

Autonomic dysfunction in gastrointestinal motility disorders

A E Bharucha, M Camilleri, P A Low, A R Zinsmeister

Abstract

The records of 113 consecutive patients with a suspected gastrointestinal motility disorder referred between January 1988 and July 1991 were retrospectively reviewed. The aims were to identify the prevalence of autonomic dysfunction in those with or without associated neurological disease and to determine the diagnostic value of testing for autonomic dysfunction. All patients had gastrointestinal manometry (3 hours fasting, 2 hours fed), 94 of 113 underwent testing of sympathetic adrenergic and cholinergic function and cardiovagal cholinergic function. All tests were scored in a standard manner. There was a significant ($p < 0.05$) but modest ($r = 0.28$) rank correlation between autonomic and motility scores. This correlation was stronger ($r = 0.67$, $p = 0.01$) in diabetic patients. The number of patients in each group with autonomic dysfunction was as follows: irritable bowel syndrome nine of 33, idiopathic upper gastrointestinal dysmotility six of 21, diabetes mellitus nine of 13, identified non-diabetic neurological syndromes six of nine, postvagotomy or abdominal surgery three of 11, and myopathic pseudo-obstruction two of seven. Autonomic testing is useful in the assessment of autonomic involvement outside the gastrointestinal tract. Logistic discriminant analysis showed that autonomic function testing did not add to the diagnostic value of motility tests in distinguishing between patients with and without irritable bowel syndrome, although a slight improvement was indicated for identifying neuropathic dysmotilities. Thus, the aetiological role of general autonomic dysfunction in irritable bowel syndrome and idiopathic and postvagotomy dysmotilities deserves further study. The addition of autonomic function tests does not add substantially to the diagnostic accuracy of clinical, radiological, endoscopic, and manometric techniques in most patients referred for evaluation of a suspected motility disorder.

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Disorders of the extrinsic nerve supply to the gut are known to be associated with clinical manifestations suggestive of gastrointestinal dysmotility.^{1,2} These disturbances may affect all levels of the pathways (sympathetic and parasympathetic) supplying the digestive tract, from the brain to the postganglionic fibre. Autonomic function abnormalities have also been documented in patients with functional gastrointestinal disorders.³⁻⁵ Experimental models of gut motor function suggest a predominant modulatory role for the extrinsic nervous system,

with primary control being exerted by the enteric nervous system.⁶ Thus, it is not clear how significantly the autonomic dysfunction impacts on gastrointestinal dysmotility and the development of functional gut disorders.

In addition, the prevalence of autonomic dysfunction among patients with gastrointestinal dysmotility remains unknown. A high prevalence of autonomic dysfunction among patients with or without known neurological disease would suggest that testing of autonomic function may be a useful alternative to the current invasive tests in the assessment of motility disturbances of the digestive tract.

Our aims were twofold: firstly to determine the prevalence of autonomic dysfunction in patients with suspected gastrointestinal dysmotility, with or without associated neurological disorders; and secondly, to assess the diagnostic value of testing autonomic function in these patients.

PATIENTS

We retrospectively reviewed the records of 113 consecutive patients with suspected motility disorders of the digestive tract referred to a single gastroenterologist (MC) at a tertiary referral clinic between January 1988 and July 1991. In all patients a detailed medical history was taken and physical examination, exclusion of mechanical obstruction or mucosal disease by endoscopy or barium radiology, and blood and urine tests include haematology and chemistry panels, erythrocyte sedimentation rate, antinuclear antibody, a serological test for syphilis (rapid plasma reagin), serum vitamin B12 and folate, serum thyroxine, and urine analysis were undertaken. A chest x ray was also performed in all patients. Other investigations were done as deemed necessary on clinical grounds. A combination of clinical, radiological, endoscopic, and manometric criteria were used to group patients into diagnostic categories. Autonomic reflex and motility investigations (described below) were performed when the patients had been off all medications except insulin for at least 48 hours. All results were compared with data from healthy controls who had been studied in an identical manner in the respective laboratories at the Mayo Clinic during the previous 5 years.

