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Review Article

Advances in the Diagnosis of GERD Using the Esophageal pH Monitoring, Gastro-Esophageal Impedance-pH Monitoring, And Pitfalls

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Abstract

PH monitoring is not capable of detecting all types of reflux, especially when the amount of acid is very low or not at all in the refluxate. Multichannel intraluminal impedance-pH monitoring (MII-pH) is used as a new method to assess bolus transport. The types of reflexes including acid, weak acid and weak alkaline MII-pH is capable of distinguishing more reflux episodes based upon use of physical and chemical parameters of the refluxate, leads to a diagnosis of normal acid reflux from abnormal nonacidic reflux. 24-h oesophagal pH monitoring can be effectively used to assess the potential relationship between symptoms and refluxes. MII-pH is capable of distinguishing more reflux episodes based upon use of physical and chemical parameters of the refluxate, leads to a diagnosis of normal acid reflux from abnormal nonacidic reflux. It can be used to confirm gastro-oesophagal reflux episodes, where has a sensitivity and specificity for diagnosing GERD in comparison with endoscopy or pH-metry.

Introduction

Gastro-oesophagal reflux disease (GERD) is a digestive disorder, which is associated with the flowing back of acid and gastric contents to the oesophagus. GERD occurs when gastroesophageal reflux causes symptoms and/or unpleasant complications, and it is described as the most common chronic upper gastrointestinal disease.

A variety of GERD clinical symptoms are commonly seen in this condition include heartburn, regurgitation, nausea, vomiting, belching, heavy stomach feelings, and epigastric pain, while atypical symptoms are associated with hoarse voice, coughing, sore throat or ear pain [1]. It is noteworthy that typical GERD has been described to be troublesome heartburn with/without regurgitation [2] [3]

Proton-pump inhibitors are commonly used as a treatment option for patients with typical symptoms of the disease, which is more than 80% effective in treating esophagitis and heartburn [2] [4]. Empirical treatment with PPIs is a method that initially leads to an assessment of more individuals with persistent symptoms despite the use of repressive therapies [5]. The most common cause of failure is the misdiagnosis of GERD with various functional disorders [6]. It has

been revealed that weakly acidic reflux episodes are other causative factors involved in the symptoms of heartburn and regurgitation [7] [8].

Diagnostic evaluations of patients with PPI-refractory heartburn and uninvestigated PPI-responsive cases are required in the absence of alarm manifestation [2] [4]. Patients suffering from GERD are generally divided into two groups of non-erosive reflux disease and erosive esophagitis [9]. Methods such as diet and lifestyle changes and protein pump inhibitors (PPIs) are recommended for the treatment of NERD [1].

It has been reported that endoscopy revealed a small percentage of patients with erosive reflux disease, whereas most patients with endoscopy-negative heartburn are considered as non-erosive reflux disease. The criteria for this attitude is described as abnormal results in pH or impedance-pH monitoring, while the normal results and unfavourable response to a PPI are categorised as functional heartburn [2] [10] [11].

Functional heartburn (FH) treatment is most commonly performed with an individual approach and is mostly an experimental therapy because the poor response to the treatment of acid suppression is abundant in which the psycho-pathological component is also present. Nevertheless, it can be said that monitoring heartburn in patients who are diagnosed with non-erosive reflux disease will be an important factor in distinguishing these individuals from those who have true FH [12] [13]. Other methods other than endoscopy should be used for monitoring of gastro-oesophagal reflux. Gastro-oesophageal refluxate, independent of mucosal lesions, is initially performed using PH monitoring in the distal oesophagus. This method is routinely used as a gold standard for diagnosis and monitoring of treatment interventions [5]. PH monitoring is not capable of detecting all types of reflux, especially when the amount of acid is very low or not at all in the refluxate. Multichannel intraluminal impedance-pH monitoring (MII-pH) is used as a new method to assess bolus transport and types of reflexes including acid, weak acid and weak alkaline [14]. The current paper was aimed to discuss the technical aspects in implementing PH monitoring and impedance-pH monitoring techniques for the detection of reflux.

Methods

We have collected all documents using a curated medical database such as PubMed, Scopus Embase, MEDLINE, Web of Science Core Collection, Google Scholar, etc.

Results and Discussion

A 24-h oesophagal pH Monitoring can be effectively used to assess the potential relationship between symptoms and refluxes. Oesophagal pH monitoring is routinely applied using catheter-based systems (Single sensor or Dual sensor) and recently without pH catheter (wireless Bravo pH capsule or OMOM PH capsule).

