

CHRONIC ABDOMINAL PAIN AND DISCOMFORT

RELEVANCE OF INTESTINAL GAS DYNAMICS

J-R Malagelada

At the present time we do not have a unifying hypothesis to explain the mechanism of chronic abdominal pain and discomfort in functional gut disorders. A number of partial hypotheses have been developed based on experimental and clinical observations. However, each of these hypotheses postulates a different physiological disturbance and it is difficult to accept that so many altered mechanisms would coexist in the same patient. Thus, we are left with various putative explanations:

- ◆ different mechanisms are interlinked in an, as yet, unidentified way
- ◆ different patients have similar symptoms based on different disease mechanisms
- ◆ none of the mechanisms identified so far are relevant and the true cause of abdominal symptoms remains to be discovered.

Mechanisms identified so far include gut dysmotility, minimal inflammation, visceral hypersensitivity and psychological disturbances. In this review, I will update and analyze the supporting evidence for each of these postulated mechanisms. At the same time, I will introduce the concept of intestinal gas dynamics and provide preliminary information concerning its relevance to the pathogenesis of abdominal symptoms in patients with functional gut disorders.

Gut dysmotility in patients with chronic abdominal pain

Regional disturbances of motility in the gastrointestinal tract have been detected in some patients with functional gut disorders and, hence, proposed as likely pathogenetic mechanisms. Unfortunately, not all symptomatic patients exhibit dysmotility. If we considered functional disorders as a single condition, symptoms would correlate poorly with abnormal motility, be it delayed gastric emptying, antral hypomotility or intestinal dysmotility.

However, motor events may be undetectable in some patients with

concurrent symptoms simply because our current measuring devices are not sensitive enough. Conversely, abnormal motor events recorded during physiological studies may not be temporarily associated with symptoms but, at other times, and in conjunction with other mechanisms (? central) disturbances in motility may, indeed, turn into uncomfortable sensations. The concept that functional gastrointestinal symptoms are derived from abnormal gut motility has also obtained some support from the therapeutic use of prokinetic agents. It must be admitted, however, than even when there is a statistically significant drug response, it is often difficult to establish a causal relation between drug-induced changes in motility and relief of symptoms in individual patients. Finally, we should consider the possibility that certain subgroups of patients may show a stronger association between dysmotility and symptoms than unselected patient populations.

Perhaps the best evidence that abnormal gut motility is a potential inductor of pain comes from oesophageal data. First of all, various oesophageal motor disorders are associated with pain. This is usually described by patients as chest pain, with or without associated dysphagia. Among painful oesophageal conditions, diffuse oesophageal spasm is best characterized¹ but other oesophageal dysmotilities such as nutcracker oesophagus, hypertensive lower oesophageal sphincter and non-specific motor disorders may be associated with sporadic pain². As always, however, the difficulty lies in proving that the motor abnormalities are directly causing the pain. There are two lines of evidence: temporal association and provocative tests. The former evidence is derived primarily from manometric studies, stationary or ambulatory, that show concurrence between abnormal motor events and pain. Unfortunately, such data provide only indirect and rather soft support. For instance, in one study³ only 18% of patients showed temporary association between chest pain and abnormal oesophageal motility. Provocative studies go one step beyond and they are based on the idea that certain stimuli would induce simultaneously motor abnormalities and chest pain in predisposed patients. Edrophonium, bethanechol or ergonovine are pharmacological stimuli that have been used for test purposes. Again, however, temporal association provides only indirect evidence. In the study conducted by Lee et al.⁴, abnormal manometry could be induced

by edrophonium in about 1/3 of patients but it was not always associated with chest pain. In another study employing ergonovine stimulation, oesophageal motor abnormalities could be detected in the majority of individuals who experienced chest pain⁵ but other origins of the pain (i.e., cardiac) could not be unequivocally excluded.

It is apparent from the above data that a causal relation between oesophageal dysmotility (spontaneous or induced) and pain is plausible but cannot be conclusively established. However, in some individuals, and, on some occasions, it seems quite evident suggesting, as indicated above, that other interacting mechanisms are important. Mucosal sensitivity to acid reflux has been excluded in some studies by concomitant oesophageal pH measurements but not in others. Visceral hypersensitivity may also play a determinant role and some patients may, indeed, share a hyperkinetic oesophagus and visceral hyperalgesia. It is even conceivable that, in some patients, both motor and sensory abnormalities would be mediated by a central mechanism activated either spontaneously or provoked by certain stimuli or environmental situations.

