EDITORIAL

A Breath of Fresh Air

Breath tests have become frequently used in diagnosing a variety of digestive diseases. They are appealing because they provide a simple, safe, low-cost way to get information on intestinal function that would otherwise be difficult to obtain. The downside, however, is that there are significant challenges with accurate analysis of the results that may lead the clinician astray.

Breath Test Basics

The general principle of breath tests is that bacterial metabolism of a test substance releases a signal that diffuses from the intestinal lumen into the circulation and eventually can be measured in exhaled air. The interaction between test substance and the gut bacteria (or microbiome) occurs either when the test substance is "too low" in the gastrointestinal tract (eg, malabsorption) or if bacteria are "too high" (ie, small intestinal bacteria overgrowth [SIBO]). Fermentation then releases a signal that may be a radioisotope (^{13}C or ^{14}C) or hydrogen gas (H_2). Because mammals do not produce H_2 de novo, the only source of H_2 in humans is bacterial metabolism of carbohydrates. Therefore, H_2 provides a nonradioactive signal that can be measured with gas chromography.[1,2]

One of the earliest available breath tests was the ^{14}C glycocholate breath test, which evaluated for bile acid malabsorption and/or bacterial overgrowth.[3] Bacterial deconjugation of the glycocholate (bile acids too low) occurs in cases of ileal dysfunction or bile acid malabsorption; it also occurs in in SIBO leading to deconjugation in the jejunum (bacteria too high). Although this was an ingenious attempt to take advantage of bile acid physiology in a clinically relevant setting, there were several drawbacks: it was a cumbersome and time-consuming test; and ^{14}C glycocholate breath test had drawbacks related to risk of radiation because ^{14}C has a half-life of 5730 years. Most importantly, interpretation of the results (ie, malabsorption vs SIBO) depended on a predictable small intestinal transit time.

Intestinal Transit Time

Intestinal transit time is the most important factor that impacts the accuracy of breath tests.[4] Several surrogate measures of intestinal transit have been proposed including time and the pattern of H_2 production. It has been customary to assume arbitrarily normal time of 90–180 minutes for orocecal transit time (OCTT) in most studies and many clinical laboratories that do breath tests regularly. However, several studies have suggested that normal transit time may be less than 90 minutes in healthy individuals, and furthermore it is problematic to assume that individuals having significant intestinal symptoms undergoing breath tests would necessarily have normal OCTT.

Another approach is to look for a double peak in the H_2 excretion curve; the early peak presumably represents small bowel metabolism (too high), and a later, larger peak an indicator of colonic metabolism. However, the double peak pattern is found infrequently and has not proved reliable. A single broad peak is much more common.[4,5] Bratten et al[6] showed that most patients with irritable bowel syndrome (IBS) and healthy control subjects met criteria for an abnormal lactulose hydrogen breath testing (LHBT) and the two groups are not well discriminated using this diagnostic method.

An alternative approach assuming intestinal transit time is to directly measure it independently with a simultaneous nuclear scintigraphy performed at the same time as the breath test. The H_2 signal is interpreted in correlation with intestinal transit measured by the scintigraphic OCTT.[7] Using this approach, Sellin and Hart[7] found about one-third (8 of 25) of patients had rapid intestinal transit with OCTT of $<$30 minutes. Riordan et al[5] subsequently demonstrated that the combined approach significantly increased sensitivity and specificity of breath tests to differentiate SIBO from rapid transit.

Breath Tests and Small Intestinal Bacteria Overgrowth

H_2 breath tests (lactulose or glucose) have generally become the procedure of choice for diagnosing SIBO, replacing jejunal aspiration with quantitative cultures or a ^{13}C or ^{14}C radiolabeled breath test. Classic SIBO has been thought to be relatively uncommon and generally has identifiable risk factors. There is clearly overlap in symptoms between classic SIBO and what has been more recently diagnosed as IBS/SIBO, including diarrhea, bloating, and abdominal pain. All of these symptoms are nonspecific.

Small Intestinal Bacteria Overgrowth: Lactulose Versus Glucose?