This method is performed in cases which do not respond to medication, where there are common GERD symptoms, such as heartburn and regurgitation. In terms of atypical GERD symptoms such as chest pain, cough, hoarseness, wheezing, and a sore throat or ear pain, if symptoms are caused by gastro-oesophageal reflux, monitoring of PH can be occasionally applied for determining therapeutic drug *effectiveness* against GERD, where it is effective in determining the association of times of reflux with atypical symptoms. This test is usually performed as part of procedures before performing an *antireflux operation* [15] [16].

A cutoff pH 4.0 is usually accepted by the most specialist for diagnosis of acid reflux episodes in both catheter-based and catheter-free devices due to the decreased pepsin's proteolytic activity in solutions with a pH higher than 4.0 and the reporting of symptoms of common reflux in intraesophageal pH below 4.0 [5] [17]. However, a pH of fewer than 4.0 units may be associated with the acid swallowing, and oesophagal exposure is likely to be overestimated. Furthermore, it has recognised that the proteolytic activity of pepsins is mainly needed for oesophagal mucosa damage [2] [18]. It should be into consideration that pepsin's proteolytic activity can be sustained up to pH 6.0 [19]. Moreover, healing of mucosal damage is achieved through reparative processes, whereas stopped at pH 6.5 [2] [20].

DeMeester score has been previously provided to quantify the *exposure* of the *distal oesophagus* to the acid based upon the use of six parameters where a DeMeester score > 14.72 shows reflux [5] [21], (Figure 1).

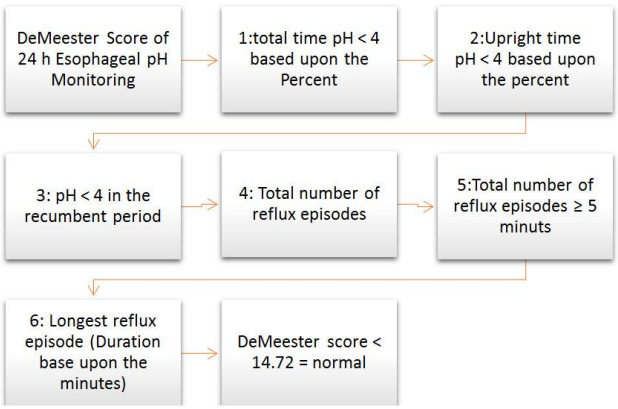

Figure 1: DeMeester Score of 24 h Esophageal pH Monitoring

The acid exposure time (percentage time pH < 4) has been applied as the most appropriate character to distinguish physiologic from pathologic reflux [22].

Both catheter and wireless-based pH monitoring is performed based on the use of the high acid concentration for the diagnosis of oesophagal reflux. This can quantitatively examine the exposure of distal oesophagal and the relationship of symptoms with acid reflux episodes. The extensive and prolonged use of this technique has made it as the gold standard in the diagnosis of GERD [5]. It should be noted, that cutoff of 4.0 has been rejected by some experts, and they believe that a cutoff value of 5 can be more effective in distinguishing healthy individuals from patients with reflux. Moreover, some studies have stated that the range of PH between 3 and 6 is better than determining just one threshold for detection [23] [24].

The normal values of the acid exposure time in different centres have been widely computed from 3.2 to 7.2 per cent. Additionally, the normative values of the acid exposure time have been reported in more than 30% of patients with reflux esophagitis [2] [22]. Accordingly, the acid exposure time is associated with limitation, therefore symptom–reflux correlation indexes have been provided to determine the association of reflux episodes with symptoms. Two important tools are available about this issue including symptom index (SI), symptom sensitivity index (SSI) and symptom association probability (SAP). The SI is described as the percentage of reflux associated symptom episodes which considered as positive when > 50%, representing at least half of the symptoms caused by GERD [5]. The SI is calculated by the following formula:

$$\frac{\text{Number of symptom episodes associated with pH} < 4}{\text{Total number of symptom episodes}} \times 100$$

This index is not able to assess the total number of cases of reflux in its calculation. (Hog et al., 2009). Moreover, there is a potential probability for false positive correlation results with an increase in the number of refluxes and a reduction in the number of symptoms. The symptom sensitivity index (SSI) has been developed as the percentage of symptom linked reflux episode based upon use of following formula [25] [26].

$$\frac{\text{Number of symptom episodes associated with pH} < 4}{\text{Total number of reflux episodes}} \times 100$$

SSI has increased by more than 10% the association of symptoms with reflux. The SSI and SI differ in their arbitrary cut off points and are based on the simultaneous frequency of reflux and symptoms, whereas the frequency of non-related reflux and episodes of symptoms are ignored in them [25] [27]. To eliminate these shortcomings, SAP can assess whether there are changes in the distribution of reflux episodes and symptoms during the monitoring by using statistical analysis, suggesting the meaningful probability of symptom–reflux correlation.

