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LETTER TO THE EDITOR

Mean nocturnal baseline impedance in gastro-esophageal reflux disease diagnosis: Should we strictly follow the Lyon 2 Consensus?

Theodoros A Voulgaris, Georgios P Karamanolis

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Abstract

Clinical practice guidelines drive clinical practice and clinicians rely to them when trying to answer their most common questions. One of the most important position papers in the field of gastro-esophageal reflux disease (GERD) is the one produced by the Lyon Consensus. Recently an updated second version has been released. Mean nocturnal baseline impedance (MNBI) was proposed by the first Consensus to act as supportive evidence for GERD diagnosis. Originally a cut-off of 2292 Ohms was proposed, a value revised in the second edition. The updated Consensus recommended that an MNBI < 1500 Ohms strongly suggests GERD while a value > 2500 Ohms can be used to refute GERD. The proposed cut-offs move in the correct direction by diminishing the original cut-off, nevertheless they arise from a study of normal subjects where cut-offs were provided by measuring the mean value ± 2SD and not in symptomatic patients. However, data exist that even symptomatic patients with inconclusive disease or reflux hypersensitivity (RH) show lower MNBI values in comparison to normal subjects or patients with functional heartburn (FH). Moreover, according to the data, MNBI, even among symptomatic patients, is affected by age and body mass index. Also, various studies have proposed different cut-offs by using receiver operating characteristic curve analysis even lower than the one proposed. Finally, no information is given for patients submitted to on-proton pump inhibitors pH-impedance studies even if new and extremely important data now exist. Therefore, even if MNBI is an extremely important tool when trying to approach patients with reflux symptoms and could distinguish conclusive GERD from RH or FH, its values should be interpreted with caution.

Key Words: Mean nocturnal baseline impedance; Gastro-esophageal reflux disease; Lyon 2 Consensus; pH-impedance; Diagnosis

Core Tip: Mean nocturnal baseline impedance (MNBI) values add significant strength to a pH-impedance study, can help the clinician identify the correct explanation for a patient's symptoms and tailor the patient's therapy. Specific MNBI cut-offs have been proposed by several studies for characterizing patients with reflux symptoms. However, caution should be taken before applying the proposed cut-offs by the Lyon 2 Consensus as patient age, body mass index and origin may affect MNBI values.

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TO THE EDITOR

Clinical practice guidelines serve as leading publications that drive clinical practice and clinicians rely on them when trying to address most common questions. Despite their immense contribution to the facilitation of relevant clinical practice, researchers and clinicians should not use them uncritically and should always try to infer the rationale behind each recommendation. As far as gastro-esophageal reflux disease (GERD) is concerned, one of the most important position papers in this field is the one produced by the Lyon Consensus[1,2]. In those influential papers, use of mean nocturnal baseline impedance (MNBI) has been recommended as an important tool for a more solid diagnosis of GERD.

Esophageal baseline impedance is a marker of esophageal mucosal integrity. It reflects alterations of esophageal mucosal epithelium structure and/or function[3]. Distal esophageal baseline impedance inversely correlates with acid exposure time[4]. More specifically, MNBI has been proven to significantly aid GERD diagnosis[5]. The first position paper generated by the Lyon Consensus was published in 2017 and it adopted specific MNBI cut-offs that support GERD diagnosis[1]. Recently, an updated second version has been released[2]. According to the Lyon 2 Consensus, an MNBI cut-off of 1500 Ohms can be applied as adjunctive evidence of GERD diagnosis, while the diagnosis of GERD can be refuted in patients with an MNBI > 2500 Ohms[2]. The 1500 Ohms cut-off is significantly lower than the one reported in the Lyon 1 Consensus which was 2292 Ohms[1].

According to epidemiological data, approximately 30% of the world's population may at some point suffer from typical GERD symptoms[6]. Such symptoms may indeed be attributed after proper work-up to conclusive GERD, reflux hypersensitivity (RH) or functional heartburn (FH), while a significant proportion of patients will be categorized as having inconclusive GERD[2,7,8]. With respect to the latter category, the discriminative ability of MNBI is needed, in order to help the clinician correctly categorize the patient and to propose the proper treatment. According to previously published data, symptomatic patients with inconclusive GERD show higher MNBI values in comparison to patients with conclusive GERD, but lower than symptomatic patients with RH[9,10]. Additionally, patients with RH show lower MNBI values when compared to patients with FH[11].

