Childhood constipation: new insights in testing, treatment and cost

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Distention of the Colon is Associated with Initiation of Propagated Contractions in Children

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Chapter 2

ABSTRACT

Background
The presence of high amplitude propagating contractions (HAPCs) has been identified as a marker of colonic neuromuscular integrity. The physiologic mechanisms of HAPCs initiation have yet to be determined. Distention secondary to colonic filling has been hypothesized as physiologic initiator.

Aim
To study the effect of intraluminal balloon distention in the colon of children with defecatory disorders.

Methods
Colonic manometry was performed with a polyethylene balloon situated at the proximal end of the catheter, which was placed in the most proximal colonic segment reached during colonoscopy. A stepwise pressure controlled distention of the balloon was performed using barostat computer (10 to 50 mmHg). Propagated contractions were defined as those that migrated over at least 3 recording sites. They were divided into HAPCs, amplitude >60mmHg and low amplitude propagating contractions (LAPCs), amplitude <60 mmHg. Children with spontaneous HAPCs or HAPCs after bisacodyl provocation were considered to have normal motility.

Results
Twenty children completed the study. Among the 14 children with normal colonic motility, balloon distention elicited HAPCs in 4 and LAPCs in 10 children. No HAPC were elicited in 6 children with abnormal motility and LAPCs were seen in 4 of them. The balloon-induced propagated contractions had similar characteristics as those occurring spontaneously and after bisacodyl provocation but the pressure needed to elicit them and their amplitude was inconsistent.

Conclusions
Intraluminal colonic distention can trigger propagated contractions in children. This mechanism of action for induction of propagated contractions is not as consistent as the motor response found in response to bisacodyl administration.
INTRODUCTION

During the past 20 years, intraluminal manometry studies have expanded our knowledge on pediatric colonic motility. Manometric studies of the colon have identified distinctive motility patterns that differentiate behavioral from organic causes of childhood constipation. As a result, colonic manometry has gone from a research tool to a diagnostic test used by several motility centers for the evaluation of children with severe defecatory disorders.

High amplitude propagating contractions (HAPCs) are the most recognizable features observed during colonic manometry. These contractions originate in the proximal colon and propagate to the rectum with an amplitude >60 mmHg and travel at least over 30 cm. The primary role of HAPCs seems to be propulsion of colonic content towards the rectum and the presence of HAPCs on colonic manometry has been identified as a marker of colonic neuromuscular integrity. Administration of colonic stimulants like bisacodyl or glycerin triggers HAPCs and is part of the routine manometry testing protocol. Although its exact mechanism of action is unknown, intracolonic administration of bisacodyl is currently used as a stimulation test during colonic manometry in children to evaluate whether patients have normal motility. Despite their important physiologic and diagnostic significance, little is known about the factors that initiate HAPCs. Physical factors such as luminal distention secondary to colonic filling have been hypothesized as physiologic initiators of HAPCs. In healthy adult volunteers, propagated contractions can be induced by balloon distention in the descending and sigmoid portions of the colon. There are no studies addressing the mechanism of initiation of HAPCs in children with defecation disorders or evaluating the effect of distention of the more proximal colon on the onset of HAPCs. This study proposed to investigate the effect of colonic distention using graded pressure stimulation and to compare the colonic response to intraluminal balloon distention with response to bisacodyl.

METHODS

Subjects
This was a prospective multicenter study performed at Nationwide Children’s Hospital in Columbus OH, Emma Children’s Hospital in Amsterdam, the Netherlands and the Goryeb Children’s Hospital at Atlantic Health in Morristown NJ. Children with complaints of refractory constipation or functional non-retentive fecal incontinence between the ages of 6-21 years referred for colonic manometry, were invited to participate. Children with organic causes for defecation disorders, including Hirschsprung’s disease, muscle disorders, patients with prior colonic surgery, spina
Bifida, mental retardation or hypothyroidism were excluded from the study. The study was approved by the Institutional Review Boards of all three institutes.