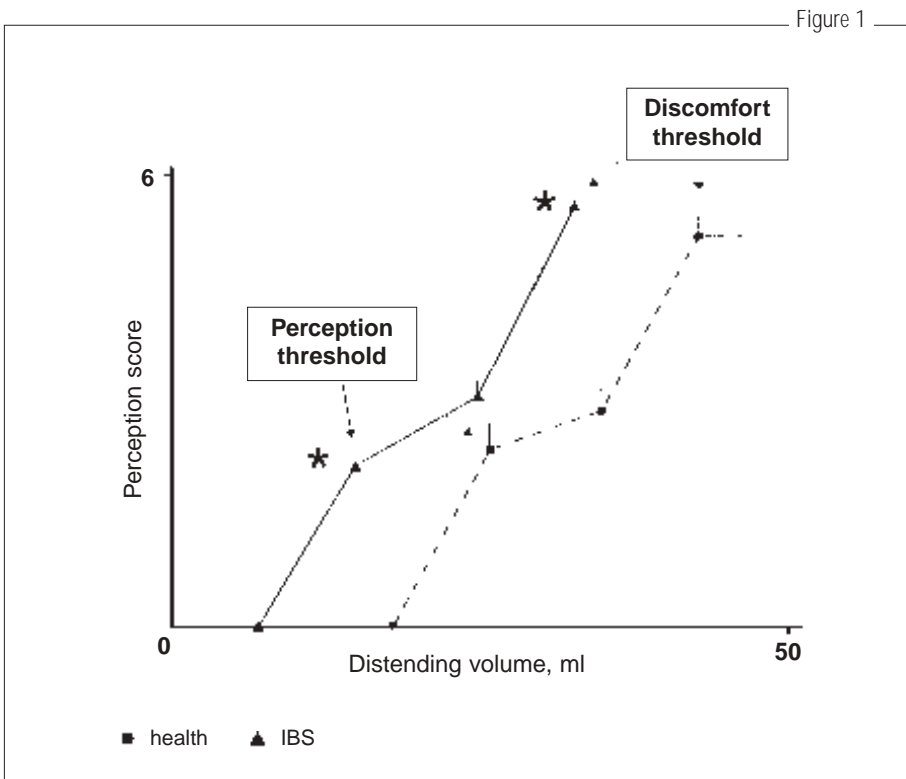
Elsewhere in the gastrointestinal tract, it is even more difficult than in the oesophagus to prove an association between dysmotility and pain, not to speak of a causal relation. In the stomach, distension (and the consequent increased wall tension) appears to be definitely associated with pain⁶. However, it is not known whether motor abnormalities can, by themselves, induce sufficient distension to induce pain, even in hypersensitive subjects. The closest that it may come to spontaneously-induced distension pain in the stomach is the clinical situation usually referred to as postsurgical gastroparesis that may develop in patients who have undergone distal gastric resection with gastroenteric anastomosis. These patients accumulate mostly solid debris in their residual stomach and very often complain of gastric pain. We have shown that their gastric wall is rather inelastic, and therefore, painful tension easily develops⁷. At the other end of the clinical spectrum, in patients with functional dyspepsia, antral hypomotility seems, in itself, unlikely to cause pain. Except, as it appears to be sometimes the case, when maldistribution of gastric postcibal content occurs with resulting antral accumulation and uncomfortable distension.

Intestinal dysmotility has been recognized rather unequivocally by clinical manometry in some conditions such as advanced diabetes, other autonomic neuropathies and in gut neuromuscular disorders associated with the clinical syndrome of chronic pseudo-obstruction⁸. Nevertheless, it has not been possible to prove that intestinal dysmotility is a direct cause of abdominal pain, and it seems more likely that “neuropathic pain” from a coexisting sensory neuropathy or pain secondary to local stasis and wall distension are responsible for the symptoms. In some individuals with irritable bowel syndrome, there is an exaggerated “minute rhythm” and/or the presence of either spontaneous or induced giant waves, particularly in the ileum, that have also been associated with pain^{9,10}.

Evidence in favour of colonic dysmotility as a cause of abdominal pain is somewhat more compelling. Early studies focused on the association between sigmoid colon dysmotility and different bowel movement patterns as well as changes in myoelectric rhythms. However, these observations did not prove subsequently too credible¹¹. Distension pain (as opposed to spasm) was also investigated by distending balloons in various colonic sites and recording the symptomatic response. Evidence for heightened perception in patients with the irritable bowel syndrome was obtained but this feature probably relates more to sensory than motor abnormalities. These bowel distension studies led to the concept that visceral hypersensitivity to mechanical, and perhaps also to other gut luminal stimuli, is responsible for symptoms as opposed to, or in conjunction with, altered contractile patterns. Indeed, the results of recent research suggest that visceral hypersensitivity plays a significant pathogenic role in functional gut disorders. However, the issue is extremely complex since it must take into account the interactions that occur between neural control of gut motility, conscious perception of gut signals and modulation at spinal and brain centres. Thus, although sensory perception hypersensitivity has been well documented in several functional abdominal disorders, the precise mechanism or even the “site” of the abnormality (gut wall, central nervous system) remains unknown. In functional gut disorders, region specificity is not, by any means, absolute. For instance, patients with irritable bowel syndrome whose pain is conventionally attributed to a colonic source may manifest

hypersensitivity both to distension of the jejunum¹² and the sigmoid colon, suggesting that the sensory disorder is widespread along the gut (Figure 1). These observations have led some investigators to embrace the concept of an “irritable gut” implying also that the faulty mechanism responsible for the hypersensitivity is located at a “central” site (either the brain or the spinal cord) rather than peripherally.