The recent spate of studies looking at SIBO and IBS has generally used LHBT, assuming transit times of 90–180 minutes.[8–10] Curiously, LHBT was initially used to measure OCTT, given that this synthetic disaccharide cannot be absorbed in the small intestine. However, there was a gradual shift to assume that lactulose could be a signal for SIBO occurring primarily in the distal small intestine. Glucose presumably would detect

proximal SIBO, but miss distal SIBO because of its rapid jejunal absorption. These studies demonstrated a high proportion of positive breath tests (presumed to be SIBO) in the IBS population.[8–10] This was in distinct contrast to jejunal aspirates, which are not more frequent in IBS than in control subjects.[11] Reports of the accuracy of LHBT and glucose hydrogen breath testing (GHBT) have varied widely. A recent expert working group concluded that the diagnostic accuracy of GHBT was 71.7%, whereas that of LHBT was 55.1%.[12]

Lactulose: Orocecal Transit Time or Small Intestinal Bacteria Overgrowth?

Over the last several years, there has been increasing evidence demonstrating that a lactulose breath test cannot distinguish between OCTT and SIBO. Yu et al[13] performed a combined LHBT with nuclear scintigraphy in 40 patients with IBS as defined by Rome II criteria; 63% had an abnormal LHBT at 180 minutes and 35% at 90 minutes. The orocecal transit time based on scintigraphic scanning ranged from 10 to 220 minutes and correlated with IBS subtype (ie, diarrhea predominant). At the time of increase in H_2, the percent accumulation of (^{99}m) Tc in the cecum was $\geq$5% in 22 of 25 (88%) cases. These findings demonstrated convincingly the futility of diagnosing SIBO with a LHBT and presumed intestinal transit times.[13,14]

Glucose: Small Intestinal Bacteria Overgrowth or Rapid Intestinal Transit?

If lactulose is not a reliable indicator for SIBO, then what about glucose? One of the dogmas of intestinal transport physiology is that, with the exception of rare congenital disorders, glucose is avidly and rapidly absorbed through sodium glucose cotransport mechanisms primarily in the jejunum and that glucose malabsorption does not occur. However, a study combining GHBT with nuclear scintigraphy demonstrated a positive H_2 signal combined with rapid intestinal transit as documented by the arrival of technetium sulfur colloid into the colon.[7] In contrast, a normal transit time with a positive H_2 signal reliably predicted SIBO. Interestingly, most patients with rapid transit in this study had a concomitant autonomic neuropathy, such as diabetes or amyloidosis.

In this issue of *Clinical Gastroenterology and Hepatology*, Lin and Massey[15] extend these observations with a large retrospective series of GHBTs combined with nuclear scintigraphy in 139 patients with a variety of gastrointestinal complaints. They concluded that 52% had true SIBO, whereas almost half had a false-positive H_2 signal because of rapid intestinal transit. This series included a significant proportion of individuals with surgery on esophagus, stomach, or small bowel, which may have skewed the results. Those with upper gastrointestinal surgery had a 65% false-positive; the nonsurgical group had a smaller (13%) false-positive proportion.

The differences in small bowel transit time among the groups were striking. The false-positive (rapid transit) group had a mean OCTT of 18 minutes, whereas the true-positive group with SIBO had a mean transit time of 79 minutes, and the true-negative breath tests had a transit time of 86 minutes. The authors examined whether shortening presumptive OCTT to 30 minutes would differentiate true SIBO from the rapid transit cases, but they were not able to separate the two groups out even with the assumption of a shorter OCTT.

This study confirms the previous observation[7] that it is possible to malabsorb glucose. The most probable explanation is that rapid transit creates flow dynamics within the intestinal lumen that severely limits mucosal contact time, preventing intestinal absorption of glucose. If this can occur with glucose, it also raises the possibility that dysmotility may lead to small bowel malabsorption of other poorly absorbed nutrients.

The Future of Breath Tests for Small Intestinal Bacteria Overgrowth

If both glucose and lactulose are unreliable markers for breath testing for SIBO, what strategies are reasonable for the clinician to consider? Empiric therapy with antibiotics is attractively simple but may lead to repeated courses of expensive antibiotics and unsatisfactory response.[4] Lin and Massey suggest that a positive GHBT be followed by a repeat breath test combined with nuclear scintigraphy. However, it may be more effective and efficient to combine the tests initially. This depends on the time and cost involved for patients and medical staff. For example, the ability to coordinate simultaneous hydrogen breath testing with a nuclear medicine imaging is not trivial and Medicare reimbursement for scintigraphy for 2015 is $301.84. It remains to be determined whether it would be more efficient to combine the breath test and scintigraphy initially.

