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NEUROGASTROENTEROLOGY AND MOTILITY DISORDERS OF THE GASTROINTESTINAL TRACT (S RAO, SECTION EDITOR)

New Metrics in High-Resolution and High-Definition Anorectal Manometry

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Abstract

Purpose of Review To review recently published diagnostic methods that use high-resolution (HR-) or high-definition- (HD-) anorectal manometry (ARM) techniques.

Recent Findings The integrated pressurized volume (IPV) is a new measure based on spatiotemporal plots obtained from HR-ARM. The IPV may be clinically useful for improving the prediction of abnormal balloon expulsion test in patients with constipation and for discriminating patients with anorectal disorders from asymptomatic controls. Combination of IPV parameters was superior to conventional manometric parameters in predicting the responsiveness to biofeedback therapy. Moreover, several novel parameters including the HR-ARM resting integral, HR-ARM squeeze profile, and anorectal asymmetry index may each be useful as predictive factors for identifying patients with fecal incontinence.

Summary HR- and HD-ARM are increasingly performed worldwide for evaluation of anorectal function. Here, we describe new metrics whose clinical significance has not been fully established. Further standardization and validation of these metrics could provide clinically important new information and could help improve our understanding of the pathophysiology of anorectal disorders.

Keywords High-resolution anorectal manometry · High-definition anorectal manometry · Constipation · Fecal incontinence

Introduction

High-resolution (HR-) anorectal manometry (ARM) and high-definition (HD-) ARM have been introduced during the last decade to obtain more precise measurements of anorectal pressure by using closely-arranged solid-state sensors [1–4]. These manometry techniques have significant diagnostic value in the assessment of anorectal disorders, similar to those described for esophageal disorders [5]. Although HR-ARM provides greater fidelity and spatiotemporal topography than does conventional ARM, only few HR- or HD-ARM metrics exists for diagnosing dyssynergic defecation and fecal incontinence. In this review, we discuss several new metrics derived from the interpretation of HR- and HD-ARM data that may have clinical relevance.

Manometry is primarily used to measure the vigor of muscular contraction. Initially, only the pressure signals from each sensor in the manometry catheter were used [6], and the area under the curve (AUC) of colonic pressure waves was used to assess muscular contractility [7]. In the early 2000s, HR-manometry based on closely-spaced and often circumferentially-arrayed sensors was introduced. This new concept of utilizing spatiotemporal plots was first used for the assessment of esophageal pressure activity, which soon led to the development of new metrics such as the integrated relaxation pressure (IRP) and distal contractile

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integral (DCI) [5]. DCI is estimated from the length of the pressurized area during a designated period, and calculated by multiplying the length, pressure, and time [5]. These concepts were also applied to other areas such as HR- ARM and HD-ARM, where manometry is used to define physiological values.

Integrated Pressurized Volume: Basic Theory

The HR-ARM catheter from the Sandhill™ system (Sandhill Scientific, Denver, CO, USA) has 23 channels, each measuring 6 cm in length and equipped with sensors. A single sensor is placed at the rectum, 6 cm from the distal tip of the catheter. Radially-arranged sensors in four-quadrant directions are placed at 1-cm intervals so that each is placed at 5, 4, 3, 2, and 1 cm from the distal tip of the catheter. HR-ARM thus measures pressure values at 23 points at a sampling rate of 50 Hz (Fig. 1a); in other words, the pressure values are recorded 50 times per second. The number of pressure sensors and the sampling rate may differ depending on the manufacturer, but there is little difference in the calculation of pressurized volume overall.

Plotting the pressure data against time generates a two-dimensional plot as shown in Fig. 1b. In contrast, the HR-ARM data already have three dimensions—time, pressure, and position; therefore, making a 3-dimensional plot sounds logical. However, unlike those of time (0.02 s) and pressure (0.1 mmHg), the spatial resolution of the HR-ARM system is relatively low (1 cm), which reduces the accuracy of the three-dimensional pressure plot as shown in Fig. 1c. To overcome this problem, the pressure data are interpolated—i.e., new data points are mathematically generated within a range of data set according to the spatial axis in order to more smoothly connect each point. We used the cubic spline interpolation method [8], which is one of the most commonly used methods for interpolation. Implementation of this algorithm is not easy for physicians; however, commercial software such as MATLAB (MathWorks, Natick, MA, USA) enables the use of this algorithm with a single line of code as follows:

Interpolated = interp1(y,Original,yy,'spline').

which calculates the interpolated data from the original data according to the y-axis. Setting yy with 10 times higher spatial resolution than y generates a smoother three-dimensional pressure plot as shown in Fig. 1d.

