Contractile patterns in the small intestine have also been estimated by automatically sensing luminal closure and the presence of radial wrinkles, using a combination of parameters to improve efficacy [16]. Additionally, telemetry has been utilized to record actual small intestinal motility [17]. Our method, if it can be shown to correlate to real motility by means of telemetry, would be useful to validate the process.

Clinical Correlates

Although initial studies reported a high sensitivity and specificity for detecting villous atrophy on VCE, recent studies suggest the sensitivity and specificity to be only about 50 % [18, 19]. In addition to assessing mucosal features, macroscopic features seen on VCE, such as the estimated width of the small intestinal lumen, can be useful to detect abnormalities. The interpretation of villous atrophy using VCE is subjective and difficult to assess in states

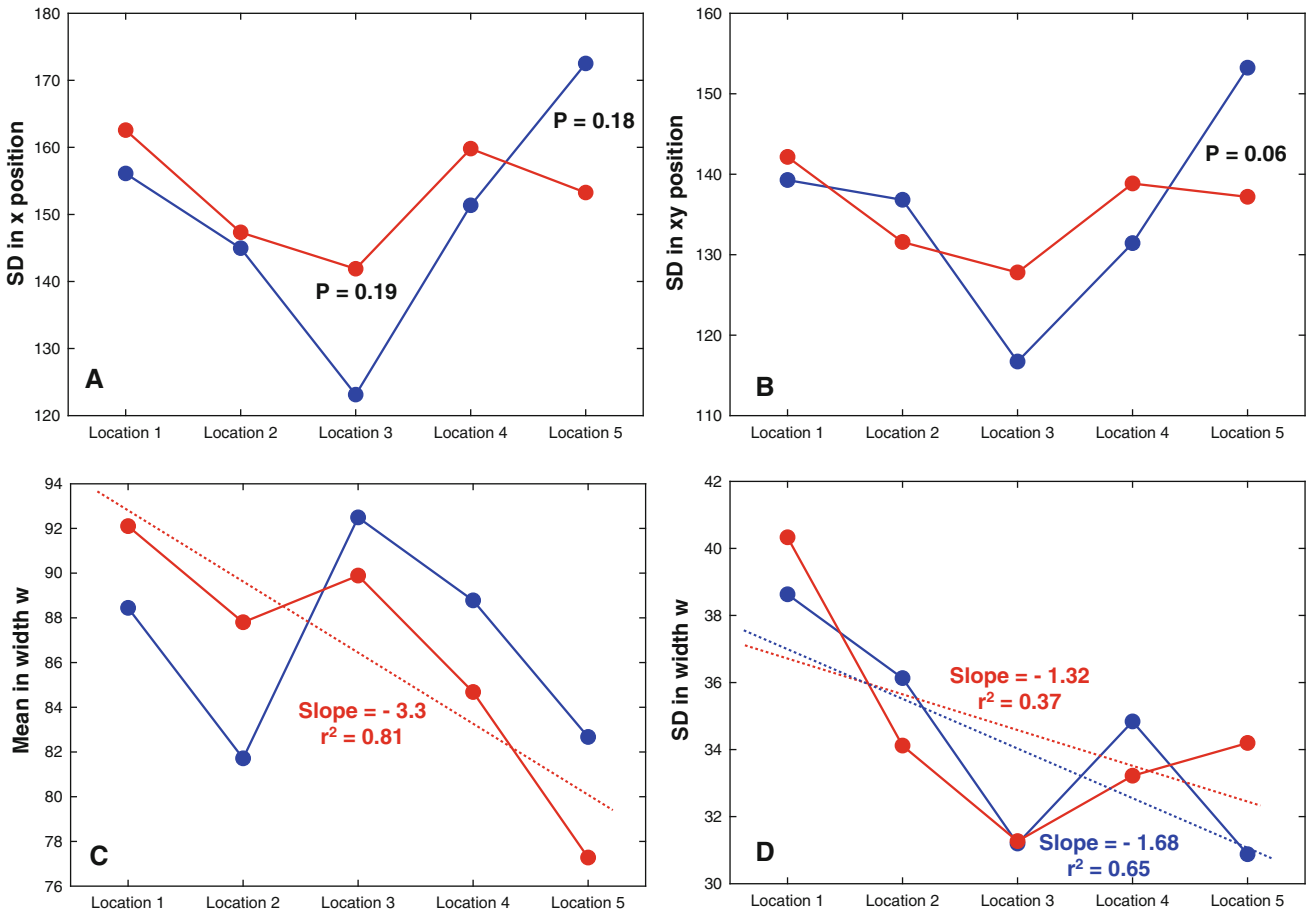

Fig. 5 Statistical relationships between classification parameters (*red* celiac, *blue* control). *p* values are shown when celiac versus control mean levels trend toward significance ($p \leq 0.2$). *Dotted lines* Linear regression lines for significant trends ($r^2 > 0.35$)

of partial villous atrophy. Quantitative image analysis of both mucosal features and motility may assist clinicians in identifying celiac patients. The changes in motility observed in celiac patient VCE images may result from diminished small intestinal folds [20]. This decrease in folding may cause more rapid changes in the *xy* position and the width of the luminal center in untreated celiac patients (Table 2, Figs. 3, 4). Motor abnormalities, as evidenced by discrete clustered contractions, large jejunal contractions, and bursts of nonpropagated contractions are present in greater percentage in celiac patients than in normal controls [21]. This is also likely to affect the lumen width and position as estimated in our study. The presence of any gastrointestinal motility disturbances associated with untreated CD may resolve after gluten withdrawal [7]. Thus, it is likely that the method may be used as a monitor of the efficacy of a gluten-free diet for healing of the small intestine, as well as for improving the yield in the diagnosis of celiac disease.

Small intestinal motility remains an understudied area [22], particularly for celiac disease patients. Our technique may be applicable to the evaluation of persistent symptoms of irritable bowel syndrome in poorly responsive celiac disease patients [23]. It should also be correlated with the symptomatology of the disease. Although the focus of our study was celiac disease, villous atrophy can also be present and possibly assessed with our quantitative technique in patients with giardia, autoimmune enteropathy, Crohn's Disease, collagenous sprue, and common variable immune deficiency (CVID). The Given Imaging system used in our study provided satisfactory image data for the assessment of celiac disease. Data acquired using other VCE systems, such as the EndoCapsule EC type 1 (Olympus America, Center Valley, PA) [24] will likely produce similar results, although this remains to be tested.

Limitations

Limitations of this study include the relatively small sample size and the small size of videoclips obtained. A larger, blinded prospective study should be conducted to further validate this technique. Our results suggest that the classification of celiac patients versus controls can be based upon dynamic estimates of wall motility. Inclusion of a

control group with severe intestinal motility disorders would be helpful to validate the technique. Three parameters were used for classification. Classification accuracy may increase if additional parameters are used, which will be the subject of future study. Our technique assumes that camera angle and distance to the mucosal surface are uniform and that coverage of the surface area of the small intestinal lumen is relatively constant during transit of the videocapsule. However, significant variation in these parameters actually occurs, an important limitation of the study. These variations may decrease the significance of the differences in estimated motility in celiac versus control videoclip images. Removal of extraneous image features prior to analysis [25] can potentially improve technique efficacy. Capsule motion may also be erratic, further limiting analysis. The study was also performed with only one capsule endoscope system, and it is unclear if these results would be different with the use of a different capsule endoscopy system.

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Conflict of interest None.

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