CLASSIFICATION OF FUNCTIONAL BOWEL DISORDERS BY OBJECTIVE

PHYSIOLOGICAL CRITERIA BASED ON ENDOLUMINAL IMAGE ANALYSIS

Running Head: Physiological classification of functional bowel disorders

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**Introduction.** We have previously developed an original method to evaluate small bowel motor function based on computer vision analysis of endoluminal images obtained by capsule endoscopy. Our aim was to demonstrate intestinal motor abnormalities in patients with functional bowel disorders by endoluminal vision analysis. **Methods.** Patients with functional bowel disorders (n=205) and healthy subjects (n=136) ingested the endoscopic capsule (Pillcam-SB2, Given-Imaging) after overnight fast and 45 min after gastric exit of the capsule a liquid meal (300 ml, 1 kcal/ml) was administered. Endoluminal image analysis was performed by computer vision and machine learning techniques to define the normal range and to identify clusters of abnormal function. After training the algorithm, 196 patients and 48 healthy subjects, completely naïve, were used as test set. **Results.** In the test set, 51 patients (26%) were detected outside the normal range (p<0.001 vs 3 healthy subjects) and clustered into hypo and hyperdynamic subgroups. As compared to healthy subjects, patients with hypodynamic behavior (n=38) exhibited less luminal closure sequences (41±2% of the recording time vs 61±2%; p<0.001) and more static sequences (38±3% vs 20±2%; p<0.001); in contrast, patients with hyperdynamic behavior (n=13) had an increased proportion of luminal closure sequences (73±4% vs 61±2%; p=0.029) and more high motion sequences (3±1% vs 0.5±0.1%; p<0.001). **Conclusion.** Applying an original methodology we have developed a novel classification of functional gut disorders based on objective, physiological criteria of small bowel function. **Keywords:** functional bowel disorders; capsule endoscopy; intestinal motility; computer vision analysis; machine learning;
INTRODUCTION

We have developed an original method to evaluate small bowel motor function based on computer vision analysis of endoluminal images obtained by capsule endoscopy. A series of features, such as phasic luminal closures, non-contractile patterns, e.g. smooth wall or open tunnel view, amount of chyme and motion of the walls and content, are quantitatively measured. Each subject is then defined by a combination of values derived from these various dimensions. Definition of normality in this multidimensional space is performed by machine learning techniques: providing a large series of normal cases, the program draws the hyperplane that defines the normal range, and hence, automatically learns to discriminate what is normal and not.(24) This may constitute a particularly valuable diagnostic tool on account of the enormous amount of data obtained in a large sample of healthy individuals and the automated algorithms that eliminate the piecemeal assessment of normality for each separate feature as well as the subjectivity of the data analyst, common to many physiological gut tests.

Comparing healthy subjects and patients with intestinal neuropathy, we showed that an initial version of this method had similar specificity, but much higher sensitivity than intestinal manometry, the current gold standard to identify intestinal dysmotility.(11) We then applied this method to a milder and not so well defined group of patients with symptoms fulfilling criteria of functional gastrointestinal disorder. In a preliminary pilot study we detected small bowel motor abnormalities in a substantive proportion of these patients; however, this proof-of-concept study was not properly controlled: because the sample size
was modest, the same cohort of subjects was used for developing and testing the algorithm.(12)

Following-up these encouraging trials, we undertook a major prospective study hypothesizing that small bowel motor dysfunction can be objectively demonstrated in patients with functional gastrointestinal disorders and that proper evaluation of bowel function may ultimately provide objective criteria for a physiological classification of these patients. Accordingly, a well-powered, properly-controlled study was designed and executed in subjects with functional gut symptoms (patients fulfilling Rome III criteria) and without (healthy subjects). In this study we also took advantage of technical advancements in the optics of the system and applied further developments for the treatment of images by computer vision paradigms and for the classification of patients by robust machine learning techniques.

MATERIALS AND METHODS

Participants

Patients with functional bowel disorders attending the Vall d’Hebron gastroenterological community clinic and healthy subjects were prospectively recruited between June 2009 and June 2012. At screening, potential candidates filled out a symptom questionnaire and consecutive patients fulfilling Rome III diagnostic criteria of functional bowel disorders were offered to participate in the study.(10) None of these subjects had participated in any previous study on intestinal motility evaluation by capsule endoscopy.(6, 11, 12) The study protocol was approved by the Ethics Committee of the University Hospital Vall
d’Hebron, and all participants gave their written informed consent before enrolment.