In disease, the gut may become hypersensitive to different forms of stimulation, as described above. The implication is that hypersensitivity determines symptoms either by making patients aware of normal motor events or by exaggerating perception of abnormal events, or both.



Gut hypersensitivity to mechanical stimuli in the irritable bowel syndrome. Note (*) the lower perception and discomfort thresholds shown by patients with irritable bowel syndrome (▲) versus healthy subjects (■). Reproduced with permission from Accarino A, Azpiroz F, Malagelada J-R¹².

Furthermore, visceral hypersensitivity is not a concept restricted to functional gut disorders. It has been recognized, for instance, in the inflamed rectum of ulcerative colitis, and there are other examples of organic conditions that exhibit gut hypersensitivity to diverse luminal stimuli.

Nevertheless, a significant problem remains on how to integrate motility and sensory disturbances. Do they coexist? Are they linked by common central control? Impaired reflex activity (for instance, a decreased gastric relaxatory response to duodenal distension) has been demonstrated in some patients with functional disorders, who are also hypersensitive to gut distension. This kind of observation suggests that not only conscious sensory systems, but also motor control systems, may be simultaneously impaired in certain patients. Although, so far, it has not been possible to establish a direct link between impaired sensitivity and disturbed motility, the latter clearly being a feature of some, but not all, patients with functional gut syndromes. The paucity of pharmacological agents to modulate visceral sensitivity constitutes a major obstacle to progress, because we cannot evaluate the hypersensitivity hypothesis by selectively blocking afferent sensory signals.

Gas in the gut

Recently, we have developed a complementary and, we believe, important concept. Abnormal motility and visceral hypersensitivity manifest both by an alteration of the dynamics of intestinal gas and by enhancing the symptomatic response to regional gas distension. Thus, it emerges that some of the best evidence linking bowel dysmotility to abdominal discomfort/pain comes, rather indirectly, from studies of gas dynamics in the bowel.

There is gas in the normal gut that originates, in part, from swallowing and, in part, from a series of chemical reactions of the foodstuffs within the gut¹³. The resulting intestinal gas load is normally unperceived. Most of it is transported along the bowel and evacuated per anus without excess accumulation¹⁴. Abdominal complaints such as bloating, borborygmi, cramps and, sometimes, frank distension are, at times, attributable to altered dynamics of intestinal gas. In fact, patients themselves

intuitively ascribe many of these symptoms to a gas problem. But, in most cases, it remains uncertain whether the symptoms are due to a gas overload, an impaired intestinal handling of gas or a poor tolerance and increased perception^{15,16}.

Based on the knowledge that gas is an important component of digestive tract content, we hypothesized that abnormal handling of normal or excessive intestinal gas loads might represent a, heretofore, unrecognized mechanism of functional gut distress. Thus, we established and validated a method for quantifying gas transit in the human gut while simultaneously assessing symptomatic responses and physiological effects, such as abdominal distension. In the course of our studies, we observed that a subgroup of healthy individuals and a significantly larger proportion of individuals with functional abdominal symptoms retain large quantities of gas, develop abdominal distension and discomfort. Gas retention and symptoms do not appear to be due to impaired anal relaxation because they remain unmodified during intrarectal gas collection. Further studies compared the effects of pharmacological gut motor inhibition and restrained voluntary evacuation on gas dynamics. Our results suggest that abdominal distension depends on the volume of gas retention, whereas symptom perception depends on gut motor activity and the mechanism of retention.

Our method for measuring intestinal gas dynamics is based on proximal jejunal infusion at a constant rate of a poorly diffusible gas mixture, with simultaneous quantification of anal expulsion rates¹⁷. We use an intestinal polyvinyl tube assembly that incorporates a gas infusion channel with multiple distal side holes over the 1 cm distal segment, an oral latex balloon with a separate inflation channel to prevent gaseous backflow and a drainage channel with multiple side holes oral to the balloon to remove accumulating secretions. In the initial studies, we also used a separate gastric polyvinyl tube, that incorporated a venting channel with multiple side holes to aspirate refluxed gas, but, in subsequent studies, we eliminated this component since there is virtually no backflow of infused jejunal gas into the stomach.

The gas mixture infused contains 88% nitrogen, 6.5% carbon dioxide and 5.5% oxygen bubbled into water for saturation. This gas mixture is designed to mimic the partial pressures of the gases in venous blood, and

