An evaluation of colorectal diseases: surgical aspects and new insights into the mechanisms of fecal continence
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General discussion and future perspectives
This thesis focuses on colorectal diseases that, depending on the severity of the disease, can be treated conservatively or with surgical intervention. Patients with mild forms of congenital anorectal malformation (CARMs) can sometimes be treated with medication alone, while severe forms of CARM need surgery within 48 hours after birth. Another example is ulcerative colitis. If patients suffering from this disease do not respond to medical treatment, the severely damaged colon needs to be surgically removed. This can be followed by the creation of an ileal pouch-anal anastomosis (IPAA) later on. On account of the fact that the long-term fecal continence outcomes of patients with such colorectal diseases can be suboptimal, our primary focus in this thesis is on the mechanisms controlling fecal continence in healthy subjects. Further on, we return to these long-term outcomes in patients suffering from different colorectal diseases.

In the fundamental studies that we present in the first part of this thesis we focus on the fecal continence reflexes, and in specific the puborectal continence reflex. To date, this reflex has not been described in the literature. The studies in this thesis are the first to do so in both patients and in healthy subjects. In the second part of this thesis we present the long-term clinical and fecal continence outcomes of patients with different colorectal diseases, including patients with CARMs and patients who underwent proctocolectomy with IPAA. In the present chapter, we discuss the findings presented, reflect on the findings in relation to the existing literature, and communicate new ideas for future research.

**Fecal continence mechanisms**

Several mechanisms regulating fecal continence have been identified in the past. Nevertheless, the fact that dysfunction of these mechanisms does not always lead to fecal incontinence points to the existence of other, as yet unidentified, mechanisms that maintain fecal continence. In this thesis we describe such a newly identified mechanism. In the study presented in Chapter 2, we demonstrated the involuntary contraction of the puborectal muscle that appeared upon activation of the puborectal continence reflex. We visualized this activation by means of the balloon retention test during which a rectal balloon was gradually filled with water, mimicking solid stool. Activation of the reflex was demonstrated by the gradual increase of pressure at the level of the puborectal muscle that appeared simultaneously with the gradual filling of the rectal balloon. In addition, we observed rotation of the anal canal in the direction of the pubic bone, thus changing the anorectal angle caused by the contraction of the puborectal muscle. As we observed the puborectal continence reflex upon gradual filling of the balloon, it appeared to be initiated upon dilatation of the proximal part of the anal canal. This observation led us to advance the hypothesis that the puborectal continence reflex is activated through a stretch receptor.

This hypothesis became more plausible by the study we presented in Chapter 3. In this study, we demonstrate that water injected into the rectum did not activate the puborectal continence reflex. Probably, the water flowed into the proximal part of the colon and failed to build up enough pressure to activate the stretch receptor. We observed an opposite phenomenon in
case of the anal-external sphincter continence reflex (AESCR) that was activated rapidly in response to even a small amount of water injected into the rectum. We postulate, therefore, that the proposed stretch receptor of the puborectal continence reflex is located deeper than the mucosa. Conversely, the receptor belonging to the AESCR has features of a contact receptor, located superficially in the mucosa. Moreover, the fact that local anesthesia applied in the anal canal prevented activation of the AESCR indicates that the AESCR is probably located very superficially in the anal canal. In summary, the AESCR is activated in case of solid and liquid stool, while the puborectal continence reflex is only activated in case of liquid stool (Table 1).

Table 1 | Schematic overview of the voluntary and involuntary continence mechanisms of the external anal sphincter and puborectal muscle

<table>
<thead>
<tr>
<th></th>
<th>External anal sphincter</th>
<th>Puborectal muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voluntary</strong></td>
<td>Short, conscious contractions during urge</td>
<td>Short, conscious contractions during urge</td>
</tr>
<tr>
<td></td>
<td>Long, unconscious contractions during most of</td>
<td>Long, unconscious contractions during most of</td>
</tr>
<tr>
<td></td>
<td>the day and during the night</td>
<td>the day and during the night</td>
</tr>
<tr>
<td><strong>Involuntary</strong></td>
<td>During solid and liquid stool</td>
<td>Only during solid stool</td>
</tr>
<tr>
<td></td>
<td>Anal-external sphincter continence reflex</td>
<td>Puborectal continence reflex</td>
</tr>
</tbody>
</table>