A SAP > 95 can be determined as positive (Figure 2), [5] [28] [29]. Studies have revealed that the evaluation of SAP and SI for non-acid reflux could provide a diagnostic value of between 16% and 33% in patients evaluated in the treatment of PPI [2] [30] [31]. Furthermore, off-PPI SAP positivity for non-acidic reflux events is only 10 to 12% of significant diagnostic value [2] [11] [32].

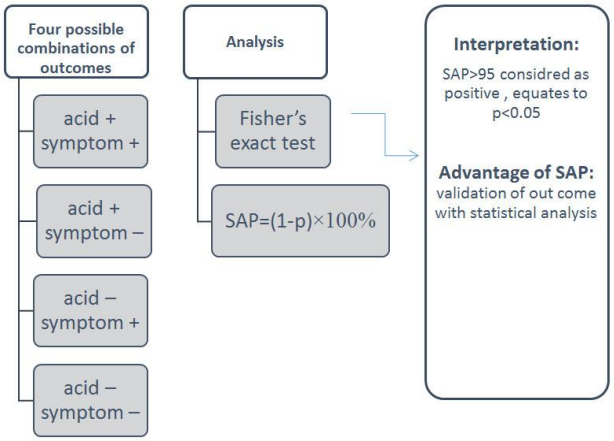

Figure 2: The analysis of contingency diagram of four possible combinations of reflux and symptoms for each segment (SAP)

The SI index is not able to assess the total number of cases of reflux in its calculation. A high amount of SI may be related to many parts of the patient's reflux episodes, and in this case, there is a great deal of chance. The superiority of the SAP is linked to its suitable statistical analysis [33].

The severity and clinical effect of the symptoms are not measured by SAP and SI, so nocturnal heartburn with unpleasant symptoms may be negative by using SAP and SI due to the calculation of these indicators based on the total 24-hour monitoring period.

Also, in low-reflux rate, the positive clinical value of SAP and SI is doubtful because the positive results in this case (low levels of reflux) are completely related to chance [2]. A study has suggested that SI and SAP are likely to be relevant in a patient with moderate to severe reflux. However, in patients with mild reflux, SI or SAP is not recommended for clinical decision making, such as whether the surgery should be performed [33] (Figure 2).

Despite the remarkable progress in the methods above, the lack of factual and reliable gold standard tests remains a problem, to which mentioned indicators are comparable [25] [34].

Two types of multichannel intraluminal

impedance (MII) are recommended for clinical evaluation that is a combination of MII with pH monitoring (MII-pH) and another MII conjugated with oesophagal manometry. MII has been initially provided to assess the movement of liquid, solid, and gas in the oesophagus without pH measurements [35].

MII-pH is another tool, which is developed with a combination of pH with impedance monitoring. This method is capable of distinguishing more reflux episodes based upon use of physical and chemical parameters of the refluxate, in which higher sensitivity and specificity for the diagnosis of GERD when comparing with other methods such as endoscopy or PH Monitoring. This method can be effective in determining acid reflux from non-acid reflux. Therefore, MII-pH indicates a situation that could rarely be affected by PPI treatment [36]. The advantages and disadvantages of MII-pH monitoring are summarised in Figure 3 [5] [37] [38]. As shown in the figure, this technique can analyse the symptoms associated with reflux in the event of acid suppression. As a result, negative results from MII-pH monitoring are very important for eliminating reflux compared to pH monitoring method [38] [39].

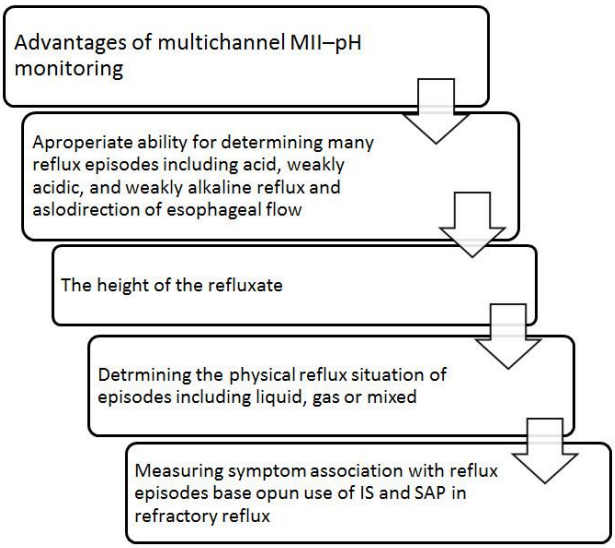

Figure 3: Advantages of multichannel intraluminal impedance (MII)

Impedance-PH Monitoring increases the diagnostic value of the GERD by 15–20% [40] [41]. Compared to a pH monitoring test, the most important feature of this test is the ability to evaluate patients with persistent symptoms, despite the use of PPIs, Impedance-PH Monitoring can also be effectively applied to the clinical evaluation of patients suffering from NERD and extra-oesophageal reflux symptoms (Figure 3) [41] [42] [42] [44].