**Test procedure**

Endoluminal images were obtained with the Pillcam capsule (Pillcam SB2 video capsule, Given Imaging, Yokneam, Israel). Tests were performed by an experienced nurse (SM). The capsule was ingested after medications that could affect gastrointestinal motility had been discontinued for at least 48 h and an overnight fast. Recording was continued for a total of 8 hours with the subjects lying comfortably on a hospital bed and the trunk raised 30° above horizontal. No adverse events were encountered.

Gastric exit of the capsule was determined by visual inspection at 10-minute intervals using a real-time viewer monitor (RAPID Access, Given Imaging, Yokneam, Israel). Forty-five minutes later, participants were requested to ingest a liquid meal (Ensure HN, Abbott, Zwolle, The Netherlands; 300 ml, 1 Kcal/ml).

**Computer vision analysis**

Small bowel images were selected by visual detection of gastric exit and cecal arrival and examined by an experienced physician (CM). Cases with morphological mucosal abnormalities (5 patients and 2 healthy subjects) and cases with post-meal period < 5 min (4 patients and 1 healthy subject) were excluded for analysis.

Four of the five patients with mucosal abnormalities were later proven to have previously unrecognized Crohn’s disease.
Endoluminal images of the small bowel were automatically analyzed by a computer vision program specifically developed for the evaluation of intestinal motility. Computer vision techniques use mathematical computation to transform specific aspects of the images into numerical scores. This process demands prior identification of biologically relevant features and subsequent development of the appropriate algorithm for analysis by a multidisciplinary team of experienced physicians and mathematicians (CM, FA, MD, SS, JV, PR).(7, 18) The following features were measured.

**Intestinal wall, lumen and luminal closures**

Endoluminal images show the intestinal wall illuminated by the light of the capsule and the dark lumen in the rear mimicking the view of a tunnel. In each image, the intensity of light of the different pixels was analyzed using a Laplacian of Gaussian model which defines the three-dimensional curve reflecting the relationship between the bright walls and the dark lumen. Two well defined non-contractile patterns were defined: a) a tunnel pattern, characterized by a peripheral band of bright wall and a central open lumen, large and dark; and b) a wall pattern, characterized by flat wall, smooth and bright, without view of lumen (Figure 1).(21)

Phasic intestinal contractions are visualized by capsule endoscopy as reversible changes in lumen size (closure / opening) within a 9-frame sequence (4.5 s). The lumen was delimited in each image as described above. Each 9-frame sequence, selected by a sliding window technique, was evaluated as a whole to determine whether it corresponded to a contractile event or not, using an automatic classifier (support vector machine) as follows. Based on a series
of examples of contraction sequences and non-contraction sequences selected by visual analysis, the program found the best discriminatory function to identify contractions.(23) Discrimination between occlusive and non-occlusive contractions (complete versus partial luminal closure) was performed by a second classifier based also on a training set of both types of contractions.

**Radial wrinkles**

Evaluation of luminal contractions requires a centered view of the intestinal lumen over the entire 9-frame sequence, and hence, a proportion of contractions are missed. Contraction of the circular intestinal muscle produces wrinkles in the intestinal wall radial to the shrinking lumen and this feature is another indicator of contractile activity (Figure 1). In each image, the amount of intestinal wrinkles was measured by structural tensor analysis, as follows. The image was treated as a topographic map in which the crests and valleys were identified and their direction towards the central lumen (point of highest entropy) was measured.(22) The detection of wrinkle frames was performed with a specific Naïve Bayes classifier.(19)

**Turbid content**

The intestinal lumen is usually clear and allows viewing intestinal walls, but in some instances the lumen contains turbid content (Figure 1). Images with turbid content were identified by color analysis. Each frame was represented by a 256 color histogram. Based on a series of examples of turbid and non-turbid (clear) frames, an automatic classifier was trained to detect the frames with turbid content.(20)
Endoluminal motion

The motion of intestinal walls and content results in a degree of dissimilarity between sequential images of the capsule video. Endoluminal motion was measured by analysis of color differences (red-green-blue composition) in consecutive images using the Earth Mover’s Distance method, which measures the degree of motion as the amount of work (expressed as units of Euclidian distance) necessary to transform the color plot of one frame into the following one.(17) Static and high motion images were defined using thresholds that have been previously established.(6) This method was applied to measure wall motion in clear frames, as well as the motion of turbid content.