Calculation of the volume under the three-dimensional pressure plot can be done by using double integrals of pressure with time and distance from the anus. This calculation can be simplified by adding the volume of rectangle pillars formed by the change in (Δ) time, Δ distance from the anus, and average

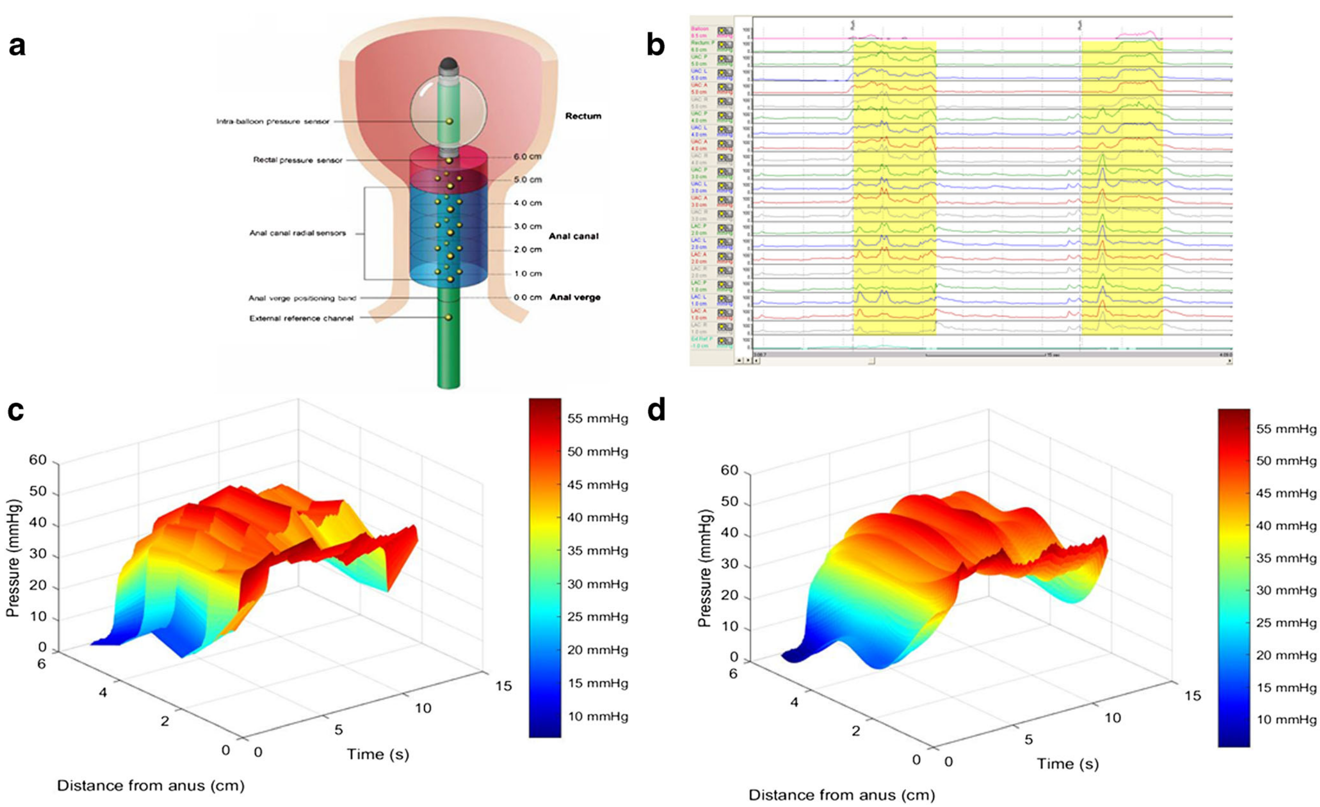

Fig. 1 High-resolution anorectal manometry (HR-ARM). **a** Structure of the HR-ARM catheter manufactured by Sandhill Scientific. **b** General manometrogram, which is a two-dimensional plot. **c** Three-dimensional pressure plot of raw pressure data from the catheter sensors. **d** Three-dimensional pressure plot of the interpolated data

pressure value within the area defined by the Δ time and Δ distance from the anus.