Neural pathway mediating the puborectal continence reflex

During anorectal surgery, or colon surgery in the pelvic floor region, it is important to avoid any accidental damage to the muscles and neurovascular structures because it may adversely affect certain physiological functions in this region. The pudendal nerve is one of the major nerves in the pelvic floor and one might expect that this nerve mediates the puborectal continence reflex. The sensory condition of the pudendal nerve can be determined by means of the anal electrosensitivity test, standard procedure during anorectal function testing. When anal electrosensitivity is decreased, a higher threshold of electrical stimuli is needed to evoke potentials indicating a poorer condition of the pudendal nerve. With this in mind, we performed the study presented in Chapter 4. We found that activity/presence of the puborectal continence reflex was not associated with anal electrosensitivity. This led us to conclude that the reflex is not regulated through the pudendal nerve. This was only the first step in our endeavor to establish the exact neural pathway responsible. The knowledge of the exact neural pathway would allow us to prevent accidental surgical damage.

Based on current anatomical knowledge, we postulate that the activity of the puborectal continence reflex might be mediated by the levator ani nerve that innervates the levator ani muscle, of which the puborectal muscle is part (Figure 1). Another possibility is a separate nerve innervating the puborectal muscle directly; such a nerve was seen in some human cadavers (Figure 2, light blue line). Even though we demonstrated no involvement of the pudendal nerve in the activity in the puborectal continence reflex, we cannot reject the possibility that the reflex might eventually be mediated through a high branch of the pudendal
nerve. This high branch could remain unaffected by the overall condition of the pudendal nerve, and is therefore not associated with the presence of the reflex. Put differently, no association between the condition of the pudendal nerve at the level of the anal canal and the puborectal continence reflex does not necessarily exclude the possibility that the reflex is mediated by the pudendal nerve, because of the high branch possibility. Two studies reported the existence of such an additional branch of the pudendal nerve innervating the levator ani muscle (Figure 2, orange line).\textsuperscript{5, 6} Interestingly, this nerve was found to branch off above the pudendal canal, which might make it less prone to pudendal neuropathy.

Figure 1  |  Medial and slightly anterior view of the hemisected pelvis. The pudendal nerve and the nerve to the levator ani are indicated.

Fecal continence during ageing
It has always been assumed that fecal incontinence is associated with ageing because the voluntary contractions of the external anal sphincter weaken progressively with increasing age.\textsuperscript{7, 8} Nevertheless, the study presented in Chapter 4 conveyed the optimistic message that the puborectal continence reflex is not associated with ageing. We point out that this is not an exceptional phenomenon. Previously, our research group demonstrated that the other fecal continence reflex, the AESCR, which mediates involuntary contractions of the external anal sphincter, also does not diminish with age.\textsuperscript{9} In neither of the studies, however, were the results compared longitudinally. Further research with an extended follow-up and analysis within the same patients including use of adequate anorectal function tests, would be extremely useful to establish the influence of age. In this way it would be possible to investigate the vitality of the various fecal continence mechanisms, including the voluntary and involuntary contractions of the external anal sphincter and the puborectal muscle.
Figure 2  |  Schematic overview of the pelvic floor, including the already known sacral nerves and the hypothetical neural pathways responsible for the puborectal continence reflex. The dark green line indicates the known pudendal nerve. The dotted section of the green line indicates the nerve branches caudal to the pelvic floor. The light green line indicates the known levator ani nerve. The light blue lines indicate the proposed separate nerve innervating the puborectal muscle directly. The orange line indicates a proposed high branch of the pudendal nerve innervating the levator ani muscle, branching off above the pudendal canal and therefore less prone to pudendal neuropathy.

Abbreviations: C, coccyx; CM, coccygeus muscle; IS, ischial spine; LAM, levator ani muscle; OIM, obturator internus muscle; PM, piriformis muscle; PRM, puborectal muscle (a part of levator ani muscle); PS, pubic symphysis; R, rectum; S, sacrum; U, uterus; V, vagina.