GASTROINTESTINAL MANOMETRY

Gastric and small bowel pressure profiles were assessed by pneumohydraulic perfusion manometry.⁷ Motility was studied for 3 hours during fasting and 2 hours after ingestion of a solid-liquid 535 kcal meal. At the end of the study, oesophageal motility was evaluated using the

Gastroenterology
Research Unit,
Department of Neurology
and Section of
Biostatistics, Mayo Clinic
and Mayo Foundation,
Rochester, MN 55905,
USA

A E Bharucha
M Camilleri
P A Low
A R Zinsmeister

Correspondence to:
Dr M Camilleri,
Gastroenterology
Research Unit, Mayo Clinic,
Rochester, MN 55905, USA.

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station pull through method with wet (1 cc) water swallows.

One of us (MC) had prospectively assessed all the manometric recordings and compiled standardised reports on them. In this analysis, patterns of the gastric and small bowel pressure profiles are analysed, with particular attention to the abnormalities recorded in previous reports of gastrointestinal motility in health and disease from this and other laboratories.⁷ These patterns include the following:

(a) An abnormal configuration and propagation of phase III of the migrating motor complex (MMC)⁸ (the presence of ≥ 3 MMCs during the 3 hour fasting period in patients with previous vagotomy or partial gastrectomy was also considered abnormal).⁹

(b) The presence of fasting or postprandial bursts of high amplitude phasic activity associated with a tonic elevation of baseline pressure.^{7, 8}

(c) Patterns suggestive of mechanical obstruction, such as persistent postprandial minute clustered contractions¹⁰ or simultaneous prolonged contractions.¹¹

(d) Postprandial antral hypomotility⁷ and pylorospasm, or a pattern of prolonged tonic and phasic pressure activity of the pylorus, usually associated with antral hypomotility.¹²

(e) Failure of the small bowel pressure profile to change from a fasting to a fed pattern, and this included the recurrence within 90 minutes of ingestion of the meal of the MMC.⁷

(f) A pattern of minute clustered contractions associated with pain.^{13, 14}

A semiquantitative assessment of the motility tracings was achieved using the scoring system

TABLE I Scoring system for upper gastrointestinal motility

	Score if abnormal
<i>Fasting:</i>	
Propagation of MMC	1.5
If previous gastric surgery, ≥ 3 MMCs/3 hours	1.5
If no gastric surgery, absence of antral component of MMC	0.5
Bursts/clusters associated with pain or tonic elevation of baseline pressure	1.5
If no MMCs, duodenojejunal hypomotility	1.5
<i>Postprandial:</i>	
Antral hypomotility	3.0
Pylorospasm	0.5
Duodenojejunal incoordination or lack of fed pattern	1.0
Bursts/clusters	1.5
MMC like activity within 90 minutes of end of meal	1.5

The maximum score of 11.0, in a subject who has not had prior gastric surgery, is possible if all of the italicised scores in the above table are scored. For this subject, an absolute score ≥ 3 is abnormal. MMC=migrating motor complex.

TABLE II Scoring system for autonomic dysfunction

<i>Sudomotor function (sympathetic cholinergic): sweating assessed at three sites:</i>
1=minor abnormality
2=2 sites reduced or 1 site absent
3=3 sites reduced or 2 sites absent
<i>Cardiovascular function: cardiac response to deep breathing and Valsalva manoeuvre:</i>
1=borderline or mildly abnormal
2=moderate abnormality of one test
3=both tests definitely abnormal
<i>Sympathetic adrenergic function orthostatic hypotension, blood pressure (BP) responses during Valsalva manoeuvre:</i>
1=mild abnormality of indices during Valsalva manoeuvre
2=no orthostatic hypotension, not abnormal Valsalva responses
3=orthostatic hypotension (SBP>30 mm Hg; mean BP>20 mm Hg)+abnormal Valsalva responses

shown in Table I. The weighting factors were based on previous experience of one investigator (MC) who has assessed over 2000 such tracings in patients with suspected motility disorders in our laboratory. A motility score of ≥ 3 was considered abnormal for subjects who completed the entire 3 hour fasting and 2 hour postprandial study and ingested at least 400 kcal of a mixed meal. The maximum score was 11, which was used as the denominator to calculate the relative abnormality score for the motility test. For those patients who were unable to eat the meal or whose antrum had been excised at previous surgery, the maximum denominator was adjusted before computing the relative motility score. Clusters of small bowel contractions that were unassociated with pain or a failure to record any MMCs during the 3 hour fasting period were not considered abnormal.

