Diagnostic Role of Anal Sphincter Relaxation Integral in High-Resolution Anorectal Manometry for Hirschsprung Disease in Infants

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Objective To investigate the possible diagnostic role of anal sphincter relaxation integral (ASRI) in high-resolution anorectal manometry (HRAM) for Hirschsprung disease.

Study design We performed conventional anorectal manometry (ARM) in 24 infants (8 with Hirschsprung disease and 16 without Hirschsprung disease) and HRAM in another 21 infants (9 with Hirschsprung disease and 12 without Hirschsprung disease) before and after October 2014. All infants underwent rectal suction biopsy for confirmation of Hirschsprung disease. We quantified rectoanal inhibitory reflex (RAIR) adequacy by calculating the ASRI in HRAM study at pressure cutoffs of less than 10, 15, and 20 mm Hg (ASRI10, ASRI15, and ASRI20, respectively) and investigated the diagnostic utility.

Results Patients with Hirschsprung disease who underwent HRAM had significantly lower ASRI10, ASRI15, and ASRI20 values than did infants without Hirschsprung disease ($P = .0002$, .0002, and .0003, respectively), indicating significant difference in internal anal sphincter relaxation during RAIR test between these 2 groups. ASRI10 exhibited a greater diagnostic accuracy, area under the curve, sensitivity, and specificity than did ASRI15 and ASRI20 for Hirschsprung disease. Moreover, the diagnostic accuracy of HRAM for Hirschsprung disease based on ASRI10 <7 mm Hg.s.cm was significantly greater than that of conventional ARM ($P = .02$).

Conclusions ASRI10 may be indicative of the adequacy of RAIR by HRAM in infants, thus assisting the diagnosis of Hirschsprung disease. The diagnostic accuracy of HRAM (based on the ASRI10 value) is greater than that of conventional ARM for Hirschsprung disease. ASRI10 may be used in an automatic HRAM analysis system for the diagnosis of anorectal motility disorders. *(J Pediatr 2017;■■:■■-■■).*

As the result of the lack of enteric ganglia in the affected bowel segment, constipation in patients with Hirschsprung disease is usually severe and frequently associated with recurrent enterocolitis, failure to thrive, bacteremia, and even mortality.[1,2] Prompt surgical intervention can restore bowel function and improve quality of life in the majority of patients with Hirschsprung disease.[3,4]

The diagnosis of Hirschsprung disease is based on a combination of clinical symptoms, barium enema study, anorectal manometry (ARM), and rectal suction biopsy with staining for calretinin or acetylcholinesterase.[5,6] Rectal suction biopsy, an invasive procedure, is considered as the gold standard modality to confirm the diagnosis of Hirschsprung disease but is unsuitable for diagnosis of short- and ultrashort-segment Hirschsprung disease.[7-9] Conventional ARM and a barium enema study are used to assist in the diagnosis of Hirschsprung disease, with a diagnostic sensitivity and specificity of approximately 80% and 95%, respectively.[10-12] Inadequate rectoanal inhibitory reflex (RAIR) is regarded as an important measure of Hirschsprung disease.[11,12] High-resolution anorectal manometry (HRAM) is a newly developed technique that uses multiple pressure sensors, computerized data acquisition and display-used, color-coded amplitude depiction, and enhanced visual and analytical assessment of sphincter function.[13] HRAM is an effective and safe method for the diagnosis of Hirschsprung disease in newborns, but the resting pressure, anal canal length, and the RAIR measures used in the study by Tang et al were identical to those used in conventional ARM.[14] From the study of Tang et al, HRAM was reported to have a sensitivity of 89% and a specificity of 83% of Hirschsprung disease that used conventional ARM measures.[14]

Measures such as contractile deceleration point, distal contractile integral, distal latency, integrated relaxation pressure, etc, have been developed for automatic high-resolution esophageal manometry (HREM).[15-21] Using these measures, the International High-Resolution Manometry Working Group developed the Chicago

ARM	Anorectal manometry
ASRI	Anal sphincter relaxation integral
AUC	Area under the curve
HRAM	High-resolution anorectal manometry
NPV	Negative predictive value
PPV	Positive predictive value
RAIR	Rectoanal inhibitory reflex
ROC	Receiver operating characteristic

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criteria for HREM studies in patients with esophageal motility disorder.[15-17] However, the interpretation of HRAM remains dependent on traditional ARM measures or phenotypic interpretation of color plots by the physician.[14,18-21]

In this study, we aimed to identify new measures that facilitate quantification of the RAIR by HRAM. We then analyzed the diagnostic accuracy of those measures for Hirschsprung disease using HRAM in comparison with conventional ARM.