Sequences of events

The analyses described above detect events in single or short series of concatenated images. To identify periods when an event appears with a certain frequency or density, sequence analysis was applied. Sequences were defined using the Adaptive Windowing Algorithm.(2) This algorithm delimits periods where the density of appearance of an event (motility feature) is homogeneous. The following sequences were identified, using pre-established thresholds, and quantified: periods with high density of luminal closures, turbid content, static images, high motion images, tunnel and wall view.

Algorithms for identification and clustering of abnormal intestinal motility

Identification of patients with abnormal motor function was performed blindly by comparing them to healthy subjects using a one-class classifier, as follows.(3) The development of the algorithm involved a stepwise approach.
First, a list of 67 parameters, derived from the combined analysis of the motility features described above, was developed based on the previous experience with this method. Two subgroups of 85 healthy subjects and 70 patients were randomly selected (3 patients were then excluded for meeting short post-meal period exclusion criteria). In these subgroups, the 63 parameters were compared and significant differences were detected in 43 of those parameters. These 43 parameters were used to discriminate normal and abnormal intestinal motor function. The normal range was defined using the same group of 85 healthy subjects as training set to construct a one-class classifier: each subject was defined by the values of the 43 selected parameters, and the program drew in this multidimensional space (with 43 dimensions) the hyperplane that defined the normal range. The algorithm was set allowing 5% outliers in the training set. Using this classifier we then evaluated intestinal motor function in the remainder group of healthy subjects (n=48) and patients (n=129), which were completely naïve to the algorithm and were used as the test set.

As the next exercise, we searched for different types of abnormal function. Patients from the training set that were identified out of the normal range by the one-class classifier were then further tested with the k-means clustering technique (Lloyd’s algorithm) to identify the existence of subgroups.(9) Two distinctive clusters of patients were identified, one exhibited characteristics of hyper-dynamic behavior, and the other of hypo-dynamic behavior. These two subgroups of patients in the training set were used to build a specific two-class classifier (including 5 parameters related to luminal...
closures, radial wrinkles, tunnel and static images) that was later used to cluster
the patients found outside the normal range in the test set.

Statistical analysis

Statistical analysis was performed using the SPSS 12.0 for Windows
statistical package. Based on the previous pilot study (abnormal motility in 30%
of the patients), the sample size of the test set was estimated expecting 10%
abnormal cases in healthy subjects. Mean values (± SE) of the parameters
measured were calculated in each group of subjects. Analysis of variance was
performed by ANOVA. Post-hoc comparisons were made by the Tukey’s test.
Distribution of abnormalities between groups was evaluated by the chi-square
test. Differences were considered significant at a p value < 0.05.

RESULTS

Demographic and clinical data

Patients fulfilling Rome III criteria of functional bowel disorder (n = 205;
51 men, 154 women; age range: 17 - 76 years) and healthy subjects without
gastrointestinal symptoms (n = 136; 61 men, 75 women; age range: 16 - 65
years) participated in the study. Demographic and clinical characteristics of
patients are further specified in Table 1.

Output of the classifier

Identification of abnormal cases

The proportion of healthy subjects in the test set identified out of the
normal range by the one-class classifier (3 out of 48) was similar to the
predefined outlier proportion in the training set (5%). A significantly greater proportion of patients in the test set, 32 of 129 patients (25%), were found outside the normal range (p< 0.000 by Chi Square). No differences in the proportion of patients outside the normal range was found whether only naive cases (n=129) or the whole group of patients were included in the test set. The latter also included the 67 cases used for the initial identification of the abnormal features to develop the classifier (51 of 196 patients, 26%) (Figure 2).

