Breath tests for functional gastrointestinal disorders: When and for what?

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RESUMEN

Las pruebas respiratorias se han utilizado durante mucho tiempo como una valiosa herramienta de diagnóstico en medicina. Ello se debe probablemente a las siguientes ventajas: no son invasivas, son fáciles de realizar y es posible llevar a cabo pruebas repetitivas. Las pruebas respiratorias tienen una amplia variedad de indicaciones y se han utilizado para explorar la fisiopatología de los trastornos gastrointestinales funcionales (FGID). Las pruebas respiratorias con hidrógeno y metano a menudo se utilizan para evaluar los FGID, pero hay que tener en cuenta varias advertencias en su metodología e interpretación. El reciente lanzamiento de las directrices de consenso de América del Norte proporciona uniformidad a estas pruebas respiratorias en un intento de estandarización. Esta revisión explora el papel del metano/hidrógeno y también las pruebas respiratorias de vaciado gástrico de carbono 13 en los FGID, específicamente el síndrome de intestino irritable (IBS), los síntomas similares al IBS y la dispepsia funcional. Revisamos el papel de las pruebas respiratorias en los FGID y cómo no solo proporcionan información de diagnóstico, sino también sobre los mecanismos fisiopatológicos que subyacen a estos trastornos. Esto, en última instancia, puede proporcionar la información necesaria para un tratamiento guiado en estos trastornos, a veces difíciles de tratar. (NeuroGastroLatam Rev. 2018;2:87-97)

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ABSTRACT

Breath tests (BTs) have long been used as a valuable diagnostic tool in medicine. Their longevity in the diagnostic realm is likely due to the following advantages: they are non-invasive, easy to perform, and capable of repetitive testing. BTs have a variety of indications and have been used to explore the pathophysiology of functional gastrointestinal disorders (FGIDs). Hydrogen and methane BTs are often used to evaluate FGIDs but have several caveats to its methodology and interpretation. The recent release of the North American consensus guidelines provides uniformity to these BTs in attempts to provide standardization. This review explores the role of methane/hydrogen and also gastric emptying carbon-13 BTs in FGIDs, specifically irritable bowel syndrome (IBS), IBS-like symptoms, and functional dyspepsia. We review the role of BTs in FGIDs and how they not only provide diagnostic information, but the pathophysiologic mechanisms that drive these disorders. This, ultimately, can provide guided treatment for these disorders that at times can be difficult to manage.

Key words: Hydrogen methane breath test. Functional gastrointestinal disorder. Small intestinal bacterial overgrowth. Sulfate-reducing bacteria. Irritable bowel syndrome. 13C breath test.

INTRODUCTION

In the field of gastroenterology, breath tests (BTs) are used as diagnostic tools that allow indirect, non-invasive, and relatively less cumbersome evaluation of several disorders by quantifying the appearance in exhaled breath of a metabolite of a specific substrate administered.

The history of breath analysis goes back to the time of Hippocrates. He asked his students to detect diseases by the smell of the breath of patients, like the smell of rotten apples indicated diabetic ketoacidosis, and the smell of urine indicated renal failure. Further with more achievements in science and technology, in the 18th century Lavoisier (father of chemistry) discovered CO₂ gas in

exhaled breath, and the alcohol BT was first initiated in the early 1950s¹.

The scientification of medicine and gastroenterology began during the latter part of the 19th century when the discovery of bacterial causes of disease revealed the potential of research in the discovery of new knowledge. It was Linus Pauling's milestone discovery of 250 unique substances present in exhaled breath that offered promising insight into breath testing².

In the 1970s, the concept of lactose malabsorption was then evaluated using hydrogen breath testing. Newcomer and his associates in 1975 studied lactose malabsorption by analyzing breath H₂ and CO₂ labeled lactose and blood sugar³. They showed the supremacy of

H₂ breath measurement for the detection of lactose malabsorption. In 1978, Bond and Levitt further used breath H₂ to conclude that some disaccharides remain unbroken and unabsorbed in small intestine due to incomplete digestion. They concluded from the result of a change in H₂ concentration in expired air after ingested sugar reached colon undigested and intact⁴. At that time, H₂ breath testing replaced blood tests where lack of blood glucose response to lactose malabsorption lead to conclusion that lactose was not digested.