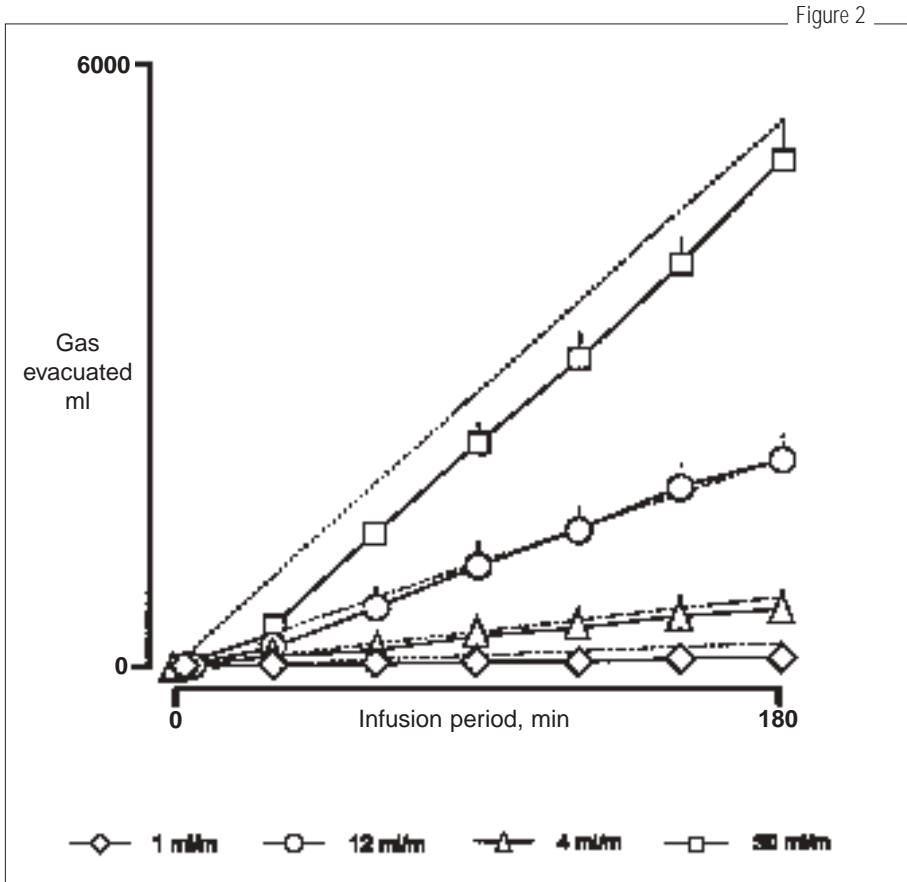
hence, to minimize diffusion across the intestinal blood barrier¹⁸.

The volume of gas passed per anus is controlled by a barostat, which is an electronic pressure clamp, that drives an air pump based on a strain gauge input^{19,20}. The barostat provides a low resistance collection line since a minimal pressure increment produced by gas evacuation, immediately activates the pump (< 5 ms lag) and displaces the volume along the line. Anal gas is collected by a low resistance external cannula that fits hermetically in between the buttocks, with the concavity lining the perineal midline, the tip ventral to the coccyx, the collection port facing the anus, and the collecting line emerging ventrally between the thighs. The open end of the anal cannula is connected via separate channels to the air pump and to the strain gauge of the barostat.

We normally intubate participants in the morning after an 8-hour fast. The intestinal tube assembly is introduced through the mouth into the intestine and we position, under fluoroscopic control, the tip of the infusion tube about 5 cm caudad to the angle of Treitz. During the study, participants lay supine in the bed at an angle of 30° to the horizontal. Once they are positioned, a non-distensible, flaccid belt is placed around their abdomen at the level of the flanks and umbilical region. The overlapping ends of the belt are adjusted by means of two elastic bands, so that the belt constantly follows changes in girth by adapting to the abdominal wall. During the study, we use a graded questionnaire to measure the intensity and the type of sensations perceived, and an anatomical questionnaire to measure the location and extension of the perceived sensations. Each sensation is independently scored on a graphic rating scale that combines verbal descriptors on a visual analog scale graded from 0 to 6²².

During the test, we calculate, at various time periods, the volume of gas retained within the gut as the difference between the volume of gas infused and the volume of gas recovered. We have performed validation studies using an inert gaseous marker, SF₆, that is neither produced nor absorbed by the gut²³.

