Paediatric constipation and functional non-retentive faecal soiling
Voskuilj, W.P.

Citation for published version (APA):
Chapter 5

The role of rectal compliance in recovery from paediatric constipation: A barostat study

Wieger P. Voskuijl, Marc A. Benninga, and Guy E. Boeckxstaens

Submitted
Abstract
Background
Since long term outcome in paediatric constipation (PC) is unfavourable, insight in prognostic factors for successful outcome may direct the therapeutic strategy. Increased rectal compliance and not decreased rectal sensitivity is the most prominent pathophysiological feature in PC. We therefore hypothesised that normal rectal compliance is more prevalent in children successfully recovered from PC compared to those with PC.

Aim
To evaluate rectal function (sensitivity and compliance) in children with longstanding PC and children recovered from constipation (RP) using pressure-controlled distension.

Methods
A pressure-controlled distension protocol (Barostat) was used to assess thresholds for rectal sensitivity (first sensation, urge to defecate and pain), and rectal compliance.

Results
42 patients with longstanding PC (30 M, mean age 11.0 ± 2.1 years) and 12 recovered children (8 M, mean age 15.2 ± 2.1 years) were studied and compared with 22 HV’s (11 M, mean age 12.7 ± 2.6 years). Sensitivity thresholds were not significantly different between the three groups. Four RP children (33%), and 21 PC children (50%) children had an increased rectal compliance (P=0.02 and P<0.0001 vs. HV’s. respectively). Between the PC and RP groups, rectal compliance was not significantly different. There were no significant clinical differences (i.e. age of onset, duration of therapy) between the RP subjects with a normal and an impaired rectal compliance.

Conclusions
Recovery from paediatric constipation is not associated with normal rectal compliance. Future, longitudinal studies are needed however, to prospectively evaluate the relationship between disturbed rectal compliance and clinical outcome.
Introduction

Paediatric constipation (PC) can be considered as a chronic disorder with an important effect on emotional well being, social- and family life of children (1,2). In more than 90% of these patients no organic or anatomic cause can be found, and therefore these patients are considered to suffer from a ‘functional’ defecation disorder (3). Treatment is symptomatic, often long lasting and as a result frustrating for the patient, parents, and caretakers. Furthermore, 5 years after intensive medical treatment, 50% of children still have complaints of constipation illustrating that therapy is often unsatisfactory (4,5). For that reason, it would be of help to identify prognostic factors associated with successful outcome.

Previous studies have identified abnormal defecation dynamics (6,7) and decreased rectal sensitivity (8,9) as important mechanisms contributing to the pathophysiology underlying PC. Consequently, normalisation of these parameters (obtained during anorectal manometry) should lead to clinical improvement, and as such represent valuable prognostic factors for clinical success. So far however, correction of abnormalities in rectal sensitivity (8,9), balloon expulsion (10,11), and defecation dynamics (6,7) was not associated with clinical improvement. This suggests that other mechanisms are of greater importance.

We recently demonstrated, using a pressure controlled distension protocol (anorectal barostat), that not decreased rectal sensitivity but increased rectal compliance was the most prominent pathophysiological feature occurring in 58% of PC patients (submitted). Based on these findings, we hypothesised that clinical success should be associated with improvement of rectal compliance. To test this hypothesis, we compared rectal compliance in children successfully treated for PC with that of children with severe constipation refractory to treatment using a pressure controlled distension protocol applied by a barostat.
Materials and methods

Subjects
In this study, a group of 76 otherwise healthy children were included. Subjects were subdivided into three groups: the first group consisted of 42 chronically constipated children refractory to conventional therapy (high fibre diet, high fluid intake, toilet training, oral and/or rectal laxatives) with or without biofeedback training. Constipation was defined as: at least two of the next four criteria: 1) a stool frequency less than three per week, 2) two or more encopresis episodes per week, 3) periodic passage of very large amounts of stool at least once every 7-30 days and 4) a palpable abdominal or rectal mass on physical examination (6). Children with organic causes for constipation, including Hirschsprung’s disease, muscle disorders, patients with prior recto-anal surgery, spina bifida (occulta), mental retardation or hypothyroidism were excluded from the study. All patients in the PC group had a history of constipation of at least two years, together with the use of oral and/or rectal laxatives for at least one year.

The second group consisted of 12 ex-PC children successfully treated and free of symptoms of constipation for at least three years (recovered patients: RP). The time cut-off point of 3 years was chosen because a recent long-term follow-up study in children with constipation suggested that after a ‘constipation free’ interval of at least three years, relapse is improbable (5). All data were compared with data from 22 healthy volunteers (HV’s) with no gastrointestinal complaints. All children were at least 8 years of age and thus able to understand the barostat procedure.