Today, various hydrogen, methane, and carbon BTs are available for diagnosing multiple gastrointestinal (GI) disorders. The aim of this review is to provide insight into the principles, methods of analysis, and performance parameters of various BTs that are available for evaluation of functional GI disorders, with a focus on hydrogen and methane-based breath testing and carbon BTs.

INDICATIONS FOR HYDROGEN AND METHANE BREATH TESTING

BTs are important for in the evaluation of patients with abdominal pain, bloating, flatulence, and altered bowel movements (diarrhea and/or constipation). Irritable bowel syndrome (IBS), a common functional GI disorder with high global prevalence (11.2%) and carbohydrate malabsorption, can present with such symptoms⁵⁻⁷.

IBS AND IBS-LIKE SYMPTOMS

Over the last decade, it has been hypothesized and proven through qualitative and

quantitative tests that gut flora play a role in the pathophysiology of IBS⁸⁻¹⁰. The increase in the study of gut bacteria has led to grow evidence for a pathophysiological mechanism in the development of IBS based on the presence of alterations in small intestinal bacterial populations¹¹⁻¹³. One hypothesis is that excessive bacteria reside in the small bowel secondary to motility abnormalities in patients with IBS. This is termed as small intestinal bacterial overgrowth (SIBO)¹⁴.

SIBO is defined as overgrowth of bacteria $\geq 10^5$ colony-forming unit (CFU) per mL of jejunal aspirate¹⁵. Some suggest that a colony count of $\geq 10^3$ CFU/mL of jejunal aspirate should also be considered as SIBO, especially in irritable bowel syndrome (IBS)¹⁶.

The SIBO hypothesis proposes that it is this expansion of bacteria into the small intestine that leads to symptoms including bloating, abdominal discomfort, and changes in stool form¹⁷. Using lactulose breath testing and small bowel aspiration, a significant of subjects diagnosed with IBS has SIBO¹⁸.

While small bowel aspiration is considered the gold standard test to diagnose SIBO, quantification of hydrogen and methane gas in breath samples remains the most inexpensive, non-invasive, and widely available test for the diagnosis of SIBO¹⁶. Human cells are not capable of producing methane or hydrogen gas¹⁹. The presence of these gases in the human breath exclusively signifies the metabolism of carbohydrate residues by gut bacteria, their absorption from the gut into the systemic circulation, and expiration through lungs (Fig. 1). Based on this principle, when lactulose or glucose is given to a patient with

FIGURE 1. Schematic drawing showing the principles behind breath testing for small intestinal bacterial overgrowth.

presumed SIBO, the changes in hydrogen and methane concentrations in sequential breath samples will indicate the presence of SIBO²⁰.

The accuracy of BTs in diagnosing SIBO has undergone significant debate. This debate is largely driven by the possibility that the rise in hydrogen and methane could be coming from colonic bacterial fermentation instead of fermentation occurring from excessive bacteria in the small intestine. Two particular studies looked at this. Yu et al. performed a study that looked at radiolabeled lactulose BT in IBS patients and found that at the time of increase in hydrogen, there was an accumulation of the radionucleotide in the cecum²¹. Lin and Massey looked at glucose BTs and concurrent scintigraphy and found that at 90 min the head of the bolus reached the cecum²². This argument has been refuted by the fact that these studies rely on the arrival of the medium to the cecum to determine orocecal transit (5% arrival technetium in cecum)²³ or “head of the labeled bolus.”²⁴ However, what this suggests is that the majority of the medium is still in the small intestine and is being actively fermented by the small bowel flora; hence, the rise of breath gases is not

necessarily due to cecal bacterial fermentation. Moreover, fermentation of sugar by cecal bacteria does take some time, and therefore, the arrival of the medium in the intestine does not equate fermentation²⁵.