**Balloon placement and materials**

A customized water-perfused manometry catheter with 8 side-holes (10 cm apart) with a polyethylene balloon situated between the proximal 2nd and 3rd side-holes was used (Mui Scientific, Mississauga, Ontario, Canada). The catheters were perfused with distilled water by a low compliance pneumo-hydraulic pump (Mui Scientific Mississaug, Ontario Canada) at a rate of 0.25 ml min-1. Pressure measured by the external pressure transducers, was amplified and digitized at 16 Hz by a pressure transducer polygraph (Medtronic Parkway, Minneapolis, MN). Balloon inflation occurred with the use of a barostat computer (Isobar-3; G&J Electronic, Ontario, Canada). Before placement of the catheters the colon was cleansed with colonic lavage solutions using a similar protocol in all centers. The catheter was placed in the most proximal colonic segment that was possible to reach using colonoscopy. Catheter position was confirmed using fluoroscopy at the time of its placement and an additional radiograph was obtained before the start of the balloon distention protocol.

**Experimental protocol**

After patients were fully recovered from sedation, colonic manometry was performed according to established standard protocol. Motility was measured during at least one hour fasting and one hour post-prandial. Then a stepwise pressure controlled distention of the balloon was performed using a barostat computer (10 to 50 mmHg in steps of 10 mmHg). Each pressure step lasted 1 min followed by a 2 minute interval with the empty balloon. This sequence was repeated twice with a 5 minute interval. During each step the child was asked to describe sensation (nothing to it hurts, using a scale from 0-7) and asked whether he felt urge to defecate. After the balloon distention protocol, intraluminal bisacodyl was given in a dose of 0.2 mg kg-1 (maximum of 5 mg) and colonic motility was recorded for another hour.

**Analysis**

The patterns of colon contractions were identified by qualitative analysis. The tracings were evaluated for the presence of all propagating contractions throughout all stages (fasting, post-prandial, distention and post-bisacodyl). Propagated contractions occurring within 2 minutes after start of inflation were considered secondary to distention. The study was considered normal when at least one normal HAPC occurred during testing, irrespective whether the HAPC occurred during
Fasting, post-prandial or induced by bisacodyl. Propagated contractions, migrating over at least 3 recording sites, were divided in HAPCs and low amplitude propagating contractions (LAPCs). HAPCs were defined as contractions with an amplitude of at least 60 mm Hg, lasting more than 10 s and propagating aborally across at least 3 recording sites. LAPCs were defined as contractions propagating across at least 3 recording sites with an amplitude less than <60 mmHg.

Contraction amplitudes (in mm Hg) were calculated by subtracting mean resting colonic pressure from the peak of colonic waves. Contraction duration was measured in seconds between the onset of the major upstroke of the contraction until the return to baseline. Contraction propagating velocity (in cm s⁻¹) was calculated by determining the time between the onset of the major upstroke of the waves at the proximal and more distal ports, divided by the distance between the ports. The gastrocolonic response was defined by an increase in colon motility occurring within 30 minutes after beginning of a meal.

Statistics

Baseline characteristics of the cohort were analyzed in a descriptive way using the statistical software package SPSS (version 14.0; SPSS Inc, Chicago, IL). For data analysis and interpretations, results are expressed as median and range. Mann-Whitney U and Fisher’s exact test were used to test for differences between groups. A p value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

We enrolled 23 patients who met inclusion criteria in the study. Three patients were excluded. In two patients the catheter was coiled in the sigmoid and in one patient the catheter was partly expelled before start of the balloon distention protocol. After reviewing the 20 motility tracings, 14 children were considered to have normal motility and six children to have abnormal motility (Table 1). There was no difference in age, gender and defecation frequency between the children with normal or abnormal motility.

