

# Functional gut disorders or disordered gut function? Small bowel dysmotility evidenced by an original technique

C. MALAGELADA,<sup>\*,†</sup> F. DE LORIO,<sup>\*,†</sup> S. SEGUÍ,<sup>‡</sup> S. MENDEZ,<sup>\*,†</sup> M. DROZDZAL,<sup>‡</sup> J. VITRIA,<sup>‡</sup> P. RADEVA,<sup>‡</sup> J. SANTOS,<sup>\*,†</sup> A. ACCARINO,<sup>\*,†</sup> J. R. MALAGELADA<sup>\*,†</sup> & F. AZPIROZ<sup>\*,†</sup>

<sup>\*</sup>Digestive System Research Unit, University Hospital Vall d'Hebron; Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Barcelona, Spain

<sup>†</sup>Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>‡</sup>Computer Vision Center, Bellaterra, Spain

## Abstract

**Background** This study aimed to determine the proportion of cases with abnormal intestinal motility among patients with functional bowel disorders. To this end, we applied an original method, previously developed in our laboratory, for analysis of endoluminal images obtained by capsule endoscopy. This novel technology is based on computer vision and machine learning techniques. **Methods** The endoscopic capsule (Pillcam SB1; Given Imaging, Yokneam, Israel) was administered to 80 patients with functional bowel disorders and 70 healthy subjects. Endoluminal image analysis was performed with a computer vision program developed for the evaluation of contractile events (luminal occlusions and radial wrinkles), non-contractile patterns (open tunnel and smooth wall patterns), type of content (secretions, chyme) and motion of wall and contents. Normality range and discrimination of abnormal cases were established by a machine learning technique. Specifically, an iterative classifier (one-class support vector machine) was applied in a random population of 50 healthy subjects as a training set and the remaining subjects (20 healthy subjects and 80 patients) as a test set. **Key Results** The classifier identified as abnormal 29% of patients with functional diseases of the bowel (23 of 80), and as normal 97% of healthy subjects (68 of 70) ( $P < 0.05$  by chi-squared test). Patients identified as abnormal clustered in two groups, which exhibited either a

hyper- or a hypodynamic motility pattern. The motor behavior was unrelated to clinical features. **Conclusions & Inferences** With appropriate methodology, abnormal intestinal motility can be demonstrated in a significant proportion of patients with functional bowel disorders, implying a pathologic disturbance of gut physiology.

**Keywords** capsule endoscopy, computer vision analysis, machine learning technique, small bowel motility.

## INTRODUCTION

It has been proposed that symptoms in patients with functional bowel disorders are produced by mixed sensory reflex dysfunctions of the gut, regardless of the underlying cause and individual predisposing/triggering factors. Intestinal manometry has proved to detect consistent dysmotility patterns in patients with intestinal neuropathies or myopathies. However, intestinal dysmotility, long assumed to be the hallmark of such functional disorders, has rarely been demonstrated by manometric methods. The paucity of objective evidence may have generated the prevailing skepticism regarding its pathogenic role.

We recently launched a new method for the evaluation of small bowel motor activity based on capsule endoscopy.<sup>1</sup> Endoluminal images are processed by computer vision techniques to quantify different features reflecting contractile and non-contractile patterns, amount of secretions and chyme, degree of wall motion and dynamics of luminal contents. Using automatic machine learning techniques,<sup>2</sup> we developed an algorithm to identify patients with severe motor abnormalities. The system proved similar specificity but higher sensitivity than intestinal manometry. Our hypothesis

## Address for Correspondence

Fernando Azpiroz, Digestive System Research Unit, Hospital General Vall d'Hebron, 08035-Barcelona, Spain.

Tel: +34 93 274 62 59; fax: +34 93 489 44 56;

e-mail: azpiroz.fernando@gmail.com

Received: 21 July 2011

Accepted for publication: 1 November 2011

was that this sensitive method is able to detect motor abnormalities in patients with functional gut disorders. Hence, our present aim was to identify among this heterogeneous group of patients the subgroup with objective intestinal motor dysfunction.

## METHODS

### Participants

Eighty patients with functional bowel disorders (25 men, 55 women; age range: 20–69 years) fulfilling Rome III criteria of irritable bowel syndrome ( $n = 42$ ), functional diarrhea ( $n = 10$ ), functional constipation ( $n = 7$ ), functional bloating ( $n = 7$ ) or functional pain ( $n = 14$ ), and 70 healthy subjects (31 men, 39 women; age range: 18–66 years) without gastrointestinal symptoms were prospectively included in the study. Patients were recruited from the gastroenterological outpatient clinic, and healthy subjects by public advertisement.