Identification of abnormal subgroups

Pooling together the 51 patients detected as abnormal, 38 cases (75%) were identified as hypodynamic and 13 cases (25%) as hyperdynamic by the two-class classifier. Hence, patients with functional bowel disorders were classified by the computer algorithm into three physiological categories: 74 % with normal intestinal motor function 19 % with hypodynamic behaviors and 7 % with hyperdynamic behaviors (Figure 2).

Healthy subjects

Overall pattern description

Healthy subjects had a mean transit time in the small bowel of 204 ± 16 minutes (in all but 4 cases the capsule reached the cecum). During most of the recording time (61 ± 2%) contractile activity was uniformly present, corresponding to luminal closure sequences (Figure 3). Overall, 30 ± 2 luminal closure sequences per study were detected, with a mean duration of 4.5 ± 0.3 min and a frequency of 8.8 ± 0.3 closures per sequence. When further analyzed by the luminal closure classifier, most contractile events (94±1%) were
occlusive. Conversely, only a relatively small part of the time (20 ± 2%) corresponded to static periods with very low motion (Figure 3). High motion sequences were only present in 0.5 ± 0.1% of the recording time. The endoluminal view appeared as a tunnel, featuring an open, large central lumen, in 7 ± 1% of the recording time; 28 ± 5% of the tunnel images were static. Characteristic sequences alternating short static periods with bursts of contractions were observed in 14 ± 2% of the recording time. During one third of the recording time (29 ± 3%) the intestinal lumen contained turbid content, which most of the time was in motion (only 17 ± 3% of the time it was static).

**Effect of meal**

The meal in healthy subjects had a profound effect and consistently stimulated intestinal motor activity. When comparing the pre-meal period with the first third of the post-meal period, there was a significant increase in luminal closures (13±4 % mean increase; p=0.001 pre vs 1\textsuperscript{st} third post-meal) and a reduction in static sequences (9±3 % mean decrease; p=0.003 pre vs 1\textsuperscript{st} third post-meal) (Figure 4). Meal ingestion was also associated with a significant reduction of alternating contractile-static sequences (12±3 % mean decrease; p<0.001 pre vs 1\textsuperscript{st} third post-meal).

The effect of the meal gradually declined as the postprandial period progressed and the capsule advanced to more distal segments of the small bowel. Contractile sequences progressively diminished along the postprandial period (74±3 %, 65±4 % and 50±4 % of time during the first, second and third parts of the postprandial period, respectively) (Figure 4). The last part of the postprandial period was characterized by a significant increase in static
sequences (p<0.001 vs second and third parts) and sequences with turbid content (49±6 % vs 23±3 % in the second third; p<0.001). One fourth (25±4 %) of the turbid sequences were static (vs 17±3 % in second third; p=0.001) (Figure 4). Tunnel sequences progressively became static during the postprandial period as the capsule progressed along the small bowel (57±7 % of tunnel images in the last third of the postprandial period were static vs 22±6 % in the second third; p=0.038).

Patients classified within the normal range

Patients allocated by the classifier into the normal range exhibited the same pattern distribution and response to meal as healthy subjects except for slight differences related to the pre-meal period (51±2 % of time corresponding to luminal closure sequences and 32±2 % to static sequences vs 61±3 and 21±2 %, respectively, in healthy subjects; p<0.05 for both) and to the presence of turbid secretion sequences in the last third of the postprandial period (33±3 % of time vs 49±6 % in healthy subjects; p=0.046).

Hypodynamic cases

Hypodynamic cases had similar small bowel transit times as compared to healthy subjects (228±20 min; p=0.358 vs health). However, static sequences covered more recording time (38±3 % vs 20±2 %; p<0.001) and were longer (195±24 vs 113±7 sec; p=0.001) throughout the pre and postprandial period (Figures 3 and 4). One third of turbid sequences were static (36±5 % vs 17±3 % in healthy subjects; p=0.004) and half of tunnel sequences (50±4 % vs 28±5 % in healthy subjects; p=0.003) were static.
Luminal closure sequences covered a smaller proportion of both the pre- and postprandial period compared to healthy subjects (41±2 % vs 61±2 %; p<0.001) and meal ingestion failed to induce a contractile response without an increase in luminal closure sequences (Figures 3 and 4). In contrast to healthy subjects, alternating contractile-static sequences were more frequent in the postprandial period, particularly in the first third (16±3 % vs 6±2 % in healthy subjects; p=0.002).