AUTONOMIC FUNCTION TESTS

The following assessments of autonomic function were performed as previously described² in 94 of the 113 patients who, for at least 48 hours, had been off all medications that could influence the test. One investigator (PAL) evaluated the results of the following tests:

(i) Supine and standing blood pressure, as a test of general sympathetic adrenergic function.

(ii) Heart rate and blood pressure responses to the Valsalva manoeuvre; a comparison of the ratio of the longest (usually in phase IV) to the shortest (usually in phase II) intervals between successive R waves were measured on the electrocardiogram (ECG). In phase II, forced expiration against a closed glottis results in reduction in venous return, blood pressure, and cardiac output. A compensatory tachycardia normally serves to maintain cardiac output and can be detected by a shortening of the interval between successive QRS complexes on the ECG. During phase IV, the glottis is open, venous return and cardiac output are restored, with overshoot of the blood pressure and compensatory bradycardia. While the test predominantly evaluates sympathetic adrenergic function, it is also dependent on intact vagal innervation.

(iii) The sudomotor axon reflex test is a quantitative evaluation of the latency, output and duration of sweating following iontophoresis of acetylcholine into the skin of the forearm, leg (proximal and distal), and foot. This test evaluates postganglionic cholinergic sympathetic function.

(iv) Heart rate responses to deep breathing, a test of vagal cholinergic function.

Results of autonomic function tests were compared with normal data, matched for age and sex. The scoring system used is shown in Table II. An a priori cut off of ≥ 3 was used to identify autonomic dysfunction in each patient. A relative autonomic dysfunction score was also computed for each patient using the maximum raw score of 9.

STATISTICAL ANALYSIS

A logistic discriminant analysis¹⁹ using both relative autonomic function and motility scores of all patients, except those with idiopathic

TABLE III Patient diagnoses

Diagnosis	No of patients
Irritable bowel syndrome:	39
Idiopathic upper gastrointestinal dysmotility:	23
Chronic idiopathic intestinal pseudo-obstruction	18
Idiopathic gastroparesis	5
Diabetes mellitus:	13
Type I	11
Type II	2
Non-diabetic neurological syndromes:	9
Paraneoplastic	3
Post-radiation	2
Post-viral dysautonomia	2
Porphyria	1
Motor neurone disease	1
After vagotomy/abdominal surgery:	17
Vagal damage	4
Billroth I	2
Roux-en-Y	8
Other abdominal surgery	3
Myopathic:	12
Progressive systemic sclerosis	6
Hollow visceral myopathy	4
Polymyositis	1
Mixed myopathic disorder	1

TABLE IV Prevalence of abnormal autonomic function (AF)

Diagnosis	No of patients	No who underwent AF tests	No with abnormal AFs (%)
Irritable bowel syndrome	39	33	9 (27)
Idiopathic upper gastrointestinal dysmotility	23	21	6 (29)
Diabetes mellitus	13	13	9 (69)
Non-diabetic neurological syndromes	9	9	6 (67)
After vagotomy/abdominal surgery	17	11	3 (27)
Myopathic	12	7	2 (29)

upper gastrointestinal dysmotility, was used to develop two models (one with just the motility score, and one with both motility and autonomic scores) for distinguishing neuropathic patients from all other patients evaluated. These models were then applied to the scores from idiopathic patients to estimate a predicted probability of neuropathic disorder for each idiopathic patient.

A separate logistic discriminant analysis used both scores from all patients to determine if autonomic tests could add to the motility test's ability to discriminate irritable bowel syndrome patients from the other subgroups combined.

Receiver operating characteristic curves (ROC²⁰) were used to summarise the sensitivity and specificity of motility tests alone *versus* motility and autonomic function tests combined in addressing the two specific aims: identification of those with neurological disorders, and differentiation of irritable bowel syndrome from the remaining patients.