Methods

Infants (27 male and 18 female; median age, 0.15 years; range, 0.05-1 years of age) with clinical symptoms of severe abdominal distension, megacolon, ileus, and severe constipation were enrolled in this retrospective analysis. We performed conventional ARM before September 2014 and HRAM after October 2014 in children. Twenty-four patients (16 male and 8 female; median age, 0.17 years; range, 0.12-1 years of age) who underwent conventional ARM and another 21 patients (11 male and 10 female; median age, 0.14 years; range, 0.05-1 years of age) who underwent HRAM at the Department of Pediatrics and Surgery of National Taiwan University Hospital were enrolled.

All patients with clinical symptoms of severe abdominal distension, megacolon, ileus, and severe constipation underwent rectal suction biopsy at our institute for confirmation of Hirschsprung disease. Eight infants (33.33%) in the conventional ARM group and 9 infants (42.86%) in the HRAM group were diagnosed with Hirschsprung disease by the pathologic interpretation. The study protocol was approved by the institutional review board of National Taiwan University Hospital.

Conventional ARM measurement was performed with a single-use polyvinyl chloride catheter (Latitude Single Use Air-Charged Anorectal Catheter GIM-6000A, Medical Management Systems [MMS] B.V., Enschede, The Netherlands) (**Figure 1**, A; available at www.jpeds.com). The catheter contained 4 individual channels at intervals of 0.7 cm, and a nonlatex balloon was located between the tip and the first side channel of the catheter. UPS2020 software (version 8.11, MMS, The Netherlands) was used for interpretation of the conventional ARM data. The mean balloon volume to induce RAIR in infants was reported to be 9.83 ± 3.6 mL in a previous study.[22] Hence, 10 cc of air was applied as the initial volume in the rectal balloon for infants to induce RAIR in conventional ARM in our institution. When anal sphincter pressures remain unchanged at the stimulation volume of 10 cc, the volume increases to 15 cc and even 20 cc. Adequate RAIR is defined as transient decrease in resting anal pressure by >50% of basal pressure in response to rapid inflation of a rectal balloon and considered absent when anal sphincter pressures remain unchanged at 20-mL volume distension.[14,23]

HRAM was performed with a silicone catheter (Part #MMS G-90170; Mui Scientific, Ontario, Canada) containing 8 individual channels with side openings spirally at intervals of 0.5 cm and a nonlatex balloon located between the tip and the first side channel of the catheter (**Figure 1**, B). All side holes were perfused with distilled water at a rate of 0.25 mL/min via a pneumatic perfusion pump (MMS). The MMS HRAM converts recorded pressures into digital data, which are displayed as color plots via the Solar GI HRM Compact Pole system (Version 9.5; MMS). In the MMS HRAM plot, warm colors (red, orange, and green) indicate pressures >15 mm Hg, and a cold color (blue) indicates pressures <15 mm Hg. The mean balloon volume to induce RAIR in infants was reported to be 9.83 ± 3.6 mL in a previous study.[22] For infants, we also used 10 cc air as the initial stimulation volume in the rectal balloon to induce RAIR in the HRAM study.

Mimicking the distal contractile integral determined by HREM to calculate the integral of contractile amplitude × duration × length (mm Hg-s-cm) of the distal esophageal contraction exceeding 20 mm Hg from the transition zone to the proximal margin of the lower esophageal sphincter, we developed a new measure, anal sphincter relaxation integral (ASRI), to quantify the RAIR by HRAM in infants.

We calculated the ASRI <10, 15, and 20 mm Hg (ASRI10, ASRI15, and ASRI20, respectively) in an observed time window to quantify the strength of RAIR. The ASRIp (indicating the calculation of ASRI below p mmHg) is calculated as follows (**Figure 2**):

$$\mathrm{ASRI_p} = \sum_{spd \in W} I\{spd \le p\} \times (p - spd) \times d \times \Delta t \quad \text{and}$$

$$I\{spd \le p\} = \begin{cases} 1, \text{ if } spd \le p \\ 0, \text{ if } spd > p \end{cases}.$$

where *spd* is the anal sphincter pressure data, *d* is the distance between 2 adjacent channels, Δt is the sampling interval, *W* is the observed window, and *I* is the indicator function (**Figure 2**). To control the possible confounding factor, only the ASRI data from the 10-cc stimulation were used in this study. The ASRI analysis was conducted with MATLAB (version 8.6 R2015b; MathWorks, Natick, Massachusetts). To enhance the resolution, the pressure data were up-sampled 2- and 5-fold in the time and space domains, respectively, through cubic interpolation. The equivalent time and spatial resolutions were 0.05 seconds and 0.1 cm, respectively.

Statistical Analyses

The STATA (version 14; StataCorp LP, College Station, Texas) and MedCalc (version 17.5; MedCalc Software, Ostend, Belgium) software packages were used for statistical analyses. Mann–Whitney *U* tests were used to assess differences in the medians and IQRs of continuous variables between the 2 groups. The Fisher exact test or χ^2 test was used to determine differences in incidence between the groups. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff for prediction and to calculate the area under the curve (AUC). The diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each diagnostic method also were calculated. A *P* value < .05 was regarded as indicative of statistical significance.

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