Prior to study entry, mucosal lesions were ruled out by visual inspection of capsule endoscopy images. Using a structured questionnaire subjective severity of bowel symptoms was scored in all participants as absent (0); mild (1) *i.e.*, well-tolerated; moderate (2) *i.e.*, interfering with daily activities; and severe (3) *i.e.*, incapacitating. Healthy subjects were required to have no symptoms. Patients were symptomatic at the time the study: diarrhea was reported by 60% of patients ( $1.8 \pm 0.1$  mean score), constipation by 29% of patients ( $1.5 \pm 0.1$  mean score), abdominal discomfort/pain by 75% patients ( $1.8 \pm 0.1$  mean score) and bloating by 77% of patients ( $1.6 \pm 0.1$  mean score). Symptom duration was over 6 months in all patients and over 1 year in 76% of them. Medical history of psychological/psychiatric disorders was present in 26% of patients. The study protocol was approved by the Ethics Committee of the University Hospital Vall d'Hebron, and all participants gave their written informed consent.

### Test procedure

Endoluminal images were obtained with the Pillcam capsule (Pillcam SB1 video capsule; Given Imaging). 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 h with the subjects lying comfortably on a hospital bed and the trunk raised 30° above horizontal.

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

### Computer vision analysis

Small bowel images were selected by visual detection of gastric exit and arrival into the cecum of the capsule. Endoluminal images of the small bowel were automatically analyzed by a computer vision program specifically developed for the evaluation of intestinal motility. The following patterns were measured.

**Turbid content** Intestinal content is usually clear, and allows viewing intestinal walls and lumen, but in some instances the lumen contains turbid secretions (Fig. 1). Images with turbid

content were identified by color analysis.<sup>3</sup> Each frame was represented by a 256 color histogram developed on the basis of 80 capsule endoscopy videos. Based on a series of examples of turbid and non-turbid (clear) frames, an automatic classifier was trained to detect the turbid frames in each video.

**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,<sup>4</sup> 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. Static sequences (very low dissimilarity in consecutive frames for at least 30 s) were defined using a pre-established threshold.<sup>1,5</sup> This method measured wall motion in clear frames as well as the dynamics of content in turbid frames.

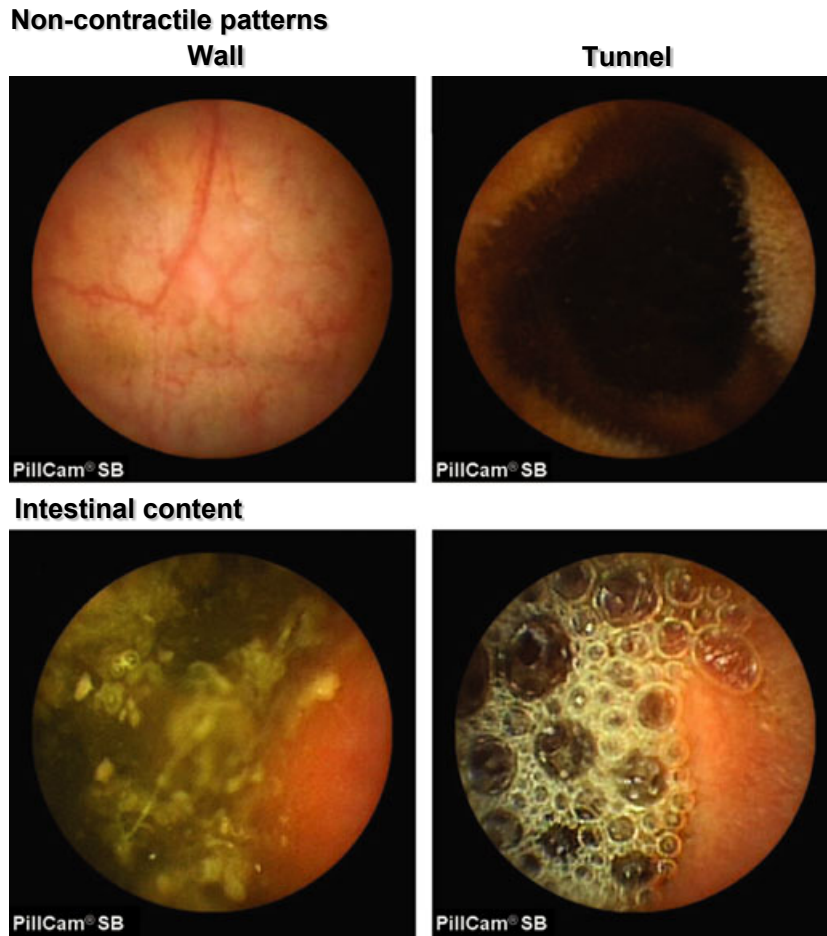
**Non-contractile patterns: tunnel and wall** In the absence of contractions, the endoluminal images may show a flat intestinal wall (reflecting a transverse endoluminal view) or a tunnel (open lumen view), depending on the position of the capsule within the lumen (Fig. 1). In each image, the intensity 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 close to the light of the capsule and the dark lumen.<sup>6</sup> A tunnel pattern was characterized by a peripheral band of bright wall and a large, dark central lumen. Conversely, a wall pattern was characterized by an image directly focusing on a smooth bright wall without a view of the lumen.