In a systematic review, Khoshini et al. found 11 studies that have attempted to validate the accuracy of breath testing in diagnosis of SIBO¹⁶. The sensitivity of glucose breath testing varied from 20% to 93% and specificity from 30% to 86%. The sensitivity of lactulose breath testing ranged from 31% to 68% and specificity ranged from 44% to 100%. In a recent comparative study, duodenal culture was positive in 62/139 (45%) patients with unexplained gas, bloating and diarrhea, and negative endoscopy, whereas glucose BT was positive in 38/139 (27%) patients. The sensitivity and specificity of glucose BT were 42% and 84%, respectively²⁴. In a recent meta-analysis of 19 studies including 888 healthy subjects, we showed that the specificity of the lactulose BT (90%, 95% CI 88-93%) is only modestly lower than glucose BT (98%, 95% CI 97-99%)²⁵. The large ranges of test characteristics of breath testing are due to striking differences in methodology in the included

studies as none of these studies used an identical approach¹⁸. This variability in methodology encompassed the preparation, substrate dosing, performance, and interpretation of breath testing. Therefore, to optimize patient care and research, a standardized evidence-based framework on breath testing was brought forward in 2017 by the North American consensus group²⁶.

Multiple patterns of hydrogen and methane production have also been described in the literature such as hydrogen predominant, methane predominant, mixed hydrogen/methane bacterial overgrowth, and flatline (non-methane and fixed hydrogen production) (Fig. 2)²⁷. Studies have shown that the type of bacterial colonization of the gut appears to be important in the expression of IBS symptom phenotype¹⁴.

Hydrogen-predominant SIBO

The link between enteric flora and a role in IBS symptoms has been long established in patients with IBS accompanied by a diarrheal component. In a study evaluating SIBO in 204 Rome II IBS patients, it was seen that in the group of patients with IBS-D, there were more hydrogen (H_2) producers during glucose breath testing¹³. An earlier study it was also demonstrated that the type of gas produced by IBS subjects on lactulose BT was predictive of their subtype of IBS. 84 subjects who met Rome I criteria for IBS with abnormal BTs were divided into three groups: constipation severity equal to diarrhea, diarrhea predominant, and constipation predominant. It was found in the diarrhea-predominant subjects with abnormal BTs, no methane excretion

was detected¹⁸. There are some data that suggest even a basal breath hydrogen in a fasting state may be higher in patients with IBS-D²⁸.

At present, an early rise in hydrogen levels ≥ 20 ppm above baseline within 90 min of the test is considered positive as recommended by the North American consensus statement²⁶. A late rise in hydrogen levels occurring after 90 min may be due to normal fermentation of sugar substrate by the colonic flora rather than bacteria in the small bowel.

Methane-predominant SIBO

Methane (CH_4) gas has been shown to inhibit intestinal transit in dogs by 59%²⁹. In human subjects, CH_4 positivity on BT has been associated with constipation. Patients with CH_4 -predominant bacterial overgrowth usually present with bloating and abdominal distention. However, they are 5 times more likely to have constipation as opposed to H_2 -predominant overgrowth. The excessive excretion of methane alone can be seen in IBS-C³⁰ while the severity of constipation directly correlated with the methane level.³¹ The choice of antibiotics for the treatment of SIBO differs between these two groups as the predominant methanogen in the human gut, *Methanobrevibacter smithii*, is resistant to many antibiotics³². At present, a methane level ≥ 10 ppm is considered positive as recommended by the North American consensus statements²⁶.

Flatline

When there is a flatline (non-methane and fixed hydrogen production) on breath testing,

FIGURE 2. Common patterns of hydrogen and methane breath testing. **A** shows a graph of a normal breath test with no evidence of excessive methane or early rise of hydrogen. The late rise in hydrogen is due to colonic fermentation. **B** shows an early rise of hydrogen within the first 90 min of the test which is positive for hydrogen-predominant small intestinal bacterial overgrowth (SIBO). **C** shows a graph that is positive for methane-predominant bacterial overgrowth. **D** shows a graph that is “flatline.” Image E shows a graph that is positive for hydrogen- and methane-predominant SIBO.

there is a concern for hydrogenotrophic bacteria. Consumption of hydrogen leads to low levels in exhaled breath. Meanwhile, methanogenic archaea are incapable of producing methane in the absence of hydrogen which is the main substrate for methanogenesis³³.