Clinical Application of Integrated Pressurized Volume (IPV) in Asymptomatic Healthy Volunteers

The current diagnostic criteria for functional defecation disorders include the diagnostic criteria for functional constipation and/or irritable bowel syndrome with constipation. Moreover, during repeated attempts to defecate, features of impaired evacuation must be made evident as demonstrated by two of the following three tests: abnormal balloon expulsion (BE) test, abnormal anorectal evacuation pattern with manometry or anal surface electromyography, and impaired rectal evacuation confirmed by imaging [9–11]. However, sometimes one of the three different tests cannot explain the findings of the other two tests or shows significant disagreement. [12, 13]. Therefore, we tried to devise a method that can unify and explain the result of other tests. IPV was developed as a parameter that may explain the result of the BE test and HR-ARM. As aforementioned, the catheter from the Sandhill system is arranged with pressure sensors of 1-cm length in four directions; therefore, we assumed a 1-cm length of pressurization along the rectoanal canal,and tried to find a factor that can predict the result of the BE test in 54 asymptomatic healthy volunteers [14]. Also, we measured the 1 cm vs. 4 cm ratio along the rectoanal canal and found that this variable showed the highest correlation with the result of the BE test. The ratio of the IPV in the upper 1 cm to that in the lower 4 cm could better predict the BE test result with (AUC 0.73, 95% confidence interval [CI] 0.53–0.92, $P = 0.04$) than without (AUC 0.70, 95% CI 0.54–0.87, $P = 0.07$) balloon distension [13]. The optimal cutoff value that maximizes both sensitivity and specificity was 0.590, at which the values for sensitivity and specificity were 0.848 and 0.625, respectively [13]. This finding was consistent with that of Bharucha et al., who also found that the outward force during balloon expulsion was the highest at 4 cm while using a latex balloon [15].

Clinical Application of IPV in Patients with Constipation

After applying the IPV to asymptomatic healthy volunteers, we further assessed its clinical utility in 204 male patients with constipation [16••]. Receiver-operating characteristic (ROC) analysis showed that the IPV ratio between the upper 1 cm and lower 4 cm of the anal canal was more useful in predicting BE time (AUC 0.74, 95% CI 0.67–0.80, $P < 0.01$) than the conventional anorectal parameters, including defecation index and rectoanal gradient (AUC 0.60, 95% CI 0.52–0.67, $P = 0.01$). Figure 2 shows the representative manometric traces in three-dimensional space in a patient in the early BE group (Fig. 2a) and a patient in the delayed BE group (Fig. 2b).

Anorectal manometric parameters are highly correlated with each other. The conventional multivariate model does not allow inclusion of predictors that correlate with ARM; therefore, a new method was needed to construct a predictive model when some variables were correlated. Principal component analysis (PCA) and partial least squares regression (PLSR) are the multivariable statistical methods that are commonly used to reduce the number of predictive variables and solve the multi-collinearity problem [17–19]. Specifically, PCA is a dimension reduction technique that transforms high-dimensional datasets into smaller-dimensional subspaces. Ratuapli et al. demonstrated that multiple manometric parameters affect the rectal BE time [20]; their PCA model yielded a sensitivity of 75% and a specificity of 75% for discriminating between healthy persons with normal BE time and either controls or patients with prolonged BE time. One drawback of the PCA technique is that it yields a standardized linear combination that only captures the characteristics of the predictive variables, and not showing how each predictive variable may be related to the target variable.

However, PLSR allows achieving of this balance and provides an alternative approach to the PCA technique. In our study, it was not necessary to understand the procedure to perform PLSR using MATLAB. We sought to confirm that the final equation derived from this PLSR technique would be able to predict the delayed BE test results with regression

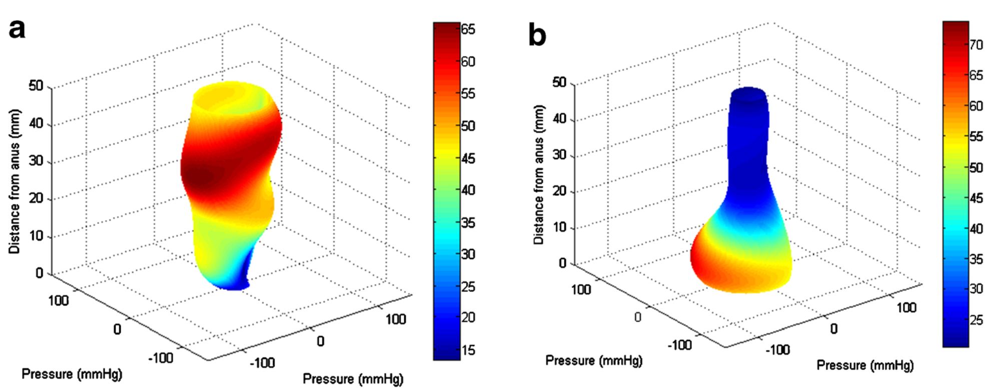

Fig. 2 Representative manometric cylinder plot during simulated evacuation in three-dimensional space from two patients—one in the early balloon expulsion (BE) group (**a**) and another from the delayed BE group (**b**)

coefficients (i.e., the importance of each variable) for IPVs. Lastly, the performance of PLSR using the derived equation could be investigated using the AUC of a ROC curve. Thus, sensitivity and specificity could be calculated by using the predictive equation derived from PLSR. As a result, PLSR analysis of a linear combination of IPV parameters yielded an AUC of 0.79 (95% CI 0.73–0.84, $P < 0.01$), with sensitivity of 70.8% and specificity of 80.7% when using a cutoff value of − 0.18 [14].