**Contractile patterns Phasic luminal closure.** Phasic intestinal contractions are visualized by capsule endoscopy as reversible changes in lumen size (closure/opening) within a nine-frame sequence (Fig. 2).<sup>1</sup> These events were detected using a cascade of sequential steps. First turbid and static sequences were filtered out. Second, each image was analyzed using the Laplacian analysis described above, and each nine-frame sequence was evaluated as a whole to determine whether it corresponded to a contractile event or not, using an automatic classifier (support vector machine)<sup>7</sup> 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.<sup>8</sup> Discrimination between occlusive and non-occlusive contractions (complete vs partial luminal closure) was performed by a second classifier based also on a training set of both types of contractions.

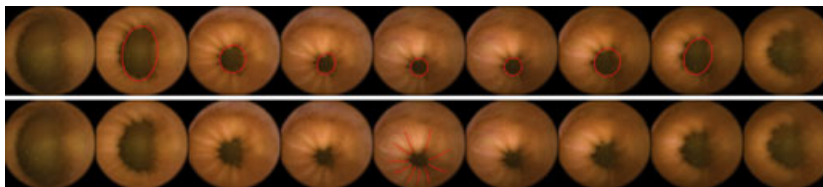
**Radial wrinkles.** Contraction of the circular intestinal muscle produces wrinkles in the intestinal wall radial to the shrinking intestinal lumen (Fig. 2). In each image, the amount of intestinal wrinkles was measured by structural tensor analysis, as follows. The image was treated as a topographic map in which the crests and valleys were identified and their direction towards the central lumen (point of highest entropy) was measured. The degree of wrinkles was measured from 0 to 1 using a radial Gaussian basis function kernel, and a threshold of 0.7 was applied.<sup>9,10</sup>

### Statistical analysis

Statistical analysis was performed using the SPSS 12.0 (SPSS Inc., Chicago, IL, USA) for Windows statistical package. Sample size estimation was based on the number of parameters used to define each subject in the classification algorithm.<sup>11</sup> Mean values ( $\pm$ SE) of the parameters measured were calculated in each group of



**Figure 1** Non-contrastile patterns and intestinal content. In the absence of contractions, the capsule can reflect a wall pattern, i.e., transverse endoluminal view, or a tunnel pattern, i.e., open lumen view. Intestinal content can be visualized as turbid secretions or as small bubbles.



**Figure 2** Contractile patterns. Luminal occlusions are visualized as reversible changes in lumen size (closure/opening) within a nine-frame sequence. Intestinal contractions produce radial wrinkles in the wall.

subjects. Analysis of variance was performed by ANOVA. *Post-hoc* comparisons were made by the Tukey's test. Potential effects of gender and age were evaluated by comparing the parameters measured in men vs women and in the older vs the younger half of healthy subjects by the unpaired Student's *t*-test. Distribution of abnormalities between groups was evaluated by the chi-squared test. Differences were considered significant at a  $P < 0.05$ .

**Algorithm for identification of abnormal intestinal motility**

Each subject was defined by 19 parameters (dimensions) derived from the patterns described above, as previously reported.<sup>1</sup>

Healthy subjects were randomized into a training set ( $n = 50$ ) and a test set ( $n = 20$ ). Based on the data of the training set, a program (one-class support vector machine combined with principal component analysis) calculated the function that best defined normal range.<sup>12,13</sup> Using this algorithm, the remaining 20 healthy subjects and the set of 80 patients were then tested to identify those outside normal range. To strengthen the stability of the classifier, the procedure was repeated 500 times using a repetitive classification method: 500 classifiers were trained with random subsets of 50 healthy subjects (ensemble classifier);<sup>14</sup> patients were tested with all classifiers and healthy subjects were tested in a mean of 143 classifiers (only when they entered the test set). A case was then defined as abnormal if it fell outside normal range in >50% of runs (majority vote).

Patients identified as abnormal were then analyzed by the K-means clustering technique (Lloyd's algorithm) to determine the existence of subgroups.<sup>15</sup> This algorithm uses an iterative refinement technique: starting from randomly selected subgroups, each case is assigned to the subgroup with the nearest mean (centroid of the cluster), and the new mean is calculated; the procedure is repeated until convergence is reached.