Children with normal motility

In the 14 children with normal motility (6 girls, median age 11.0, range 7.7-20.1 years), indication to perform the colonic manometry study was severe constipation in 13 children and fecal incontinence in one child. The median duration of symptoms was 10.5 (4.7 – 20.1) years. The children with constipation had a median defecation
frequency of 2.5 (1.0-10.0) times/week while taking laxatives. Daytime fecal incontinence was present in 50% children and nighttime fecal incontinence in all but one child. Twelve children had normal motility throughout the entire colon while two children had normal motility up to the recto-sigmoid area. One patient (pt CO) felt urge to defecate and was able to push out the catheter after bisacodyl administration. We therefore believe that the catheter had moved more distally, making it possible to only see two high amplitude contractions in the first two channels while the other sensors had moved to the sigmoid.

### Children with abnormal motility

In the six children who had abnormal motility (3 girls, median age 9.2, range 6.2-16.3 years), indication to perform colonic manometry was chronic constipation in 5 children and fecal incontinence in one. Median duration of symptoms was

<table>
<thead>
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<th>Patient</th>
<th>Balloon location</th>
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<th>Balloon induced LAPCs</th>
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2.3 (1.4-15.6) years. Defecation frequency in the children with constipation was 2.5 (0.0 – 7.0) times/week while taking laxatives and three of these children also suffered from fecal incontinence. Three children had persistently low amplitude contractions, one with minimal motor activity throughout the entire study and one with no HAPCs. In the other child only high amplitude simultaneous contractions were seen in two channels and none in the others.

**Balloon placement and propagating contractions**

*Children with normal motility*

As shown in Table 1, the balloon was placed in the distal colon in 8 children and in the proximal colon in the remaining 6 children. All children showed HAPCs after administration of bisacodyl. Balloon distention elicited propagating contractions (Figure 1) in 11/14 children (73%): HAPCs were noted in four children and LAPCs in 10 children. There was no statistically significant difference in elicited propulsive activity when comparing the balloon placement in the more proximal or more distal colon (p= 0.58). In 8 children all 5 pressures steps could be completed, in the other 8 children the sequence had to be aborted at 40 mmHg because they expressed discomfort. The pressure needed to elicit contractions was variable (10 – 50 mmHg) and was not consistent among different subjects and within the same individuals for both LAPCs and HAPCs. The characteristics of all propagating contractions are summarized in Table 2. No spontaneous or post-prandial HAPCs were seen as they occurred only after balloon distention or bisacodyl administration. In three children who showed propagated contractions, the balloon-evoked HAPCs amplitudes were lower than the bisacodyl-induced HAPCs; in one child it was the same. The duration and velocity of the HAPCs were comparable. Differences were not statistically significant. LAPCs seen during fasting, postprandial period and after bisacodyl provocations were also similar to LAPCs induced by balloon distention. Only one child did not perceive any sensation during the testing, all others reported some degree of discomfort (varying from “I can feel something” to “it hurts”). At a median
step of 40 mmHg 9/14 children reported enough discomfort that the next step was omitted. Five children felt an urge to defecate during the balloon distention at a median pressure step of 40 mmHg. Three out of those five children also complained of cramping when they felt the urge and all those children showed a propagated contraction at that time. The symptoms were not consistent over time since the children did not always expressed urge at the same pressure step in the following distention rounds.

Children with abnormal or undetermined motility
All balloons were placed in the distal part of the colon (Table 1). Balloon distention with variable pressures resulted in LAPCs in 4/6 children. No HAPCs were seen. As with the LAPCs in the children with normal motility, the balloon-evoked propagated contractions had similar characteristics compared to the spontaneous occurring contractions. (Table 2) Three children complained about pain during balloon distention; in one child the protocol had to be aborted. Only one child felt urge to defecate and this was not related to any colonic contraction.

### DISCUSSION

This study demonstrates that intraluminal balloon distention of the colon can initiate propagated contractions in children. The stimulated contractions, both HAPCs and LAPCs, were comparable to those found throughout the rest of the motility study. Given that we were only able to elicit HAPCs in 4 patients with normal motility and in none of those with abnormal motility, intraluminal colon distention is not likely
to be the main physiological initiator of HAPCs and at this point should not replace bisacodyl infusion, which is integral part of colonic motility testing in children.