Sulfate-reducing bacteria are hydrogenotrophic and their overgrowth can lead to a flatline pattern. Overgrowth of sulfate-reducing bacteria is thought to play an important role in patients with IBS³⁴. An association was found between bacterial-derived hydrogen sulfide (H_2S) and visceral hypersensitivity. H_2S is known to act as gaseous neurotransmitters inducing the contraction of detrusor muscle in the urinary bladder³⁵. A study done by Banik et al. has shown that H_2S produced by sulfate-reducing bacteria may play a role in pathogenesis of SIBO. The author suggested that breath H_2S could be considered as potential noninvasive biomarker for diagnosis of SIBO among patients with IBS-D³⁶.

In a recent abstract by our group, we showed that in subjects that produce a flatline, they were positive for H_2S , using a new four gases (H_2 , CH_4 , H_2S , and CO_2) detection device. H_2S -positive subjects exhibited a diarrhea-predominant pattern³⁷.

Carbohydrate malabsorption

Undigested or poorly digested carbohydrates generate an osmotic force driving water into the lumen of the small bowel and leading to decrease transit times of bowel contents which then reach the colonic flora producing fermentation of this carbohydrate³⁸. This may result in symptoms including abdominal

pain, excessive gas, bloating, and variable diarrhea, especially in patients with visceral hypersensitivity³⁹.

IBS-like symptoms can also be seen in carbohydrate malabsorption⁴⁰. However, symptom profiles of these patients are non-specific and clinical history alone cannot differentiate carbohydrate malabsorption and IBS.

The principle behind carbohydrate malabsorption BT is similar to that behind BTs used to diagnose SIBO. Gut bacteria generally produce hydrogen gas during fermentation of carbohydrates. In bowel, bacteria can only do this when dietary carbohydrates are not absorbed in small intestine and stay as undigested material as it travels along the digestive tract into large intestine. Although some of the hydrogen gas produced by the bacteria is expelled as flatus or in making other molecules such as sulfides, acetate, and short-chain fatty acids, most of the gas is absorbed across the lining of the large intestine into bloodstream. The gas is then transported to lungs through the bloodstream and from blood it is exchanged into the airways of lungs and breathed out⁴¹. At present, any rise (early or late) in hydrogen levels ≥ 20 ppm above baseline during a 3-hour test is considered positive for the diagnosis of lactose or fructose malabsorption as recommended by the North American consensus statement.

A study done by Wilder-Smith looked at fructose and lactose malabsorption based on positive breath testing in patients with the diagnosis of functional GI disorders based on Rome III criteria. Malabsorption occurred in 45% with fructose, 32% with lactose, and 16%

with both⁴². Other studies reported a prevalence of fructose malabsorption in patients with the diagnosis of functional dyspepsia (FD) or unexplained GI symptoms between 40% and 73%⁴³. In patients with suspected IBS, it is estimated that up to one-third of patients may have dietary fructose intolerance⁴⁴.

It should be noted that in the presence of SIBO, fructose and lactose are prematurely exposed to excessive small intestinal bacterial composition that will lead to early fermentation and elevation of exhaled gases^{45,46}. Therefore, performance of a lactulose or glucose BT to rule out SIBO should be considered before carbohydrate malabsorption breath testing to minimize false-positive results²⁶. Nucera et al. further confirmed this by showing that the number of positive fructose BTs in IBS patients with positive lactulose tests dropped from 62% to 3% after 1 week of antibiotic treatment⁴⁷.

Sucrase insufficiency has also been identified as a cause of carbohydrate malabsorption that can cause IBS and IBS-like symptoms. Malabsorption of this disaccharide, sucrose, has been also been found to be causally involved in functional GI disorders (FGIDs)⁴⁸.

BTs and gastric emptying (GE)

GE can be measured directly or indirectly. Direct methods include echography, scintigraphy, and MRI⁴⁹. Scintigraphy remains the most cost-effective, simple, and widely available technique to confirm the presence of delayed GE. However, there exist alternative approaches for the assessment of GE such as

¹⁴C or the safer, non-radioactive ¹³C breath testing using octanoate, spirulina, or acetate incorporated into a solid or liquid meal⁵⁰. ¹³Carbon BTs have the advantage of avoiding radiation associated with scintigraphy.