## RESULTS

The capsule reached the colon and, hence, visualized the whole small bowel in the majority of subjects, healthy subjects and patients alike (Table 1). No adverse events were observed either in patients or in healthy subjects. Using the majority vote (outside normal range in  $\geq 50\%$  of runs) the classifier identified as abnormal 29% of patients with functional bowel

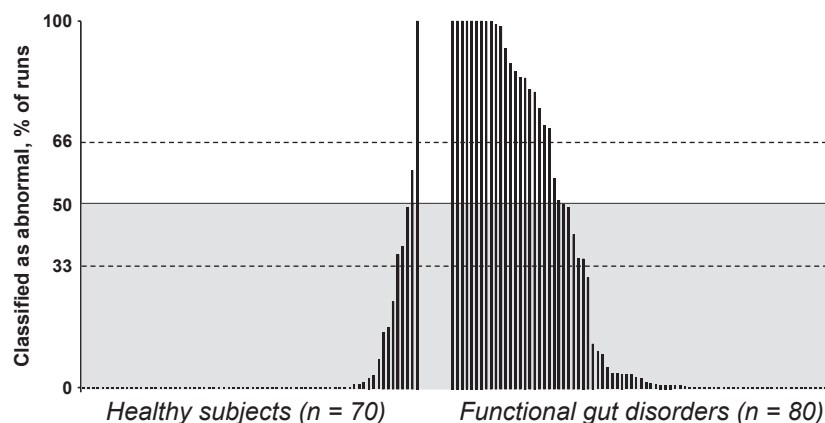
disorders (23 of 80), and as normal 97% of healthy subjects (68 of 70) ( $P = 0.000$  by chi-squared test).

Moreover, using different thresholds, the ensemble classifier provides a measure of certainty (Fig. 3): 26% of patients and 1% of healthy subjects were in the abnormal zone (above the 66% cut-off), 65% patients and 93% healthy subjects were very likely normal (below the 33% cut-off), while a relatively low proportion (9% of patients and 6% of healthy subjects) remained in the gray zone (between 66% and 33% cut-offs). The amount of cases within these three regions of equal probability (one-third each) indicates that, in contrast to healthy subjects (65 normal, 4 uncertain, 1 abnormal), patients had a bimodal distribution (52 normal, 7 uncertain, 21 abnormal).

**Table 1** Motility evaluation by endoluminal vision analysis in healthy subjects and patient subgroups

	Healthy subjects	Patients						
		Normal	<i>P</i> vs health	Hyperdynamic	<i>P</i> vs health	Hypodynamic	<i>P</i> vs health	<i>P</i> hyper vs hypo
Subjects, <i>n</i>	70	57		13		10		
Capsule reaching colon, %	74	84		92		90		
Gastric exit time, min	41 ± 5	46 ± 5	0.911	37 ± 10	0.992	77 ± 22	0.053	0.109
Transit time, min*	218 ± 12	206 ± 15	0.917	136 ± 19	<b>0.032</b>	185 ± 29	0.754	0.628
Luminal closures min <sup>-1</sup>	4.2 ± 0.1	4.3 ± 0.2	0.952	6.7 ± 0.6	<b>0.000</b>	2.6 ± 0.3	<b>0.001</b>	<b>0.000</b>
Frames with wrinkles, %	6.8 ± 0.4	7.9 ± 0.5	0.245	11.1 ± 1.3	<b>0.000</b>	6.8 ± 1.7	1.000	<b>0.021</b>
Turbid, images %	14 ± 1	10 ± 1	0.211	10 ± 3	0.637	14 ± 4	0.993	0.710
Turbid images, degree of motion	2.2 ± 0.1	2.1 ± 0.1	0.725	2.8 ± 0.3	<b>0.018</b>	1.8 ± 0.2	0.357	<b>0.004</b>
Turbid images, % static	19 ± 2	21 ± 2	0.816	10 ± 2	0.246	38 ± 6	<b>0.001</b>	<b>0.000</b>
Clear images, degree of motion	1.7 ± 0.0	1.6 ± 0.0	0.216	2.0 ± 0.1	<b>0.001</b>	1.1 ± 0.1	<b>0.000</b>	<b>0.000</b>
Clear images, % static	27 ± 1	32 ± 2	0.118	20 ± 3	0.351	55 ± 3	<b>0.000</b>	<b>0.000</b>
Duration of static sequences, s	44 ± 2	47 ± 3	0.919	34 ± 5	0.445	92 ± 14	<b>0.000</b>	<b>0.000</b>

Mean ± SE of relevant parameters are shown; \*time between gastric exit and cecal entry when the capsule reached the colon. Note: Significant *P* values in bold.



**Figure 3** Intestinal dysmotility identified by the ensemble classifier. Five hundred classifiers were trained with random subsets of 50 healthy subjects. Each bar represents the percentage of times a given subject was classified as abnormal (vs 3% healthy subjects,  $P = 0.000$ ) were detected outside the normal range in  $>50\%$  of runs. Dotted lines represent the 66% and 33% cut-offs.

## Healthy subjects

The majority of images ( $86 \pm 1\%$ ) provided a clear view of the intestinal wall and lumen, and only a relatively small proportion of images showed turbid content. A mean of  $860 \pm 44$  phasic luminal occlusions per study was detected. Images with marked radial wall wrinkles were observed in one-third of luminal occlusions. Approximately one-fourth of the images were static, i.e., corresponded to static sequences (Table 1). No significant differences in any of the parameters measured (Table 1) in men ( $n = 31$ ) vs women ( $n = 39$ ) nor in the older vs the younger half of healthy subjects were detected. Similar findings were observed in the subjects in which the capsule reached the colon and in those who did not.