Despite almost three decades of research on colonic motility, little is known about the mechanisms regulating HAPCs, the propagated contractions that are associated with defecation.\(^2\), \(^3\), \(^8\) Prolonged manometry testing in adults has shown a diurnal pattern with a reproducible increase in generalized colonic activity upon awakening.\(^9\) A significant increase in number of HAPCs is also seen after ingestion of a meal.\(^9\), \(^10\) It is possible that several different stimuli are responsible for initiating HAPCs, such as hormonal release, mucosal irritation and luminal distention although no definitive evidence for any single specific mechanism has been found yet.

Studies of colonic motility in adults have demonstrated that chronically constipated subjects exhibit significantly fewer HAPCs and a decreased frequency of urge to defecate, suggesting that one pathophysiological mechanism for constipation may be the decreased propulsive ability of the colon.\(^2\) In contrast to those findings, King et al. have recently reported normal frequency of HAPCs during 24 hour manometry testing in children with slow transit constipation.\(^11\) They did however find a significantly lower total frequency of propagating contractions and therefore hypothesized that the presence of HAPCs alone is not sufficient to establish normal colonic motility. These results confirm that results found in adults may not be extrapolated to children.

So far, emphasis has been placed on HAPCs as a marker of normal colonic motility but lately there are indications that LAPCs might be just as important. LAPCs occur more commonly than HAPCs but few studies have investigated such propulsive activities. Bassotti et al. have characterized and described LAPCs in healthy volunteers and stated that the average daily number of LAPCs was approximately ten times as high as the number of HAPCs.\(^12\) Simultaneous colonic manometry and high-resolution scintigraphy showed that LAPCs in the proximal colon, with contractions as low as 2-5 mmHg, were as likely to be associated with colonic movements as HAPCs.\(^13\) This could possibly explain the fact that some patients in whom HAPCs are absent or greatly reduced, normal transit is found in the large bowel.\(^14\)

Whether balloon distention of the colon will find a place among the stimulation tests performed during colonic manometry is unclear at this point. It may serve to identify a population of children who may have more subtle motility abnormalities than those identified by bisacodyl testing. We were able to induce HAPCs in some children with balloon distention but not in as many as bisacodyl did. The mean amplitudes of propagated contractions after balloon distention were lower (85 vs. 105 mmHg) than after bisacodyl, but given the small numbers of study subjects this difference did not reach statistical significance. The bisacodyl stimulation may be so powerful that it may trigger propagated contractions even in children in whom colonic distention (possibly a more physiological stimulus) does not.
One of the main limitations of our study was that placement of the colonic catheter with its bulky polyethylene balloon proved to be challenging. Many of the study children had very dilated and tortuous recto-sigmoid colons resulting from the long duration of their symptoms which made it difficult to reach the cecum when carrying the motility catheter with the colonoscope. This resulted in different final locations of the catheters and balloons. We were therefore not able to place the balloon as proximal as we had planned. Out of the four children showing HAPCs after balloon distention, three of them had the balloon placed in the transverse colon. Although we did not find a difference between the position of the balloon and the initiation of propagating contractions, this might be due to our small sample size. We chose to limit distention to 50mmHg having used those pressures in the past in the rectum and stomach without problems. Although it could be possible that higher pressures are needed to induce HAPCs, the fact that 12/23 children expressed enough discomfort to abort the protocol makes it unlikely that we could have used higher pressures. None of the children showed evidence of having a dilated colon on their pressure-volume curves and none exceeded the maximum volume of 500ml. Another limitation is these studies were performed in patients, not in healthy children due to obvious ethical reasons.

In conclusion, we found that intraluminal colonic distention triggers propagated contractions in children with defecation disorders. Although we were able to induce HAPCs in some children, the distention did not provide consistent results compared to bisacodyl provocation. Further studies are needed to further elucidate the mechanisms that are responsible for the initiation of propagating contractions, both HAPCs and LAPCs. Until further research is done into its clinical significance, colonic balloon distention in children should remain a research tool.