Future Approach for IPV

In a study on patients with constipation, IPV showed good correlation with the patients' symptoms, especially obstructive defecation symptoms in the anal canal [16••]. Importantly, we used these new parameters to identify the predictors for success of biofeedback therapy and other treatments for constipation [21•]. In this pilot study, we constructed a predictive model for biofeedback responders by applying the concept of IPV to patients who underwent HR-ARM; ROC analysis demonstrated that the IPV in the upper 1 cm of the anal canal and a linear combination of 8 IPV parameters using PLSR was a promising method with an AUC of 0.84. Thus, IPV may be applied for prediction of the effectiveness of biofeedback therapy [21•].

Other New Metrics in Fecal Incontinence

The conventional parameters including resting and squeeze sphincter pressures are based on the linear waveform of pressure and are measured from a single sensor on the manometry catheter. The resting and squeeze pressures are known to be different between patients with fecal incontinence and healthy controls. However, one study showed that there were no significant differences between patients with fecal incontinence and healthy controls when assessed with conventional resting and squeeze pressures [22].

Therefore, parameters with higher discriminatory powers are needed. The novel HR-manometry can measure the whole sequence of resting and squeeze pressures via the densely arranged sensors and the resulting spatiotemporal plots. The concept of integrated pressure over a certain period can therefore be applied to measure anal sphincter tone during resting and squeeze states. The novel parameters including HR-ARM resting integral (HR-ARM-RI) and HR-ARM squeeze profile (HR-ARM-SP) are good examples [23•]. Compared with conventional parameters, HR-ARM-RI and HR-ARM-SP both showed better detection of anal hypocontractility and significantly improved diagnostic accuracy for discriminating between 85 healthy controls and 403 patients with fecal incontinence [23•].

Several studies have shown that anal canal pressures are highly asymmetric in the axial and circumferential directions, as assessed with the HD-ARM catheter [1, 24]. Zifan et al. calculated the anorectal asymmetry index with an interpolated 16 × 16 matrix from HD-ARM data by using MATLAB [25••]. The authors showed that the anorectal asymmetry index is dependent on the symmetricity of the anal sphincter. Finally, the authors revealed that a combination of pressure values, anal sphincter area, and reflective symmetry values showed better discrimination between 20 patients with fecal incontinence and 20 control subjects, with an AUC of 1.0 [25••].

Limitations of the Study

The IPV parameters are based on the Sandhill system catheter, which has a 23-channel mode and 4-mm diameter. However, a recent paper used the IPV ratio with a HD-ARM catheter that has 256 channels and a rigid 10.75-mm probe and failed to show significant difference between 36 healthy volunteers and 40 patients with constipation [26]. The rigid, larger diameter HD-ARM probe as opposed to the flexible Sandhill Probe may in part explain this discrepancy. Moreover, the normal values from different catheters are significantly different and can be influenced by sex, parity, and race [27]. Despite the wide application of HR- and HD-ARM, there is significant variability in the protocols used for performing manometry, data analysis, and interpretation among different institutions, as well as differences in the equipment from different manufacturers [28]. For these reasons, these novel parameters from different catheters may not show reproducible results. Nevertheless, application of these novel parameters using different manometric systems together with expert assessment and correlations may provide improved consensus and standardization of HR- and HD-ARM.

Conclusions

HR- and HD-ARM are new techniques developed for the assessment of anorectal function, and they use closely arranged sensors that allow more detailed measurements and analysis. However, there is a need for metrics that better describe anorectal function and correlate with symptoms in patients with constipation and fecal incontinence. The novel technique of using IPV alongside HR-ARM could be a useful parameter for discriminating patients with delayed BE, and between healthy persons and patients with constipation. Furthermore, our preliminary results show that a combination of IPV parameters is superior to conventional parameters in predicting responsiveness to biofeedback therapy.

The HR-ARM-RI (resting integral) and HR-ARM-SP (squeeze profile) parameters with the HRM system together with pressure values, anal sphincter area, and reflective symmetry values with the HD-ARM system may provide the best discrimination between patients with fecal incontinence and control subjects. We hope that these new metrics contribute to improved understanding of the pathophysiology of anorectal disorders.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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