## Patients with functional bowel disorders

Patients classified as normal exhibited similar features to healthy subjects. Those identified as abnormal were then further analyzed. These patients clustered into two subgroups with distinctive features when compared to healthy subjects and between themselves (Fig. 4).

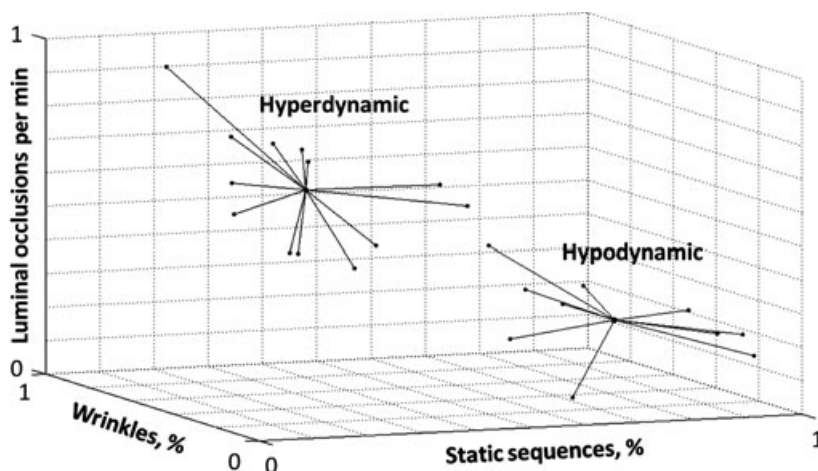
Thirteen patients exhibited hyperdynamic behavior, with a significantly shorter transit time than healthy subjects ( $136 \pm 19$  min vs  $218 \pm 12$  min, respectively;  $P = 0.032$ ). As compared with healthy subjects, patients with a hyperdynamic behavior exhibited more luminal closures ( $6.7 \pm 0.6$  vs  $4.2 \pm 0.1$  closures  $\text{min}^{-1}$  in health;  $P = 0.000$ ), more images with radial wall wrinkles ( $11 \pm 1\%$  vs  $7 \pm 0.1\%$  of images with wrinkles in health;  $P = 0.000$ ) and higher degree of

motion of both clear ( $2.0 \pm 0.1$  vs  $1.7 \pm 0.0$  EMD value in health;  $P = 0.001$ ) and turbid frames ( $2.8 \pm 0.3$  vs  $2.2 \pm 0.1$  EMD in health;  $P = 0.018$ ) (Table 1).

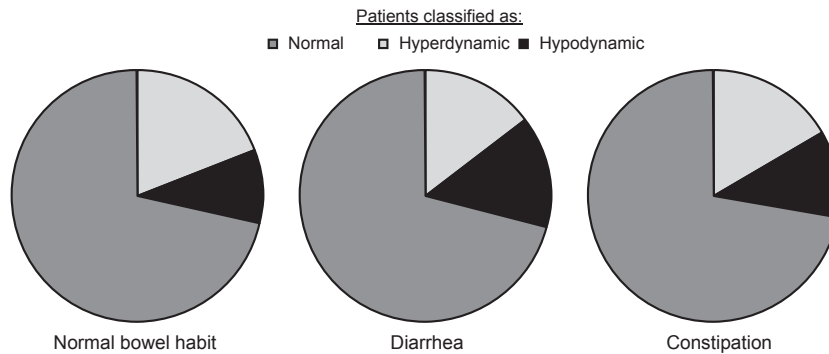
Ten patients showed a hypodynamic behavior, characterized by less luminal closures ( $2.6 \pm 0.3$  closures  $\text{min}^{-1}$ ;  $P = 0.001$  vs health) more static images, both clear ( $55 \pm 3\%$  vs  $27 \pm 1\%$  in health;  $P = 0.000$ ) and turbid ( $38 \pm 6\%$  vs  $19 \pm 2\%$  in health;  $P = 0.001$ ) and longer static sequences ( $92 \pm 14$  s vs  $44 \pm 2$  s in health;  $P = 0.000$ ). However, total transit time (in those cases in which the capsule arrived to the cecum) was similar to healthy subjects ( $185 \pm 29$  min and vs  $218 \pm 12$  min, respectively;  $P = 0.754$ ). Gastric exit time tended to be longer in the hypodynamic group, but the difference was not statistically significant (Table 1). The percentage of cases in which the capsule reached the colon was not significantly different among subgroups ( $P = 0.264$  by Pearson chi-square), and conversely similar findings were detected independently of colonic arrival.