Irritable Bowel Syndrome: Small Intestinal Bacteria Overgrowth and Beyond

Breath testing demonstrates increased bacterial fermentation in IBS; however, the conventional breath testing does not clearly delineate whether this is caused by SIBO or increased colonic carbohydrate metabolism. Several studies, including those of Lin and Massey, emphasize that the latter may be more frequent than previously recognized. A recent study measuring intestinal pH and short-chain fatty acids also suggests that patients with IBS may have increased bacterial fermentation in the colon, but not the small intestine.[16]

The last few years have brought a wealth of information on motility, the microbiome, barrier function, the effect of antibiotics, bile acid metabolism,[17] and diet on intestinal function. Much of it is akin to the old tale of the three blind men and the elephant (ie, focusing on only one factor in an incredibly complex system). It is critical to delineate which factors are primary and which are secondary. It is hoped that future studies will be able to synthesize this information into a comprehensive model of intestinal function in health and disease.

JOSEPH H. SELLIN, MD
Baylor College of Medicine
Houston, Texas

References

1. Levitt MD. Production and excretion of hydrogen gas in man. N Engl J Med 1968;281:122.
2. Bond JH, Levitt MD. Effect of dietary fiber on intestinal gas production and small bowel transit time in man. Am J Clin Nutr 1978;31(Suppl 10):S169–174.
3. Fromm H, Hofmann AF. Breath test for altered bile-acid metabolism. Lancet 1971;971:621–625.
4. Saad RJ, Chey WD. Breath testing for small intestinal bacterial overgrowth: maximizing test accuracy. Clin Gastroenterol Hepatol 2014;12:1964–1972.
5. Riordan SM, McIver CJ, Walker BM, et al. The lactulose breath hydrogen test and intestinal overgrowth. Am J Gastroenterol 1996;91:1795–1803.
6. Bratten JR, Spanier J, Jones MP. Lactulose breath testing does not discriminate patients with irritable bowel syndrome from healthy controls. Am J Gastroenterol 2008;103:958–963.
7. Sellin JH, Hart R. Glucose absorption associated with rapid intestinal transit. Am J Gastroenterol 1992;87:584–589.
8. Shah ED, Basseri RJ, Chong K, et al. Abnormal breath testing in IBS: a meta-analysis. Dig Dis Sci 2010;55:2441–2449.
9. Pimentel M, Lezcano S. Irritable bowel syndrome: bacterial overgrowth–what's known and what to do. Curr Treat Options Gastroenterol 2007;10:328–337.
10. Pimentel M, Lembo A, Chey WD, et al; for the TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22–32.
11. Posserud I, Stotzer PO, Björnsson ES, et al. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. Gut 2007;56:802–808.
12. Gasbarrini A, Corazza GR, Gasbarrini G, et al. Methodology and indications of H2 breath testing in gastrointestinal diseases: the Rome consensus Conference. Aliment Pharmacol Ther 2009;29(Suppl 1):1–49.
13. Yu D, Chesseman F, Vanner S. Combined orocaecal scintigraphy and lactulose hydrogen breath testing demonstrate that breath testing detects orocaecal transit, not small intestinal bacterial overgrowth in patients with IBS. Gut 2011;60:334–340.
14. Connoly L, Chang L. Selected summaries. Gastroenterology 2011;141:1118–1121.
15. Lin EC, Massey BT. Scintigraphy demonstrates high rate of false-positive results from glucose breath tests for small bowel bacterial overgrowth. Clin Gastroenterol Hepatol 2016;14:203–208.
16. Ringel-Kulka T, Choi CH, Temas D, et al. Altered colonic bacterial fermentation as a potential pathophysiological factor in irritable bowel syndrome. Am J Gastroenterol 2015;110:1339–1346.
17. Vijayvargiya P, Camilleri M, Shin A, et al. Methods for diagnosis of bile acid malabsorption in clinical practice. Clin Gastroenterol Hepatol 2013;11:1232–1239.

Correspondence
Address correspondence to: Joseph H. Sellin, MD, Baylor College of Medicine, Houston, Texas 77555. e-mail: sellin@bcm.edu.

Conflicts of interest
The author discloses no conflicts.

Most current article

http://dx.doi.org/10.1016/j.cgh.2015.10.027