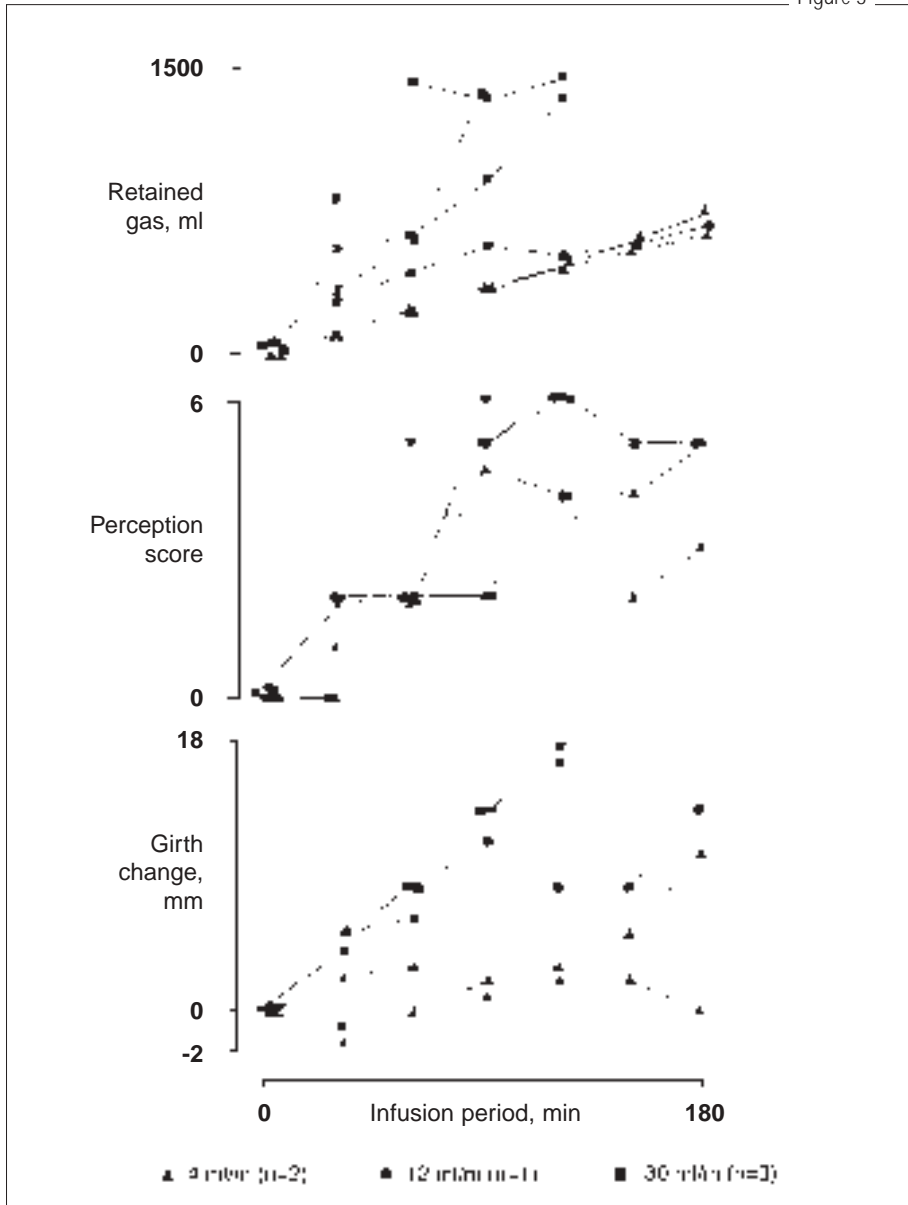
In most normal individuals, gas loads, within a very broad range (1 to 30 ml/min), are appropriately handled by the gut so that evacuation rates parallel infusion rates with no apparent gas retention within the gut (Figure 2). Thus, in our studies greater volumes of gas infused were associated with both an increased number of evacuations and larger gas volumes per evacuation.



Gas evacuation during continuous intestinal infusion of gas; dose response study in different groups of healthy subjects. Note the close approximation between gas infusion and evacuation rates. Reproduced with permission from Serra J, Azpiroz F, Malagelada J-R¹⁷.

In most of our normal study subjects, gas retention within the gut was in the range between +400 ml and -400 ml; some subjects that evacuated more gas than infused had a negative balance of retention. There is, however, no noticeable interindividual variability in the dynamics of intestinal gas. Six out of 46 normal volunteers in our initial studies retained gas above the 400 ml. Furthermore, in contrast to the remainder of the subjects who promptly equilibrated evacuation and infusion rates, these 6 subjects progressively retained gas during the study (Figure 3).

Figure 3



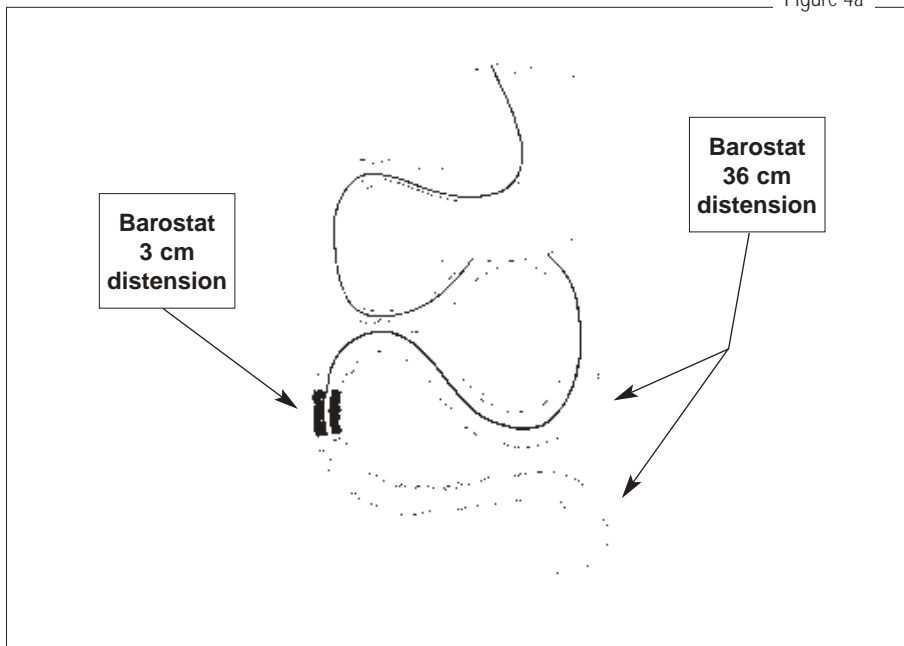
Gas transit, symptoms and abdominal distension in 6 subjects with >400 ml of gas retention during a gas challenge test. Reproduced with permission from Serra J, Azpiroz F, Malagelada J-R¹⁷.