## Clinical-physiologic correlations

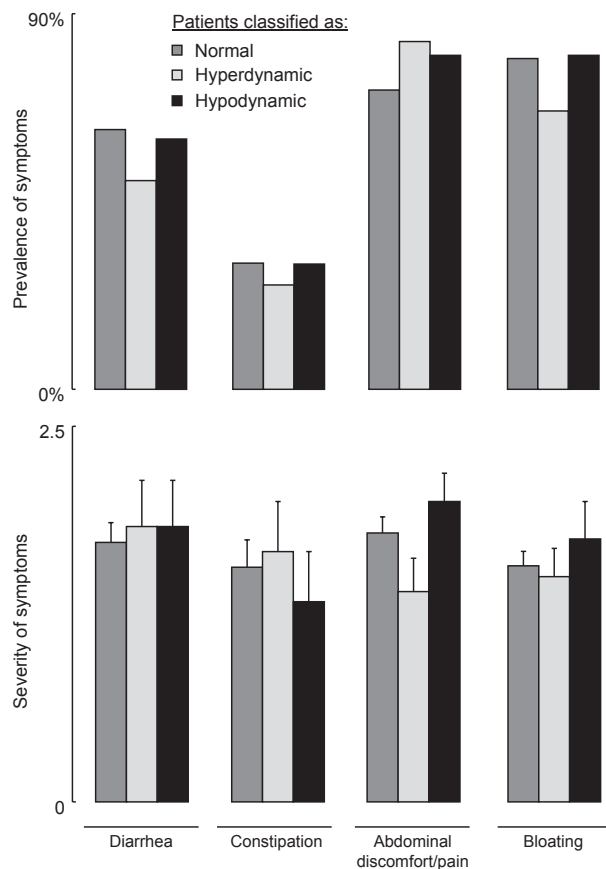
The distribution of patients classified as having normal, hyper- or hypodynamic behavior was similar among the clinical subgroups (Fig. 5). Conversely, the prevalence and severity of constipation, diarrhea, abdominal pain/discomfort and bloating was similar among patients with normal, hyper- and hypodynamic behavior (Fig. 6); likewise, illness duration was similar in the three groups (over 1 year in 72%, 80% and 92%, respectively). No difference in psychological/psychiatric co-morbidity was found among groups.



**Figure 4** Clusters of patients with abnormal motility identified by endoluminal motility analysis. Each case is represented by three parameters (normalized from 0 to 1) in a three-dimensional space. The cases grouped into two distinct clusters, one which showed a hyperdynamic behavior (more occlusions and wrinkles and less static), and the other a hypodynamic behavior (less occlusions and wrinkles and more static).



**Figure 5** Dysmotility in relation to bowel habit. Similar motor findings were detected in patients with diarrhea, constipation and normal bowel habit.



**Figure 6** Clinical patterns in patients with normal, hypodynamic and hyperdynamic behavior. The prevalence (%) and severity (scored from 0 to 3) of diarrhea, constipation, abdominal discomfort/pain and bloating was similar within the three physiological subgroups.

## DISCUSSION

Our data indicate that a subgroup of patients with functional gut disorders exhibit small bowel motor abnormalities. Furthermore, these patients can be

segregated into distinctive clusters based on objective motor parameters.

Despite the relatively small body of experimental evidence, previous studies from different laboratories provide evidence of small bowel motor dysfunction in functional bowel disorders. Kellow *et al.* were among the first to show abnormal motility patterns in IBS patients using ileal manometry, a laborious and technically challenging method, which probably explains why it has not been assiduously employed.<sup>16,17</sup> Later, other groups provided spotty, albeit largely consistent, evidence of small bowel dysmotility in IBS.<sup>18–23</sup>

In our laboratory, we previously applied a non-manometric technique, the gas challenge test, to study small bowel motility in functional disorders. This method, which uses a continuous infusion of gas into the jejunum, showed that healthy subjects are basically able to propel and clear as much gas as is infused from the gut without discomfort. The gas challenge test proved to be very sensitive, and also showed highly reproducible variations in gas transit induced by physiologic stimuli. Different studies using these tests have consistently shown that a proportion of patients with irritable bowel syndrome and functional bloating develop gas retention and symptoms in response to intestinal gas loads that are well-tolerated by healthy subjects;<sup>24–26</sup> these data suggest that these patients have abnormal intestinal function. Interestingly, when patients with manometrically proven intestinal dysmotility and severe clinical symptoms underwent the same test, they exhibited a similar, though more severe dysfunction. Subsequent studies measuring the transit of radiolabeled gas with scintigraphy further showed that the motor abnormality in patients with functional bowel disorders predominantly affected the small bowel rather than the colon,<sup>27</sup> which coincides with the small bowel dysmotility now detected by endoluminal vision analysis.