Results

CLASSIFICATION OF PATIENTS AND PREVALENCE OF AUTONOMIC DYSFUNCTION

The following diagnostic categories were identified in 113 patients: irritable bowel syndrome (n=39); idiopathic upper gastrointestinal dysmotility (n=23); diabetes mellitus (n=13); identified non-diabetic neurological (n=9); previous vagotomy or other abdominal surgery (n=17); and myopathic pseudo-obstruction (n=12). The specific diagnoses in each category are listed in Table III. The results of autonomic testing for each group are listed in Table IV. The

relative motility and autonomic scores are shown in Figures 1 and 2. All patients with diabetes mellitus had autonomic function tests, and 64% of these patients had autonomic dysfunction. Three of four diabetic patients with normal autonomic function had normal gastrointestinal motility.

Among the remaining subgroups of patients, the prevalence of autonomic dysfunction ranged from 27–29%.

CORRELATION BETWEEN AUTONOMIC AND MOTILITY SCORES

There was a significant ($p < 0.05$) but modest ($r = 0.26$) rank correlation between autonomic and motility scores in the entire group. In the subgroup of patients with diabetes mellitus, this correlation was stronger ($r = 0.68$; $p = 0.01$); similarly, a significant correlation was noted in the combined group of patients with diabetes mellitus and non-diabetic neurological syndromes ($n = 22$; $r = 0.49$; $p < 0.05$).

LOGISTIC DISCRIMINANT ANALYSIS

The model based on data from patients with diabetes mellitus and identified neurological syndromes showed that at a specificity of 72%, the addition of the autonomic function score to the motility score increased the sensitivity for identifying a neuropathic disturbance from 73 to only 76% (Fig 3). In this analysis the addition of the autonomic score changed the corresponding cut off in predicted probability of a neuropathic disturbance from 0.376 for the motility score alone to 0.394 for the combined motility and autonomic scores.

The second logistic discriminant model could distinguish irritable bowel syndrome from non-irritable bowel syndrome patients at a specificity of 80%, with a sensitivity of 90%. Once again, the autonomic function score did not increase the accuracy of the motility test to differentiate these two groups (Fig 4).

Discussion

Our study shows that autonomic dysfunction is frequent in patients with symptoms suggestive of gastrointestinal dysmotility when a neurological diagnosis is clinically identifiable, as listed in Table III. Of the remaining patients referred for evaluation of a clinically suspected motility disorder at a tertiary referral centre, the prevalence of visceral autonomic dysfunction is around 27–29%, and is virtually the same in all diagnostic groups. Our study does not permit us to determine whether dysautonomia is of aetiological importance in patients with irritable bowel syndrome, idiopathic upper gastrointestinal dysmotility, and those with previous vagotomy or abdominal surgery. However, our findings confirm the frequent association of motility disorders with autonomic dysfunction. Other workers have reported vagal dysfunction of variable severity in patients with gastro-oesophageal reflux.^{3,4,15} In our group of patients who had previously undergone vagotomy or abdominal surgery, the diagnosis of autonomic dysfunction was based on tests which evaluate

thoracic and peripheral autonomic pathways that are unaffected by the abdominal surgery. It is possible that subtle autonomic dysfunction may have preceded the surgical treatment. Although functions of the infradiaphragmatic vagus nerve, such as the pancreatic polypeptide response to hypoglycaemia or sham feeding,¹⁶ were not evaluated in these studies, the tests used in this study are comprehensive. In fact, Buyschaert *et al*¹⁸ have previously shown that, in conditions such as diabetes mellitus, which are associated with a length dependent neuropathy, abnormal cardiovascular reflexes are an excellent predictor of dysfunction of the abdominal vagus.

Our data also suggest that autonomic dysfunction may result in gastrointestinal dysmotility of varying severity. Some of these dysmotilities are manifest clinically and on special testing (for example by manometry) as either irritable bowel syndrome or idiopathic upper gastrointestinal motility disorders. In some patients the symptoms may have been severe enough to lead to surgical treatment before referral to our clinic.