We observed that the intensity of perception was related to the volume of gas retained within the gut. Neither the rate of infusion, nor the amount of gas propelled through the gut, appear to influence perception. Therefore, the dynamics of intestinal gas play a key role in determining perception of gas in the bowel. If the gas moves normally, it is expelled without retention or symptoms. By contrast, if relatively small volumes exceeding 400 ml accumulate, then symptoms develop. Interestingly the type of abdominal sensations produced by gas accumulation is similar regardless of the volume of gas retained and the intensity of perception. Thus, subjects who retained more gas reported the same sensations as the others, and, even more remarkable, they did not report any difficulty expelling gas per anus. Normal individuals who were not gas retainers did not develop any significant abdominal distension. However, in subjects who retained more than 400 ml gas, there was a concomitant and progressive increase in girth (Figure 3).

The mechanisms that produce displacement of gas within the gut are not well known. Our data demonstrate a distinctive gas and chyme discrimination within the gut, since, at high infusion rates, gas transit was expeditious, but despite the large volumes of gas evacuated per anus no subject reported a call for stools. Previous investigators have shown that intestinal propulsive activity for solids and liquids depends on different patterns of phasic motor activity^{24,25} but the role of this type of motor activity in moving gas is conceivably small. High amplitude propagated contractions in the colon have been related to faecal mass movements²⁶. Again, the role of these known contractile patterns in moving gas is unknown and further research will have to be undertaken to characterize the specific motility pattern responsible for gas propulsion. An intriguing issue addressed by our studies is the quantity of intestinal gas that would trigger symptoms. Our data indicate that gas volumes above the 400 ml range may induce conscious perception, predominantly sensation of abdominal bloating. It is interesting that the subjects who retained gas did not report any difficulty in evacuating gas which suggests that the retention site is located proximal to the rectum. The mechanisms involved in gas have not been well characterized but presumably depend on bowel distension. It has been shown that a small amount of gas may induce symptoms when the intraluminal pressure and the tension on the gut wall reach a certain level.

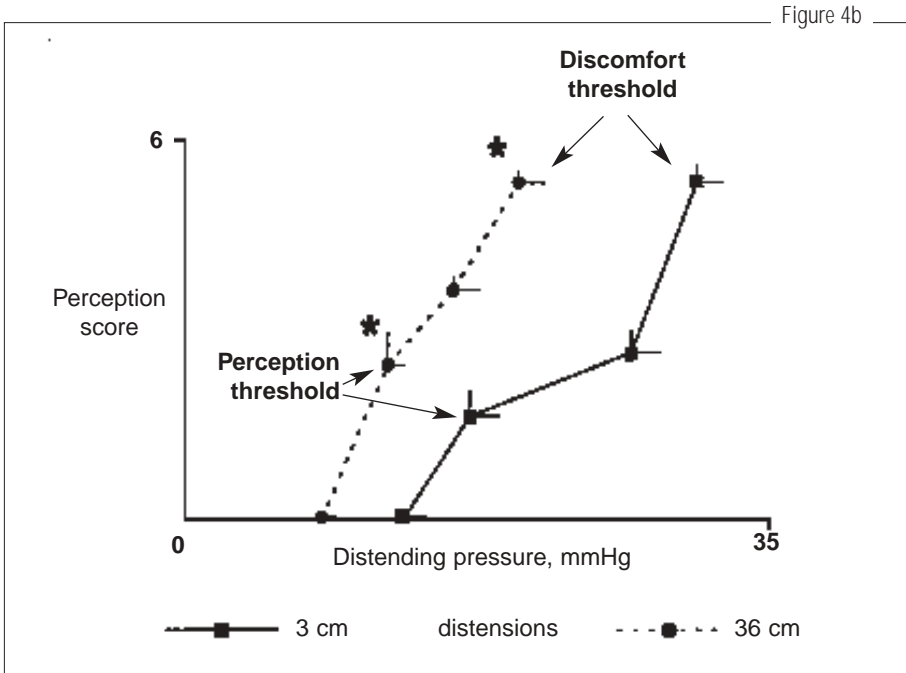
However, the presence of another gas bubble, even at a distant site in the gut, considerably increases the intensity of perception^{27,28}. Likewise, a given amount of gas, when distributed along a large segment of intestine, induces symptoms at a lower wall tension that may be required in a shorter loop because of summation effects. Along these lines, it is remarkable that, as shown by a recent study in our laboratory, a volume of only about 200 ml air contained in a 36 cm tubular bag within the jejunum, induced discomfort (Figure 4a and 4b)²⁸.

Figure 4a



Experimental method. Isobaric intestinal distensions were applied over a short (3 cm) and a long segment (36 cm) by means of two separate barostats in healthy individuals. The long bag was divided into two compartments sharing pressure and volume connections, and the short bag was located in-between.