The amount of images with turbid content was not different as in healthy subjects, but content appeared static in a larger proportion of the images, particularly in the second and last thirds of the recording time (Figure 4). The number and length of tunnel sequences was also greater in hypodynamic cases compared to healthy subjects (15±2 % vs 7±1 % in healthy subjects; p<0.001). This difference was mainly observed in the second and third periods of the postprandial period (Figure 4).

**Hyperdynamic cases**

As compared to healthy subjects, hyperdynamic cases had significantly shorter transit times (137±27 min; p=0.015). They exhibited less static sequences than healthy subjects (20±2 sequences per video vs 40±3; p=0.029) and this difference was even more pronounced when compared to patients with hypodynamic behavior (Figures 3 and 4). By contrast, high motion sequences were present in 3±1 % of the recording time, significantly more than in healthy subjects (0.5±0.1 %; p<0.001) and hypodynamic cases (0.9±0.2 %; p<0.001). The proportion of luminal closure sequences in the pre-prandial period was similar to healthy subjects and a pronounced increase after meal ingestion was
observed (Figures 3 and 4). These contractile sequences were much longer (7±1 min; p=0.012 vs health) with higher contraction frequency (10.1±0.5 vs 8.8±0.3 closures per sequence; p=0.033) and covered almost the whole postprandial period, (p<0.05 vs health in the first, second and third parts of the postprandial period; Figure 4).

Hyperdynamic cases also had a reduced proportion of sequences with intestinal content throughout the small bowel (5 ± 2%; p = 0.001 vs health) and content was virtually always in motion without static turbid sequences) (Figure 4).

Correlation of clinical and physiological criteria

When comparing cases detected with abnormal motility versus those with normal motility no differences were detected in none of the following parameters: gender, age, Rome III diagnosis, symptom scores, presence of diarrhea/constipation/pain or duration of symptoms (Table 1). The proportion of patients on drugs that could affect motility (prokinetics, spasmylytics, antidepressants and opiates) was the same between all groups (p = 0.3051).

Specifically, three patients (1.5% of the whole population) were on opiates (discontinued by protocol 48h before the study) and two of them exhibited normal motility and one hypodynamic behavior.

DISCUSSION

Applying an original methodology we have developed a novel classification of functional gut disorders based on objective, physiological...
criteria of their small bowel function. Two distinctive subgroups of patients characterized by hypodynamic and hyperdynamic behavior were identified.

Over the past 25 years, patients with unexplained digestive manifestations have been pooled together under the umbrella of functional gut disorders, and then sub-classified based on symptom criteria. This exercise has advanced the field by bringing into the light and developing a common terminology for a large group of disorders that previously had not been well characterized. However, clinical diagnostic criteria appear to have limited value in determining the underlying mechanism of the symptoms and, conversely, current technologies, often fail to detect physiological gut abnormalities in these patients. For instance, no consistent abnormalities have been found by small bowel manometry, the present gold standard, in patients with functional intestinal symptoms, except for some rare cases of enteric neuropathy or myopathy, that are now considered a separate (“organic” type) entity.(15) For the majority of patients, manometry does not identify distinctive features that could be used as physiological diagnostic criteria.

To overcome the limitations of small bowel manometry and to obtain a more comprehensive evaluation of small bowel motility, we adopted an entirely different approach. Taking advantage of the endoscopic capsule device, we analyzed endoluminal images looking for indices of mechanical function of the small bowel, including contractile patterns (occlusive and non-occlusive lumen closures, radial wrinkles), non-contractile patterns (tunnel and wall) and presence of endoluminal content. The presence and motion of intestinal content is an important measure of mechanical function also quantified by the system. In the present study we introduced into our method the analysis of sequences of
events. This represents a major conceptual advance because it goes beyond recording isolated events, e.g. single contractions, and provides an integrated measure of intestinal mechanical function.

Comparisons of elements defined by massive volumes of data requires reliable computational treatment and were performed by machine learning techniques, that provided with training sets learn to classify new cases in a test set.(24) In the present study, owing to the large sample size, the population was split in two subgroups, one was used to develop the algorithm (training set) while the other was used to test it. The fact that the test set was completely naïve to the algorithm makes results robust and potentially adaptable to other populations of patients with functional bowel disorders.