To help grasp the gastroesophageal reflux disease, MII-pH may be a very suitable technique for diagnosis of non-acid reflux. However, the clinical practice of this method has some limitations that have been previously explained by different studies controversial results can be found in the clinical study:

1) Diagnosis of reflux episodes may be interrupted by lowering the impedance of MII-pH [45].

2) A catheter-based MII-pH monitoring will cause the patient's poor tolerance for monitoring pH-impedance [45].

3) Dietary changes during the MI-pH evaluation may lead to a poor predictor of gastroesophageal reflux [45].

4) Studies have reported a different prevalence of week- acid reflux. In the terms of PH impedance analysis, studies have shown that moderate and severe esophagitis exhibit similar or slightly higher levels of weakly acidic reflux than healthy subjects [46] [47]. On the other hand, very similar finding has been achieved in terms of distal esophageal exposure to weakly acidic reflux ate in patients with a non-erosive reflux disease (NERD) and esophagitis [48]. Regarding the available residence, the division of patients with weak acid reflux and physiological acid reflux as reflex, can raise one question, which Alkaline reflux is rarely seen [46] [49].

5) In context of esophageal bolus transit, measurement of bolus clearance with internal impedance does not determine the abnormal functioning of the esophagus, especially in terms of minor malformations [45].

6) The existing tool does not determine the reliability between small and large volumetric storage by with failed bolus transit, where it limits the clinical interpretation and physiological diagnosis of pathologic fluid from pathologic fluid [45].

7) There are other limitations that make the diagnosis even more difficult such as pathologic changes in the esophageal mucosa (esophagitis), which may reduce the baseline impedance values, and consequently the diagnosis of bolus movement in the esophagus will be complicated [16] [50]. Moreover, mucosal changes in the esophagus may also contribute to the disruption of the esophagus and transition of esophagus material, where eventually lead to the maintenance of liquids in the esophagus [50].

8) In patients with impotence syndrome, it is possible that the level of esophageal acid exposure time and reflux be increased using MII-pH, which may lead to problems with the diagnosis of GERD. The flow of gas or air in the MII-pH monitoring method can be performed manually due to the lack of automatic tools. Applying a meal to manometry has been revealed to be time consuming for diagnosis and treatment strategies in terms of rumination, where lead to dissatisfaction with the patient's intubation [45] [51] [52].

9) MII-pH is not appropriate to predict response to treatment. Based on available studies,

MII parameters for non-acid reflux are not predictive of patients with GER in response to PPIs [8] [53] [54]. However, the base impedance is mentioned that could be a good predictor for the response to treatment with PPI [45]. A stud indicated that showed that base impedance might have the necessary efficacy in predicting therapeutic outcomes in patients who suffer from sensitivity of the esophagus and functional heartburn [45] [55] [56].

10) MII-pH monitoring was not effective in the postoperative period of antireflux surgery, in addition, false-positive results of the MII-PH monitoring (50%) was reported that makes the test clinically meaningless in asymptomatic individuals with negative PH monitoring [46] [57] [58].

11) There are other limitations that make the diagnosis even more difficult such as pathologic changes in the esophageal mucosa (esophagitis), which may reduce the baseline impedance values, and consequently the diagnosis of bolus movement in the esophagus will be complicated [16]. Moreover, mucosal changes in the esophagus may also contribute to the disruption of the esophagus and transition of esophagus material, where eventually lead to the maintenance of liquids in the esophagus [50].

12) The base impedance on the MSI-pH has been clinically showed to have the utility of measuring at sleeping period when there is no swallow [45].

13) High cost than pH monitoring (about 4-fold).

14) Lack of normative data among children

Conclusion

A 24-h oesophagal pH Monitoring can be effectively used to assess the potential relationship between symptoms and refluxes. Both catheter and wireless-based pH monitoring have been associated with the high acid concentration for the diagnosis of oesophagal reflux. Leading quantitative examined the exposure of distal oesophagal and the association of symptoms with acid reflux episodes.

The wireless oesophagal pH test is associated with the patient's comfort and mobility, where have a significant effect for measuring over long periods of time.

MII-pH is capable of distinguishing more reflux episodes based upon use of physical and chemical parameters of the refluxate, leads to a diagnosis of normal acid reflux from abnormal nonacidic reflux. It can be used to confirm gastro-oesophagal reflux episodes, where has a sensitivity and specificity for diagnosing GERD in comparison with endoscopy or pH-metry. Evidence suggests that bolus clearance does not have the ability to diagnose effectively symptomatic patients from asymptomatic patients using intraluminal impedance, and consequently may be relatively limited in patients with minor manometric abnormalities [45].

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