More recently, we have studied a group of patients with non-specific functional gut disorders (unexplained abdominal pain and/or bloating) and observed that gas infusion was well tolerated by healthy subjects, but induced abdominal discomfort and substantial gas retention in many.



Experimental results. Perception of fixed-pressure intestinal distensions applied over the short segment and the long segment of small bowel. Reproduced with permission from Serra J, Azpiroz F, Malagelada J-R²⁸.

Gas retention and symptoms were not attributable to impaired anal evacuation, because they were unmodified during intrarectal gas collection. Thus, a significant proportion of patients with functional gut disorders have impaired handling of intestinal gas loads, and exhibit gas retention and/or symptoms.

Biliary dysmotility in patients with chronic abdominal pain

Evidence that functional type biliary motor disturbances can give rise to abdominal pain is fairly compelling, although not overwhelming. Sphincter of Oddi dysfunction has been proposed as a cause of postcholecystectomy pain in the absence of calculi. Such patients often describe their pain as being identical to that experienced prior to removal of the gallbladder. However, pain may not be limited to the

epigastrium or right upper quadrant, and atypical referral patterns do occur. Sphincter of Oddi dysfunction may have either a structural or physiological basis, or both. Structural abnormalities may consist in narrowing and irregularity of the intraduodenal segment of the distal choledochus (papillary stenosis), whereas physiological abnormalities relate primarily to abnormal contractile activity whether or not associated with actual hypertrophy of the sphincteric muscle. Sphincter of Oddi dysfunction is, therefore, a condition that may be diagnosed either by imaging techniques (anatomy or anatomy and physiology) or motility recording techniques (physiology), or a combination of both. An indirect diagnosis of sphincter of Oddi dysfunction may be obtained from point elevation of liver enzymes coinciding with an episode of pain. In fact, such an event remains one of the most reliable clinical clues, with a much higher predicting value than pain which, even when described by the patient in a highly persuasive manner can be rather non-specific.

There are three recognizable forms of sphincter of Oddi dysfunction based on the presence of ductal dilatation, elevated liver enzymes or delayed drainage of the common bile duct at the time of endoscopic retrograde cholangiography or hepatobiliary scintigraphy (^{99m}TC -HIDA) scan. Patients with suggestive pain and all three of the findings are classified as having type I sphincter of Oddi dysfunction. The majority of these patients are found to have elevated basal sphincter pressures during biliary manometry and tend to respond to endoscopic sphincterotomy. Patients with two of the three associated findings, or type II sphincter of Oddi dysfunction show elevated basal pressures at sphincter of Oddi manometry about 50% of the time. In turn, the majority of those patients with elevated pressures experience significant pain relief after endoscopic sphincterotomy. Patients who have pain but lack any of the associated findings, or type III sphincter of Oddi dysfunction, are less predictable both in the frequency of elevated basal sphincter pressures and positive response to sphincterotomy²⁹.

Conclusions

It is, to some extent, surprising that a common symptom such as abdominal pain, in the absence of evident organic disease, remains, much of a mystery as to its origin and mechanism. Nevertheless, considerable progress has been made in recent years. We now recognize that there are common

pathogenetic features in pain arising from various segments of the digestive tract including the oesophagus, the colon and the biliary tract.

The most relevant link appears to be disturbed regulation of motility and visceral hypersensitivity, both perhaps arising from spinal or brain dysfunctions since the central nervous system plays a major role in the regulation of digestive tract physiology. But there are other, perhaps less esoteric, factors involved. One of these is gas. Recent studies conducted by our laboratory indicate that the dynamics of intestinal gas are the key to preventing accumulation of gas inside the bowel. Some normal individuals and a substantial fraction of patients with the irritable bowel syndrome are incapable of moving gas inside the bowel with the consequent pooling and distension of segments of bowel.

It seems logical to conclude from this information that motility disturbances may impair intestinal gas transit and that conscious perception of bowel distension by gas may be amplified by visceral hypersensitivity phenomena, resulting in significant abdominal pain and other symptoms. Thus, at this point, we put forward the hypothesis that functional type gut pain may be generated by various "local" mechanisms: spasm, perhaps most relevant in the oesophagus, distension, by gas in the bowel, by impaired bile flow in the biliary tract, etc.

For these local mechanisms to elicit pain or discomfort, however, visceral hypersensitivity either from amplified wall afferent signals or by anomalous central nervous system modulatory and reception symptoms would be important, since similar stimuli in normal people may go unperceived.

In any event, only further observations and a better understanding of basic mechanisms will provide a clue.

REFERENCES

1. Richter JE. *Motility disorders of the esophagus*. In: Yamada T, Alpers DH, Owyang C, Powell DW and Silverstein FE, editors. *Textbook of Gastroenterology*. Philadelphia: Lippincott; 1991;1083-122.
2. Kahrilas PJ. *Nutracker esophagus: an idea whose time has gone?* *Am J Gastroenterol* 1993;88:167-9.