Procedure and equipment
A rectal polyethylene balloon with infinite compliance and a maximum volume of 510 ml was connected to a computer-driven barostat device (Synectics Visceral Stimulator; Synectics, Netherlands). The balloon was fixed on a silicone catheter with an outside diameter of 4 mm and an inside diameter of 3 mm, allowing a flow of air of 38 ml/sec. Before and after each study, the balloon was checked for leakage.

Experimental protocol
Pain medication and all medication known to affect the gastrointestinal motility were discontinued 48 hours before the barostat procedure. One week before the
study, the parents and the child were invited to the motility unit to be intensively informed about the equipment and the barostat procedure. Only PC patients received bowel preparation consisting of at least three enemas on three consecutive evenings before the day of the study (Klyx: sodium-dioctylsulfosuccinate / sorbitol; 120 ml). If on rectal examination faeces were present in the rectum, subjects were asked to defecate. Emptiness of the rectum was checked once more by rectal digital examination. The subjects were placed in the left lateral position. The lubricated balloon was introduced into the rectum without the use of endoscopy.

The balloon was unfolded by a stepwise increase (30 ml per step) until a maximum volume of 150 ml. With the balloon still inflated the catheter was pulled back against the pelvic floor. After deflation and a 15 minute period of equilibration, the minimal distension pressure (MDP) was determined by stepwise increasing the intra-balloon pressure (1 mm Hg steps for 1 minute). MDP was defined as the pressure resulting in an intra-balloon volume of at least 30 ml and at which the volume changes to breathing could be identified. Determination of MDP was followed by a rectal adaptation period of 15 minutes.

Rectal sensitivity to distension was evaluated using an intermittent distension procedure with steps of 3 mmHg lasting 1 minute and intervals of 1 minute at MDP. At every pressure step the child was asked to score sensation immediately and after 30 seconds. An ordinal scale from 0-5 was used (12): 0=no sensation, 1=first sensation, 2=urge to defecate, 3=moderate urge to defecate, 4=severe urge to defecate, 5=pain. In case of pain, the balloon was immediately deflated. The study protocol was approved by the medical ethical committee of the Academic Medical Centre. All subjects and/or parents gave informed consent.

Analysis

Rectal sensitivity

Thresholds for first sensation, urge to defecate and pain were determined from the intermittent distension protocol and expressed as pressure above MDP. If individuals did not report urge or pain, the highest possible pressure value was assigned (i.e. MDP + 39 mmHg).
Rectal compliance

Rectal compliance, a measure of rectal distensibility and a resultant of the elastic properties of the rectal wall (13), was calculated using a non-linear mixed-effect model for fitting the pressure volume curves of each individual (14,15). The pressure volume curves were constructed using the mean volume of the last 15 seconds (when equilibration of the volume was reached) at each of the consecutive pressure steps.

In a first analysis all curves were fitted individually to a 4 parameter logistic curve, using non-linear regression analysis. This provided the parameters C (compliance: maximum slope in the Volume-Pressure curve), V0 (volume at time point zero), and Vm (maximum volume) for each individual as well as their standard errors. The fourth parameter was only introduced to improve the fit of the logistic curves. It consisted of a hypothetical starting volume at negative infinite pressure, common to all patients. The value of this parameter itself is of no importance and therefore not reported. The SD of the within patient measurement error was assumed to be equal for all individuals.

In a second analysis the individual parameters C, V0 and Vm were assumed to be derived from a 3-dimensional normal distribution, leading to a non-linear mixed effect regression analysis. No assumptions were made about the correlations between the three parameters. Group means and SD's for C, V0 and Vm were derived from this analysis, which corrected these values for within-patient variability.

Statistical analysis

Baseline patient data are expressed as mean (± SD). Sensation thresholds and rectal compliance are described as median value above MDP together with their 5th and 95th percentile. Thresholds above the 95th percentile of the median of the HV's (i.e. 'cut-off'), were considered abnormal. Because of the distribution of data, non-parametric tests (Kruskal-Wallis / Mann Whitney) were used for comparing sensation thresholds and rectal compliance between groups. The Chi-square test was used to compare the number of patients in each group, who reached the threshold for sensation of urge, pain, and compliance. Differences were considered statistically significant when the p-value was less than 0.05.
Results
Subject characteristics
Forty two PC patients with chronic constipation unresponsive to therapy (30 boys, mean age 11.0 ± 2.1 years; range 8 – 15 years) and 12 RP children (8 boys, mean age 15.2 ± 2.1 years; range 10 - 17) were studied and compared to 22 HV’s (11 boys, mean age 12.7 ± 2.6 years; range 7 – 16 years). Mean duration of symptoms in PC patients before barostat testing was 7.2 ± 2.8 years. Recovered patients had been constipated with a mean duration of 4.9 ± 2.2 years and were now symptom-free before barostat testing with a mean period of 6.7 ± 2.9 years. Other clinical characteristics are shown in table 1. Age at time of onset of constipation was not different between PC (3.8 ± 2.5 years) and RP (3.6 ± 1.5 years) children. RP subjects were 8.5 ± 2.2 years old at time of recovery.