It has become increasingly clear that patients with functional bowel disorders are pathophysiologically heterogeneous, and the current data show that the method of endoluminal image analysis identifies a subgroup with intestinal dysmotility. Furthermore, based on objective motility parameters, these patients with dysmotility clustered into two distinctive subgroups showing hyper- or hypodynamic behavior. The motor abnormalities in the subgroup of patients with hypodynamic behavior present some similarities to those in patients with manometrically proven dysmotility and severe clinical symptoms, such as intestinal pseudo-obstruction or reduced tolerance to feeding with inability to maintain normal body weight. Specifically, in a previous study dysmotility patients exhibited less luminal occlusions, less degree of motion of both turbid and clear images and longer static sequences.<sup>1</sup> Similar findings could be experimentally reproduced, at least in part, in healthy subjects by the administration of glucagon, a potent smooth muscle relaxant.<sup>5</sup> Conversely, accelerated transit time in patients with hyperdynamic behavior was associated with more contractions and endoluminal motion, implying a predominantly peristaltic activity.

In the present study no correlation between motor abnormalities detected by our endoluminal technique and clinical features in patients with functional bowel disorders could be identified. A possible explanation could relate to the poor clinical expression of intestinal dysfunction. Indeed, different intestinal stimuli, such as distension, transmucosal electrical nerve stimulation and thermal stimuli, have been shown to elicit a reduced repertoire of sensations, which were indistinguishable in most cases, while the type of perception (or its interpretation) exhibited interindividual variations. Moreover, the symptoms in patients with abnormal intestinal manometry, i.e., the clinical expression of intestinal dysmotility, are heterogeneous, and the same manometric pattern may be associated with different symptoms: abdominal pain, diarrhea, constipation or even pseudo-obstruction.<sup>28–30</sup>

All healthy subjects, except two outliers, were consistently found to be within normal range. The outliers, and also borderline cases, could correspond to subclinical dysfunctions. The motor abnormalities detected in patients by endoluminal image analysis, and previously by the gas challenge test, may not produce relevant functional impairment with the normal chyme load in ordinary circumstances; however, these motor abnormalities, together with some degree of sensory dysfunction, may produce digestive symptoms. Conceivably, more motor abnormalities

could become patent under challenge conditions. As a matter of fact, the capsule itself could be acting as a provocative stimulus. The technique of endoluminal vision by capsule endoscopy used in the present study presents obvious limitations in terms of single observation point, partial field of view, poor localization of the intestinal area under exposure and incomplete intestinal transit in studies not reaching the cecum, which may also reduce the sensitivity of the method and underestimate the incidence of motor dysfunction. This method provides a global overview of intestinal motor function by integrating information of the chain of mechanical actions and reactions taking place in the gut: muscular contraction, wall motion, content propulsion and transit of the capsule itself; the meaning and interpretation of this information is in a different dimension than that defined by conventional recording techniques, which makes comparisons hard to establish. Studies were conducted primarily in the fed state, with a similar fast to fed ratio (about 1 : 4) in healthy subjects and patients. Potential changes induced by the meal (fast vs fed pattern) were confounded by capsule progression and regional differences in the gut that could not be accounted for.

In previous clinical trials using symptom-based selection criteria, the benefit of potentially effective treatments for functional gut disorders was blurred possibly due to the pathophysiological heterogeneity of these conditions, which constituted a major drawback in the development of new treatments. The use of objective, physiological criteria may allow more precise and appropriate selection of patients in future clinical trials.

## ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported in part by Given Imaging, the Spanish Ministry of Education (Dirección General de Investigación, SAF 2009-07416), and Fundació La Marató TV3 (MARATV3\_072010). *Ciberehd is funded by the Instituto de Salud Carlos III.*

The authors thank Maria Maluenda for performing capsule studies; Panagiota Spyridonos and Fernando Vilariño for their contribution to the computer vision analysis program; Maite Casaus and Anna Aparici for technical support; Christine O'Hara for English editing of the manuscript and Gloria Santalieu for secretarial assistance. *Writing assistance:* English editing of the manuscript supported by SAF 2009-07416.

## AUTHORS' CONTRIBUTIONS

CM study concept and design; study management, analysis and interpretation of data; manuscript revision; FDI acquisition and analysis of data; SS computer vision analysis; SM acquisition and analysis of data; PR computer vision analysis; JS recruitment and evaluation of patients; AA recruitment and evaluation of patients;

JRM study concept and design, manuscript revision; FA study concept and design, drafting of the manuscript, study supervision, analysis and interpretation of data.

## COMPETING INTERESTS

The authors have no competing interests.

## FINANCIAL DISCLOSURE

Supported in part by Given Imaging.