Read¹⁷ has elegantly indicated the difficulty in categorising the spectrum of more severely affected patients with apparently functional gastrointestinal disease. While intestinal manometric criteria may help make this distinction,⁸ the similar prevalence of dysautonomia found in our study provides support for Read's contention

that the terms irritable bowel syndrome and pseudo-obstruction may merely 'describe' different categories in the spectrum of functional gastrointestinal disease.¹⁷

The second major objective of our study was to evaluate the diagnostic utility of autonomic function testing. Based on the fact that a similar proportion of patients with irritable bowel syndrome, idiopathic upper gastrointestinal dysmotility, and previous surgery in our series had autonomic dysfunction one would correctly anticipate that these tests would not permit a clear distinction of the irritable bowel syndrome group from the rest. Indeed, the logistic discriminant models showed that autonomic tests did not add to the diagnostic value of the motility study. Among patients with diabetes and other identifiable neurological syndromes, autonomic tests were abnormal in 69%, compared with the motility test which was abnormal in 73%. Thus, if motility testing is not available, the non-invasive autonomic tests may be useful in confirming the presence of visceral denervation in those patients with symptoms suggestive of gut dysmotility. It must also be stressed that autonomic testing is extremely useful in assessing autonomic involvement outside the gastrointestinal tract.

Two patients with hollow visceral myopathy had abnormal vasomotor and sudomotor responses. The low amplitude fasting and post-prandial intestinal pressure profiles suggested a myopathic disorder. Thus, the occurrence of visceral or vasomotor autonomic dysfunction does not necessarily imply that the gut dysmotility is the result of the neuropathic dysfunction.

Since only 27–29% of patients with idiopathic upper gastrointestinal dysmotility or post-abdominal surgery have evidence of autonomic dysfunction, it is possible that disorders of the efferent extrinsic neurological pathways are not aetiologically important in these conditions. However, it is important to note that our data do not assess visceral afferent function or the enteric nervous system, which are presently believed to be at least partly responsible for the development of symptoms or abnormal motor function in the functional gastrointestinal syndromes. Among patients with previous vagotomy, it is likely that abdominal vagal denervation, which was not tested in our study, resulted in gastrointestinal dysmotility.⁹

Within the constraint dictated by a tertiary referral centre, we believe our study of 113 consecutive patients is unique since it encompasses all major subclasses of motility disorders from idiopathic dysmotility to gut motor dysfunction secondary to identifiable neurological syndromes. The standardisation of motility and autonomic tests and high proportion (83%) of patients who underwent both tests allow estimates of the prevalence of autonomic dysfunction among patients referred to a centre specialising in gut motility disorders. Autonomic dysfunction is frequent among patients with identifiable neurological syndromes who present with gastrointestinal symptoms. Autonomic dysfunction of an idiopathic nature is present in a minority of patients with functional gastro-

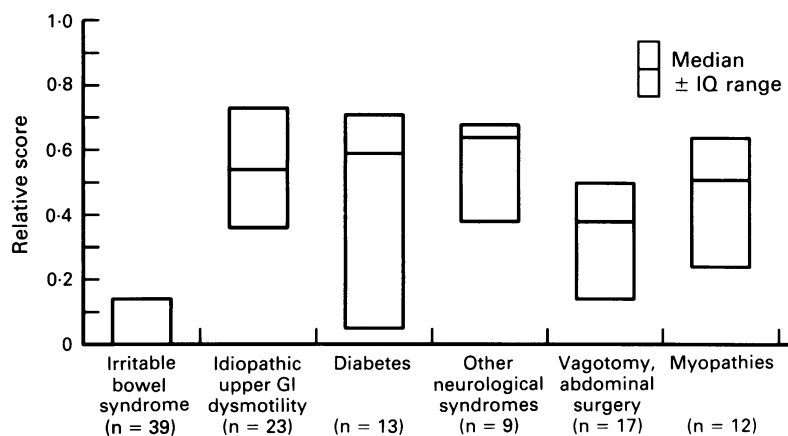


Figure 1: Distribution of gastrointestinal motility scores in different patient groups. Raw scores were computed by the system shown in Table I. Relative scores were obtained from dividing the maximum possible for an individual patient.