Table 1 Subject characteristics at time of barostat

<table>
<thead>
<tr>
<th></th>
<th>HV’s N = 22</th>
<th>RP N = 12</th>
<th>PC N = 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defecation frequency</td>
<td></td>
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</tr>
<tr>
<td>N / week</td>
<td>7 ± 0</td>
<td>6.8 ± 0.6</td>
<td>2.1 ± 1.8</td>
</tr>
<tr>
<td>Min-max</td>
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<td>(5.0-7.0)</td>
<td>(0-8.0)</td>
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<tr>
<td>Encopresis frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N / week</td>
<td>0</td>
<td>0</td>
<td>9.6 ± 13.7</td>
</tr>
<tr>
<td>Min-max</td>
<td></td>
<td></td>
<td>(0-70)</td>
</tr>
<tr>
<td>% of subjects with faecal impaction</td>
<td>0</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Laxative treatment before barostat (months)</td>
<td>0</td>
<td>27.7 ± 23.2</td>
<td>50.9 ± 37.4</td>
</tr>
<tr>
<td>Min-max</td>
<td></td>
<td>(4.5-84.0)</td>
<td>(13-180)</td>
</tr>
</tbody>
</table>

Results are shown as mean (±SD)

Minimal Distension Pressure (MDP)
MDP was 5 ± 2 mmHg in PC children, 4 ± 2 mmHg in children with RP, and 4 ± 2 mmHg in the HV’s (NS between all three groups). The mean volume in the barostat balloon at MDP was 38 ± 28 ml in PC patients, 34 ± 33 ml in children with RP, and 31 ± 13 ml in the HV’s (NS).
Thresholds for first sensation

mmHg above MDP

- PC
• HV's
• RP

upper limit of normal
= 6 mmHg above MDP

Figure 1a: Thresholds for first sensation.

Thresholds for urge

mmHg above MDP

- PC
• HV's
• RP

upper limit of normal
= 19 mmHg above MDP

Figure 1b: Thresholds for urge to defecate.

Thresholds for pain

mmHg above MDP

- PC
• HV's
• RP

upper limit of normal
= 39 mmHg above MDP

Figure 1c: Thresholds for pain.
Rectal sensibility to distension

**First sensation**
The threshold for first sensation was 3 (0-6) mmHg above MDP in HV’s (median (5th-95th percentile)), with 6 mmHg (95th percentile) as the upper limit of normal range. No significant difference in thresholds for first sensation was found between the three groups (PC: 3 (0-23) mmHg, RP: 3 (0-3) mmHg, and HV’s: 3(0-6) mmHg above MDP, respectively). In the PC group, 7 patients (17%) had a threshold for first sensation above the upper limit. This was not significantly different compared with HV’s and RP children (figure 1a).

**Urge to defecate**
The threshold for urge to defecate was 6 (0-19) mmHg above MDP in HV’s, with 19 mmHg (95th percentile) above MDP as the upper limit of normal range. The 3 groups were not significantly different with respect to urge to defecate (PC: 6 (0-37) mmHg, RP: 6 (3-12) mmHg, and HV’s: 6 (0-19) mmHg above MDP). 7% of PC children (NS vs. HV’s and RP) but none of the RP group had an urge to defecate above the upper limit. Two PC children reported no urge to defecate (figure 1b).