## REFERENCES

- Malagelada C, De Iorio F, Azpiroz F *et al.* New insight into intestinal motor function via noninvasive endoluminal image analysis. *Gastroenterology* 2008; **135**: 1155–62.
- Waljee AK, Higgins PD. Machine learning in medicine: a primer for physicians. *Am J Gastroenterol* 2010; **105**: 1224–6.
- Swain MJ, Ballard DH. Color indexing. *Int J Comput Vis* 1991; **7**: 11–32.
- Rubner Y, Tomasi C, Guibas LJ. The earth mover's distance as a metric for image retrieval. *Int J Comp Vis* 2000; **40**: 99–121.
- De Iorio F, Malagelada C, Azpiroz F *et al.* Intestinal motor activity, endoluminal motion and transit. *Neurogastroenterol Motil* 2009; **21**: 1264–8.
- Russ J. *The Image Processing Handbook*, 5th edn. Boca Raton, FL: CRC Press, 2007.
- Noble WS. What is a support vector machine? *Nat Biotechnol* 2006; **24**: 1565–7.
- Vilarino F, Spyridonos P, Deiorio F, Vitria J, Azpiroz F, Radeva P. Intestinal motility assessment with video capsule endoscopy: automatic annotation of phasic intestinal contractions. *IEEE Trans Med Imaging* 2010; **29**: 246–59.
- Spyridonos P, Vilarino F, Vitria J, Azpiroz F, Radeva P. Anisotropic feature extraction from endoluminal images for detection of intestinal contractions. *Med Image Comput Assist Interv* 2006; **2**: 161–8.
- Vilarino F, Spyridonos P, Vitria J, Malagelada C, Radeva P. Linear radial patterns characterization for automatic detection of tonic intestinal contractions. *Lect Notes Comput Sci* 2006; **4225**: 178–87.
- Vapnik V. *The Nature of Statistical Learning Theory*. New York: Springer Verlag, 1995.
- Camci F, Chinnam RB. General support vector representation machine for one-class classification of non-stationary classes. *Pattern Recogn* 2008; **41**: 3021–34.
- Ringner M. What is principal component analysis? *Nat Biotechnol* 2008; **26**: 303–4.
- Rokach L. Ensemble-based classifiers. *Artif Intell Rev* 2010; **2**: 1–39.
- Lloyd SP. Least-squares quantization in PCM. *IEEE Trans Inf Theory* 1982; **28**: 129–37.
- Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. *Gastroenterology* 1987; **92**: 1885–93.
- Kellow JE, Phillips SF, Miller LJ, Zinsmeister AR. Dysmotility of the small intestine in irritable bowel syndrome. *Gut* 1988; **29**: 1236–43.
- Clemens CH, Samsom M, Roelofs JM, Berge Henegouwen GP, Smout AJ. Association between pain episodes and high amplitude propagated pressure waves in patients with irritable bowel syndrome. *Am J Gastroenterol* 2003; **98**: 1838–43.
- Kumar D, Wingate DL. The irritable bowel syndrome: a paroxysmal motor disorder. *Lancet* 1985; **8462**: 973–7.
- Schmidt T, Hackelsberger N, Widmer R, Meisel C, Pfeiffer A, Kaess H. Ambulatory 24-hour jejunal motility in diarrhea-predominant irritable bowel syndrome. *Scand J Gastroenterol* 1996; **31**: 581–9.
- Simren M, Castedal M, Svedlund J, Abrahamsson H, Bjornsson E. Abnormal propagation pattern of duodenal pressure waves in the irritable bowel syndrome (IBS) [correction of (IBD)]. *Dig Dis Sci* 2000; **45**: 2151–61.
- Small PK, Loudon MA, Hau CM, Noor N, Campbell FC. Large-scale ambulatory study of postprandial jejunal motility in irritable bowel syndrome. *Scand J Gastroenterol* 1997; **32**: 39–47.
- Wackerbauer R, Schmidt T, Widmer R, Pfeiffer A, Morfill G, Kaess H. Discrimination of irritable bowel syndrome by non-linear analysis of 24-h jejunal motility. *Neurogastroenterol Motil* 1998; **10**: 331–7.
- Caldarella MP, Serra J, Azpiroz F, Malagelada JR. Prokinetic effects in patients with intestinal gas retention. *Gastroenterology* 2002; **122**: 1748–55.
- Serra J, Salvioli B, Azpiroz F, Malagelada JR. Lipid-induced intestinal gas retention in irritable bowel syndrome. *Gastroenterology* 2002; **123**: 700–6.
- Serra J, Villoria A, Azpiroz F *et al.* Impaired intestinal gas propulsion in manometrically proven dysmotility and in irritable bowel syndrome. *Neurogastroenterol Motil* 2010; **22**: 401–2.
- Salvioli B, Serra J, Azpiroz F *et al.* Origin of gas retention and symptoms in patients with bloating. *Gastroenterology* 2005; **128**: 574–9.
- Accarino A, Azpiroz F, Malagelada JR. Distinctive motor responses to human acute salmonellosis in the jejunum and the ileum. *J Gastrointest Mot* 1993; **3**: 5.
- Quigley EM. Enteric dysmotility: validating the Wingate/Bangkok classification. *Gastroenterology* 2010; **139**: 346–8.
- Stanghellini V, Cogliandro RF, De Giorgio R *et al.* Natural history of chronic idiopathic intestinal pseudo-obstruction in adults: a single center study. *Clin Gastroenterol Hepatol* 2005; **3**: 449–58.