Present data show that about one fourth of patients who meet Rome III criteria for a functional bowel disorder have abnormal small bowel mechanical function that cluster into two distinct subgroups, either with hypodynamic or hyperdynamic behavior. The hypodynamic behavior, which is the more frequently encountered, resembles that observed in patients with proven enteric neuropathy or myopathy (diminished contractility, frequent static and tunnel sequences), albeit to a milder degree and without obvious pooling of secretions. Also, patients with hypodynamic behavior displayed short alternating static and luminal occlusion sequences in the first third of the postprandial period, which we speculate may correspond to the “minute rhythm pattern” described in intestinal manometric studies.(4, 8) By contrast, patients with hyperdynamic behavior displayed frequent, almost continuous, trains of contractions.

For this study we did not correlate our findings with other methods evaluating a single parameter such as transit of chyme. The higher sensitivity of
our method might be precisely related to the fact that it takes into consideration a combination of parameters reflecting wall dynamics and movement of content to classify abnormalities. External imaging of the abdomen by magnetic resonance has been recently applied for the evaluation of intestinal mechanical function, and also shows promising results in the identification of indices of abnormal small bowel function in functional patients.\(^{(13, 14)}\)

The lack of correlation between symptom patterns and capsule findings may have several explanations. Functional bowel disorders classified by clinical criteria are heterogeneous, i.e. the same symptoms may be produced by different pathophysiological mechanisms. Discrepancy between motor behavior and symptoms has been previously shown in a study correlating manometric abnormalities and symptoms in patients with intestinal dysmotility, where hypomotility was associated to diarrhea.\(^{(5)}\) Another study showed that patients with diarrhea in acute salmonellosis exhibit prolonged silent periods in the distal half of the small bowel.\(^{(1)}\) The lack of correlation might also be related to potential limitations of our system. We acknowledge that only the small bowel motor function was evaluated and that in some patients symptoms may originate from other areas of the digestive tract, e.g. the colon, or are related to sensory dysfunction of the small bowel.

In the last instance, our observations push the field forwards beyond symptom analysis and towards an objective diagnosis of pathological gut activity. The effectiveness of therapy of functional bowel disorders directed by clinical criteria is limited. It could be speculated that patients with hypo or hyperdynamic behavior may respond to drugs with specific action on intestinal
motility, specifically prokinetics versus muscle relaxants, or antalgics in case of normal motility. (16)

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Disclosures

Figure legends

Figure 1. Examples of motility features by endoluminal imaging. Note contraction with luminal closure and radial wrinkles, non-contraction images of the intestinal wall (tunnel and wall pattern) and image of intestinal lumen occupied by turbid content.

Figure 2. Classification of functional bowel disorders by endoluminal image analysis. The majority of healthy subjects fall within the normal range (positive scores). Patients outside the normal range (negative scores) may exhibit hypo- or hyperdynamic behavior.

Figure 3. Examples of sequence analysis. Note in the healthy subject intestinal stimulation in response to meal and evident hypo- or hyperdynamic behavior in the two patients outside the normal range. For clarity, only luminal closure and static sequences are illustrated.

Figure 4. Mechanical function of the small bowel. Note in healthy subjects intestinal stimulation in response to meal that progressively declined; patients outside the normal range exhibited distinctively hypo- or hyperdynamic behavior.
Table 1. Clinical and demographic data of patients

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<td>&gt;12 mo</td>
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¹ by Rome criteria; ² main symptom score on a 0-3 scale; ³ patients divided based on classifier output: within the normal range, hypodynamic behavior and hyperdynamic behavior; ⁴ by chi-square; ⁵ by ANOVA
REFERENCES


Figure 1

- luminal closure
- tunnel pattern
- wall pattern
- turbid content
Figure 2

- **normal range**
- **classification score**

Healthy subjects: within normal range

Patients: hyperdynamic behaviour, hypodynamic behaviour
Figure 3

meal ingestion

healthy subject

patient 1: hyperdynamic

patient 2: hypodynamic

45 min

sequences: luminal closures static
Figure 4

* p<0.05 between groups by ANOVA
† % of recording time, occupied by sequences
‡ post-meal period divided in 3 equal intervals