The Lyon 2 amendment which lowered the MNBI value used as supportive evidence for GERD diagnosis was a first step in the right direction, as since the publication of the Lyon 1 Consensus, many studies have proved that significantly lower values than 2292 Ohms should be used for GERD diagnosis[12,13]. The proposed cut-offs were based on a pivotal and extremely important publication which unfortunately did not aim to discover MNBI values that could, with the best area under the curve, sensitivity/specificity, diagnose or refute GERD diagnosis, but rather to define the normal values among normal subjects without symptoms[14]. With this in mind, the authors selected the lowest normal value (mean-2 standard deviation) of normal subjects as an MNBI value that should be used as supportive evidence for GERD diagnosis and the highest one to refute it. In a recently published study, patients with inconclusive and conclusive GERD showed mean MNBI values < 1500 Ohms, while more than one study presented data where mean MNBI values in patients with RH and FH were below 2500 Ohms[11]. Therefore, in clinical practice, the proposed cut-offs, adopted from a study of normal subjects and not symptomatic patients, may direct the clinician in the direction of disorders belonging to the spectrum of reflux disease. Nevertheless, they cannot be used as firm evidence of a specific diagnosis. Values in the grey zone of 1500-2500 Ohms, most commonly observed in symptomatic patients, may be observed across all possible diagnoses suitable for a patient with reflux symptoms. Though as stated before, since there is a gradient of MNBI from patients with conclusive GERD to patients with FH, larger studies are required. Such studies should use ROC curve analysis to define specific cut-offs, and hence distinguish between every disorder in the reflux spectrum. Clearly MNBI possesses this ability, as multiple studies have indicated that mean MNBI values differ across conclusive GERD, inconclusive GERD, RH and FH. Unfortunately, the cut-offs proposed by the Lyon Consensus 2 statement do not possess this discriminative ability.

It should be noted that several published papers have used receiver operating characteristic (ROC) curve analysis to propose specific MNBI cut-offs for conclusive GERD diagnosis. A previous study from the United Kingdom showed that the best cut-off for conclusive GERD diagnosis was 1278 Ohms, while in a study from China of patients with refractory GERD symptoms, a cut-off of 1941.8 Ohms was shown to refute conclusive GERD[11,13]. Differences in MNBI values in

the abovementioned studies can be explained by the same pivotal study by Sifrim *et al*[14] which proved that regional MNBI differences exist. Moreover, in a second study the authors included patients with symptoms refractory to proton pump inhibitors (PPIs), but not having a previous diagnosis of conclusive GERD. In the study of normal subjects, a trend towards different MNBI values among different age groups was also shown. This was further supported by the British study that presented data that even among symptomatic patients MNBI is independently affected by age and by body mass index (BMI)[11]. For these reasons, application of the proposed cut-offs by the Lyon Consensus should not be universally adopted. Thus, when using MNBI values to diagnose GERD with greater confidence, clinicians who interpret pH-impedance studies should adopt discriminating MNBI values provided by ROC curve analysis from studies carried out in their region and not those provided by the Lyon 2 Consensus. Furthermore, in the future, new MNBI values provided by larger studies, corrected by age and BMI may be even more accurate in discriminating symptomatic patients with conclusive GERD, inconclusive GERD or RH.

Finally, it must be stated that all the abovementioned values were obtained from studies involving patients who were off-PPIs. Even if not stated clearly in the Lyon Consensus position paper, the proposed cut-off values refer to off-PPIs pH-impedance studies. As 30% of patients with GERD symptoms will have refractory GERD and should be submitted to an on-PPI study, a future position statement should include a recommendation for the value of MNBI in diagnosing refractory GERD among patients submitted to an on-PPI study. A recent large study proved the diagnostic ability of MNBI in this setting and provided specific cut-offs for refractory GERD diagnosis among patients submitted to the on-PPI study[15]. It should be noted that the proposed value from the study was higher than 1500 Ohms (1897 Ohms). In this specific setting, extra care should be taken by the pH-impedance interpreter; experimental data have shown that in entities setting GERD diagnosis, such as Barrett Esophagus, extremely low MNBI values are observed per se[16].

In conclusion, MNBI values add significant strength to a pH-impedance study, can help the clinician identify the correct explanation for a patient's symptoms and tailor the patient's therapy. However, caution should be taken before applying the proposed cut-offs by the Lyon 2 Consensus, due to the aforementioned limitations. However, it is clear that, when diagnosing a patient with reflux symptoms, MNBI possesses great diagnostic potential that is yet to be revealed.

FOOTNOTES

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