**Pain**
The threshold for pain was 20 (9-39) mmHg above MDP in HV’s, with 39 mmHg (95th percentile) above MDP as the upper limit of normal range. The threshold for pain was not significantly different between the 3 groups (PC: 21 (9-39) mmHg, RP: 26 (15-39) mmHg, and HV’s: 20 (9-39) mmHg above MDP. Nine PC patients (22%), and 2 RP children (17%) did not report pain at all (Both NS vs. HV’s). One RP patient reported pain at 39 mmHg above MDP (figure 1c). There were no significant clinical differences such as defecation frequency, number of years with and without symptoms of constipation, age at onset and age at end of symptoms of constipation, and months of laxative use between the RP’s with a normal and an increased threshold for pain.
Rectal compliance

The rectal compliance (median (5th – 95th percentile)) was 16 (12-20) ml / mmHg in HV’s. In HV’s, 20 ml / mmHg (95th percentile) was the upper limit of normal range. The rectal compliance of RP children was 19 (12-29) ml / mmHg and was not significantly different compared to the PC group (20 (12-43) ml / mmHg) and not different from the HV’s either (16 (12-20) ml / mmHg). The rectal compliance of PC children was significantly different compared to HV’s (P<0.0001, Mann Whitney). Four RP children (33%), and 21 PC children (50%) children had an increased rectal compliance (P=0.02 and P<0.0001 vs. HV’s, respectively (Chi-square)). The rectal compliance of PC and RP children was not significantly different (figure 2).

There were no significant clinical differences like defecation frequency, number of years with and without symptoms of constipation, age at onset and age at recovery of constipation, and months of laxative use between the RP subjects with a normal and an increased rectal compliance.

Figure 2: Rectal compliance.
Discussion

Recently, we demonstrated that increased rectal compliance and not decreased rectal sensitivity was the major pathophysiological mechanism in severely constipated children (submitted). Since previous studies were unable to identify prognostic rectal parameters (6-11), we hypothesised that achievement of clinical success, defined as normal defecation without encopresis without the use of laxatives, would be reflected in the normalisation of rectal compliance. Although a trend towards normalisation of compliance was observed (figure 2), only 8 out of 12 (66%) patients recovered from constipation had a normal rectal compliance. It might be therefore argued that besides normalisation of rectal compliance other mechanisms are likely to be involved in the recovery from childhood constipation.

In previous studies assessing the relation between anorectal parameters and treatment failure in PC (2,16), abnormal defecation dynamics and the consequent inability to defecate water filled balloons were related to unsuccessful outcome. Nevertheless, normalisation of defecation dynamics using biofeedback training has been shown not to be related to successful outcome (6). Furthermore, a balloon defecation test could not reliably predict recovery from PC (11). Additionally, rectal sensitivity to distension was demonstrated not to be involved achieving clinical success in PC (17). Moreover, another study investigating the effect of treatment on recto-sigmoidal motility before, during, and after laxative treatment (18) showed that motility values were not different between patients recovered from constipation and those who were still constipated.

It might be questioned to what extent various abnormalities in anorectal function disturbances (sensitivity/defecation dynamics/compliance/motility) are causative pathophysiological mechanisms in childhood defecation disorders and not merely epiphenomena. Since so far no studies showed a relation between normalisation of disturbed anorectal parameters and achieving successful outcome, questions arise on the true value of these anorectal parameters in the underlying pathophysiology.

Despite clinical recovery, rectal parameters, such as rectal sensitivity, have been reported to remain disturbed (19). One might argue that these persistent abnormalities in rectal function might put recovered patients at risk to relapse (19). Indeed, a high relapse rate (50%) was observed in constipated children after initial successful outcome (5). In this paper, premature cessation of laxative therapy
and male sex were demonstrated to be responsible for relapse. Although our current study showed persistent increased rectal compliance in 33% of recovered patients, it is not possible to distil from our data that persisting increased rectal compliance enhances the probability of relapse. To investigate whether rectal compliance is primary or secondary to constipation, whether an increased rectal compliance decreases the probability of successful outcome, and if there is effect of treatment on rectal compliance can only be properly investigated in a prospective study.

A drawback of this study is the small sample size of recovered patients (N=12). Since 1993 we yearly contact our cohort of children with constipation who participated in two randomised controlled trials evaluating the effect of biofeedback training and/or laxatives (5). In this prospective collection of data, all patients (N=418) including children free of symptoms of constipation are monitored on a yearly basis. Of all patients contacted only 12 were willing to participate in the current study. Due to the cross-sectional design of this study, we are not informed about the rectal compliance prior to treatment, making it impossible to evaluate the effect of treatment. Longitudinal studies are therefore needed to clarify this issue and to assess if rectal compliance can be modulated with therapy and is associated with clinical success.

In conclusion, this barostat study could not identify rectal compliance as a prognostic factor for recovery from constipation. A third of children who are clinically symptom free of constipation still had an increased rectal compliance. A prospective study evaluating rectal compliance is needed to better investigate the relation between rectal compliance, the effect of laxative treatment, and the achievement of clinical success in paediatric constipation.
References