3. Breumelhof R, Nadorp JHSM, Akkermans LMA, Smout AJPM. *Analysis of 24-hour esophageal pressure and pH data in unselected patients with non cardiac chest pain.* Gastroenterology 1990;99:1257-64.
4. Lee CA, Reynolds JC, Ouyang A, et al. *Esophageal chest pain: value of manometries.* Dig Dis Sci 1987;32:682-8.
5. Alban Davies H, Kaye MD, Rhodes J, et al. *Diagnosis of esophageal spasm by ergometrine provocation.* Gut 1982;23:89-97.
6. Mearin F, Cucala M, Azpiroz F, Malagelada J-R. *The origin of symptoms on the brain-gut axis in functional dyspepsia.* Gastroenterology 1991;100:999-1006.
7. Azpiroz F, Malagelada J-R. *Gastric tone measured by an electronic barostat in health and postsurgical gastroparesis.* Gastroenterology 1987;92:934-43.
8. Camilleri M, Malagelada J-R, Stanghellini V, et al. *Gastrointestinal motility disturbance in patients with orthostatic hypotension.* Gastroenterology 1985;88:1852-9.
9. Kellow JE, Eckerskey GM, Jones MP. *Enhanced perception of physiological intestinal motility in the irritable bowel syndrome.* Gastroenterology 1991;101:1621-7.
10. Thompson DG, Laidlow JM, Wingate DL. *Abnormal small-bowel motility demonstrated by radiotelemetry in a patient with irritable colon.* Lancet 1979;22/29:1321-3.
11. Latimer P, et al. *Colonic motor and myoelectric activity: a comparative study of normal subjects, psychoneurotic patients and patients with the irritable bowel syndrome.* Gastroenterology 1981;80:893-901.
12. Accarino A, Azpiroz F, Malagelada J-R. *Selective dysfunction of mechanosensitive intestinal afferents in the irritable bowel syndrome.* Gastroenterology 1995;108:636-43.
13. Levitt MD, Bond JH. *Volume, composition, and source of intestinal gas.* Gastroenterology 1970;59:921-9.
14. Levitt MD. *Volume and composition of human intestinal gas determined by means of an intestinal washout technic.* N Engl J Med 1971;284:1394-8.
15. Poynard T, Hernandez M, Xu P, et al. and Cooperative Study Group. *Visible abdominal distension and gas surface: description of an automatic method of evaluation and application to patients with irritable bowel syndrome and dyspepsia.* Eur J Gastroenterol Hepatol 1992;4:831-6.
16. Maxton DG, Martin DF, Whorwell PJ, Godprey M. *Abdominal distension in female patients with irritable bowel syndrome: exploration of possible mechanisms.* Gut 1991;32:662-4.
17. Serra J, Azpiroz F, Malagelada J-R. *Intestinal gas dynamics and tolerance in humans.* Gastroenterology 1998; 115:542-50.
18. Foster RE. *Physiological basis of gas exchange in the gut.* Ann NY Acad Sci 1968;150:4-12.

19. Azpiroz F, Malagelada J-R. *Physiologic variations in canine gastric tone measured by an electronic barostat*. Am J Physiol 1985;247:G265-G272.
20. Azpiroz F, Malagelada J-R. *Gastric tone measured by an electronic barostat in health and postsurgical gastroparesis*. Gastroenterology 1987;92:934-43.
21. Azpiroz F. *Sensitivity of the stomach and small bowel: human research and clinical relevance*. In: Gebhart GF, editor. Progress in pain research and management. Vol. 5, Visceral pain. Seattle: IASP;1995;391-428.
22. Gracely RH. *Studies of pain in normal man*. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. Edinburgh: Churchill Livingstone; 1994;315-36.
23. Jonmarker C, Castor R, Drefeldt B, Werner O. *An analyzer for in-line measurement of expiratory sulfur hexafluoride concentration*. Anesthesiology 1985;63:84-8.
24. Bueno L, Fioramonti J, Ruckebusch Y. *Rate of flow of digesta and electrical activity of the small intestine in dogs and sheep*. J Physiol (Lond) 1975;249:69-85.
25. Ehrlein HJ, Schemann M, Siegle ML. *Motor patterns of small intestine determined by closely spaced extraluminal force transducers and videofluoroscopy*. Am J Physiol 1987;253: G259-G267.
26. Christensen J. *The motility of the colon*. In: Johnson LR, editors. Physiology of the gastrointestinal tract. Vol. 1. 3rd ed. New York: Raven; 1994;991-1024.
27. Serra J, Azpiroz F, Malagelada J-R. *Perception and reflex responses to intestinal distention in humans are modified by simultaneous or previous stimulation*. Gastroenterology 1995;109:1742-9.
28. Serra J, Azpiroz F, Malagelada J-R. *Modulation of gut perception in humans by spatial summation phenomena*. J Physiol (Lond) 1998;506:579-87.
29. Geenen JE, Hogan WJ, Dodds WJ, et al. *The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter of Oddi dysfunction*. N Engl J Med 1989;320: 82-7.

ADDRESS FOR CORRERSPONDENCE

MALAGELADA J-R, Prof, MD

Hospital General Vall D'Hebron, Digestive Diseases Dept.

Pg. Vall d'Hebron, 119-129

08035 Barcelona Spain

Fax: +34 93 209 62 05