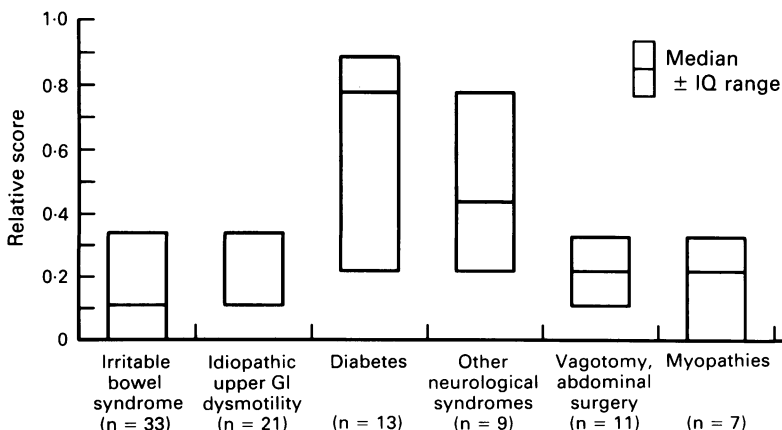


Figure 2: Distribution of autonomic function scores in different patient groups. Raw scores were computed by the system shown in Table II. A maximum score of 9 was used to obtain relative scores for each patient.

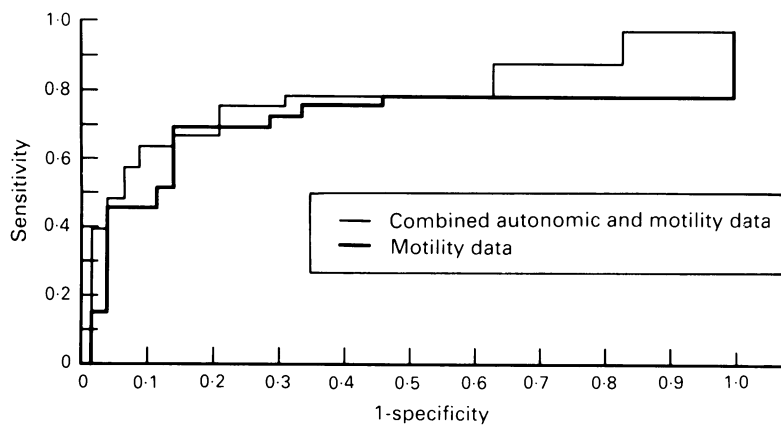


Figure 3: Receiver operating characteristic curve comparing accuracy in diagnosis of a neuropathic disorder of motility score alone and combined motility and autonomic function data based on logistic discriminant models. Note the similarity of curves suggesting autonomic data do not add to accuracy of the motility test.

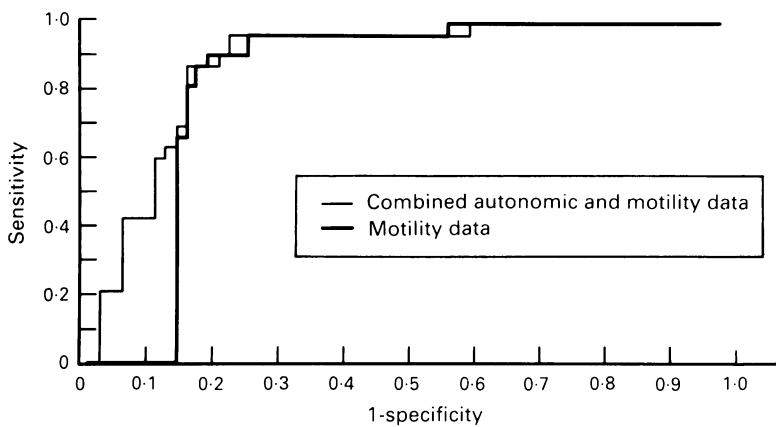


Figure 4: Receiver operating characteristic curve comparing accuracy in diagnosis of irritable bowel syndrome of motility score alone and combined motility and autonomic function data based on logistic models. The similarity of the curves indicates autonomic data do not add to the accuracy of the motility test.

intestinal disorders and may contribute to the aetiology in these patients. Finally, although autonomic testing adds little to the diagnostic accuracy of a gastrointestinal motility study in patients with a suspected motility disorder, they may contribute significantly to identifying autonomic involvement outside the digestive tract and to the diagnosis of patients with identified neurological syndromes and gut symptoms when

motility studies are not available or contraindicated.

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