The carbon BT technique is based on the principle that post-gastric substrate processing is uniform, and therefore, GE is the rate-limiting step of ^{13/14}CO₂ breath excretion. Once the meal reached the duodenal lumen, the ^{13/14}C is rapidly absorbed through the intestinal mucosa and oxidized to CO₂ in the liver. The appearance of ^{13/14}CO₂ in the breath after oral administration of ^{13/14}C depends mainly on the GE of the substrate into the duodenum (this is the rate-determining step). The other metabolic steps (absorption and oxidation) do not influence the rate of breath ^{13/14}CO₂ excretion (Fig. 3).^{51,52}

Different substrates used can be attached to different meal forms. ^{13/14}C-octanoate and ¹³C-spirulina are used to label the solid components of test meals and the acetate is utilized to label fluids. Given its safety profile and ease of use, it has been used to evaluate GE in patients with functional gastroduodenal disorders, mainly FD.

BTs AND FD

According to Rome IV criteria, FD is defined as the predominant presence of one or more symptoms including bothersome postprandial fullness or early satiation (postprandial distress syndrome or [PDS]), epigastric pain (epigastric pain syndrome or [EPS]), or epigastric burning, occurring for the past 3 months with the onset occurring at least

FIGURE 3. General methodology of breath test analysis using ^{13}C -labeled substrates for the study of gastric emptying⁵².

6 months before diagnosis, in the absence of evident structural disease^{53,54}. Globally, the prevalence of FD has been noted to vary between 11% and 29.2%⁵⁵.

The pathogenesis of FD is likely multifactorial and still unclear; however, impaired GI motility with delayed GE, impaired gastric accommodation after ingestion of a meal, and gastric and duodenal hypersensitivity to distension and intraluminal contents seem to play a role in a subset of patients⁵⁶.

A study done by Haag et al. looked at the GE time measured by ^{13}C -octanoic BTs and asymptomatic blood donors, symptomatic blood donors (with recurrent abdominal pain/discomfort), and subjects diagnosed FD or IBS. Symptoms were assessed using a bowel disease questionnaire and the most bothersome symptom complex identified (dysmotility-type dyspepsia, ulcer-type dyspepsia, or IBS). GE time ($t_{1/2}$) was significantly longer in blood donors with FD symptoms (99 min) and FD patients (110 min) compared with asymptomatic controls (76.7 min) but was not significant in subjects with IBS symptoms subjects diagnosed with IBS⁵⁷.

A more recent study done by Vanheel et al. investigated the presence of gastric sensorimotor dysfunction and its possible association with symptom scores in the PDS, EPS, and overlap groups as defined by the Rome III criteria. 284 FD patients underwent a ^{14}C -octanoate BT to assess GE. The prevalence of gastric hypersensitivity, impaired gastric accommodation, and delayed GE in the total entire study was ~37%, 37%, and 23%, respectively, in concordance with previous reports⁵⁸⁻⁶⁰. The study did not find any differences between the Rome III subgroups in the prevalence of delayed GE; along with no differences between gastric hypersensitivity and impaired gastric accommodation. The gastric half-emptying time, however, was significantly higher in the overlap group compared with the EPS group⁶¹.

Unfortunately, the relationship between GE and FD remains controversial. Unlike the two above studies, Shindo et al. have reported slower GE in PDS patients compared with EPS patients⁶². Other studies also did not detect an association of delayed GE with the subgroups^{63,64}.

CONCLUSION

Breath testing can be helpful in determining the pathophysiologic mechanism behind FGIDs. At present, in clinical practice, BTs are being performed with various substrates for a range of established and unestablished indications (e.g., SIBO, carbohydrate malabsorption, and GE time).

Hydrogen and methane BT have long been used in the evaluation of functional GI disorders. With the new North American consensus guidelines, there now exists standardization in its investigation and interpretation²⁶.

As with the many other modalities evaluating GE and FD, carbon BTs and its significance and utility are this functional GI disorder will need further investigation.

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