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Hydrogen breath test and intestinal gas production

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Abstract. **Despite extensive use in clinical practice, difficulties regarding interpretation of hydrogen breath test are still very frequent, even on research grounds. After the administration of a non-absorbable sugar, such as lactulose, an increase of breath hydrogen and methane is evident; this phenomenon is considered an index of colonic fermentation. It is not clear, however, if the levels of these compounds correlate with the presence and severity of functional symptoms, nor if they accurately reflect gas production at colonic level. So far, apart from flatulence, we have no indications regarding the ability of hydrogen or methane to act as biomarkers of intraluminal events. On the other hand, it has been shown that in functional bowel disease a colonic dysbiosis exists, and that the modification of bacterial flora might result in a reduction of symptom severity. Consequently, it is not clear if hydrogen and methane colonic production could have a role in the pathophysiology of functional complaints, but it is possible that other fermentation products should be taken into consideration, such as acetate, propionate, and alcohol.**

Keywords:
Breath test, Hydrogen, Methane, Colonic fermentation, Bloating.

Five years ago, the activities of a Working Team aimed at producing data for a Consensus Conference on the clinical application and accuracy of the hydrogen breath test started and in 2009 an articulated paper summarizing the statements was published[1]. The need for a global reassessment of the indications, methodology and, more extensively, the clinical utility of the test arose from many criticisms: despite extensive use in clinical practice, controversial and divergent results, difficulties regarding interpretation of the tests and sometimes erroneous conclusions were frequent, even on research grounds. A previous Italian survey, published in 1997, stigmatized the presence of many methodological issues among gastroenterological centers[2], but this paper was not followed by any standardization. The aim of the Rome Consensus was, therefore, to establish the use, indications and methodology of the test in order to define a correct approach. In the last few years, a considerable reduction in the absolute number of scientific papers dealing with the hydrogen breath test was evident and the reason can be found in the lack of effort aimed at improving the accuracy of the test or at defining new clinical applications. Under this light, functional symptoms due to alteration of intestinal gas production, possibly linked to intestinal microbiota alterations, such us bloating, abdominal discomfort, abdominal distention, increased borborygmi, might be studied with the hydrogen breath test. Intending "overgrowth" as the numeric increase of bacterial population, the term "dysbiosis" defines the modification of the normal composition and activity of the microbiota, configuring a pathologic condition for the host. In IBS there is a clear evidence of qualitative modifications of intestinal microbiota, while the few studies reporting quantitative data showed negative results[3-5]. The term dysbiosis thus seems more appropriate.

The importance of functional complaints in clinical practice and, in particular, how frequent bloating is, is well known as also shown by a recent Italian survey on chronic constipation[6]. It is conceivable that in a subgroup of bloaters the modification of bacterial flora might result in a reduction of bacterial gas production and a consequent reduction of symptom severity. Anecdotal cases of bloater patients successfully treated with antibiotics are reported in the medical literature[7], and it is common experience to encounter them. This makes it difficult to categorically exclude that, in such a subgroup of patients, the modification of bacterial flora fermentation is not the target of treatment and, consequently, bacterial fermentation capacity is not an appropriate target of a diagnostic test. Oral administration of lactulose, a non absorbable sugar, increases bacterial fermentation at colonic level in a dose-de-

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pendent manner[8,9]. However, if we calculate breath hydrogen excretion per g of administered substrate, the rate of production is the same, suggesting that this parameter should be considered as a characteristic of that patient, harbouring that specific microbiota[9]. As intestinal gas production strictly correlates with breath excretion[10], the calculation of the area under the time-concentration curve may offer a numeric quantification of this parameter.

In an unselected group of patients with functional gastrointestinal disorders and bloating, we showed that cumulative breath hydrogen excretion is higher than healthy volunteers[11]. However, this result was not subsequently confirmed by other studies[12], and even by our group[13], suggesting that other variables should be considered. In the relationship between intraluminal events and symptom occurrence, it is obvious that, first of all, visceral sensitivity plays a pivotal role, as we recently showed in the subgroup of intolerant patients with lactose malabsorption[14]. However, to rule out the possibility that the measurement of the parameter reflecting the biologic event was imperfect, we modified this calculation in order to optimize its accuracy. Considering the 4-hour period from the oral administration of the substrate makes the parameter strictly dependent on the transit of the substrate. Accordingly, we calculated the AUC for a 4-hour period starting from the arrival of the substrate in the cecum[15]. This modification makes it possible to significantly improve the accuracy of the measurement, as cumulative breath hydrogen excretion was significantly higher in patients with severe flatulence, a symptom exclusively dependent on intestinal gas production[16], than in non flatulent patients. Unfortunately, cumulative breath hydrogen excretion did not correlate with flatulence severity and it was not possible to show a significant difference between bloater and non bloater patients. Similarly conflicting results were also evident when considering a group of IBS patients[15] and, taken together, these observations make us doubtful about the accuracy of the test and its clinical utility.

The real question, however, is whether hydrogen and/or methane cumulative breath excretion are really accurate biomarkers of colonic fermentation. Accordingly, simultaneous breath and rectal sampling after oral lactulose administration was performed, in order to clarify gas kinetics at colonic level. Hydrogen and methane cumulative breath excretion and cumulative rectal production were not significantly correlated and, more interestingly, while every patient who produced hydrogen at colonic level showed hydrogen excretion in the breath, a considerable number of patients showed methane production at colonic level, but not breath methane excretion. This result excludes the use of breath methane as a biomarker of colonic events[17]. Finally, both hydrogen and methane cumulative colonic production did not correlate with symptom severity, nor with stool characteristics.

These results, if confirmed, exclude a role of hydrogen and methane gas production in the pathophysiology of functional complaints, but also disagree with a putative role of methane on gastrointestinal transit[18] and IBS-C subtype[19,20]. It is possible that other fermentation products should be taken into consideration, such as acetate, propionate, and alcohol, but so far, apart from flatulence, we have no indications regarding the ability of hydrogen or methane to act as biomarkers of intraluminal events, apart from a subgroup of lactose malabsorbers, non hydrogen producing patients[21].

Conflict of interest

The Authors declare that they have no conflict of interests.

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