Adapted from Figure 3 in the article entitled The Contribution of the Levator Ani Nerve and the Pudendal Nerve to the Innervation of the Levator Ani Muscles; a Study in Human Fetuses, by Wallner et al, European Urology, 2008;54(5): 1136-1144

Patients with congenital anorectal malformations

Sometimes, fecal problems occur as a result of congenital disruption of the anatomy. Congenital anorectal malformation (CARM) is such a disorder whereby the anorectum is not properly developed. There are mild forms of CARM, such as a slightly anterior placed anus, and severe forms such as a fistula from the rectum ending in the bladder. To treat patients with such congenital disorders, one needs to first arrive at proper diagnosis. Obviously, the severe forms are not difficult to detect, but mild forms can be difficult to detect by a midwife or parents. Because these malformations are rare, recognizing them can also be difficult for a doctor.
The study presented in Chapter 5 confirms our finding that mild forms of CARM were often diagnosed late, or not diagnosed at all. In addition, the study described the underestimation of the prevalence of CARMs in female patients because mostly mild forms of CARM occur in this group. Suffering from a mild form of CARM often results in chronic constipation. Not being aware of the disorder implies no treatment, resulting in unnecessary complaints. The fact that female patients with CARMs are often underdiagnosed also has significant implication from the gynecological point of view. It is known that patients with CARMs are at an increased risk of obstetric complications, such as introital stenosis, retained vaginal septum, and an abnormal perineal body, resulting in third or fourth degree ruptures during vaginal delivery.\textsuperscript{10} To prevent a total rupture in these patients, caesarian section should be the preferred mode of delivery in patients with CARMs. Properly diagnosing female patients with CARMs can, therefore, prevent them from suffering the obstetric complications mentioned. Long-term follow-up studies are needed of women with CARMs who gave birth. Awareness that CARMs might be the underlying reason for constipation is especially needed in female patients, because they often suffer from mild forms that are difficult to detect.

In the study presented in Chapter 6, we analyzed the presence of congenital heart defects in patients with CARMs. We demonstrated that even mild forms of CARMs can be associated with major congenital heart defects. These in turn can give rise to complications if an anesthesiologist is unaware of it prior to surgery.\textsuperscript{11-14} Furthermore, patients with congenital heart defects undergoing non-cardiac surgery have a greater perioperative risk of cardiac arrest and mortality.\textsuperscript{15-17} In patients born with severe forms of CARM, such surgery even needs to take place within 48 hours after birth.\textsuperscript{18} Although patients born with mild forms of CARM do not always need corrective surgery, they still need to undergo anesthesia for an electrostimulation test, which to date is the golden standard to determine whether surgical correction of anal canal within the sphincter complex is needed. Thus, almost all patients with CARMs need to undergo general anesthesia, whether it is within 48 hours after birth or at a later stage. It is, therefore, important to know whether a patient with CARM also suffers from a concomitant congenital heart defect. In our study, we observed no newly diagnosed heart defects in patients who were older than three months of age at the time CARM was diagnosed. The heart defects will probably also be noticed within this time frame. Altogether, we recommend screening for concomitant congenital heart defects in patients with CARMs younger than three months of age.

**Fecal continence reflexes in patients with congenital anorectal malformations**

Because patients with CARMs frequently experience fecal incontinence, one would expect that these patients were born without properly developed fecal continence mechanisms, or that these functions were accidentally altered during surgical correction. Voluntary contractions of the external anal sphincter and the puborectal muscle are known to be mediated through the pudendal nerve. These voluntary contractions are thought to play the only crucial role in fecal continence; therefore, corrective surgery for CARMs has been geared towards preventing
damage to this nerve. During posterior and anterior sagittal anorectoplasty, surgeons dissect in the medial plane to prevent neurovascular damage because the nerves run from lateral to medial.19 Nevertheless, because the patients still experience fecal incontinence frequently, we originally postulated that this condition resulted from the absence of the fecal continence reflexes described by us previously. With this in mind, we performed the study presented in Chapter 7. Surprisingly, we observed that almost all the patients with CARMs had fecal continence reflexes, even patients with the most severe forms. This meant that these patients should be able to become continent. To analyze in detail the phenomenon that patients with CARMs still frequently experience fecal incontinence, even with the fecal continence reflexes intact, we investigated other causes of fecal incontinence. We found that almost all patients suffered from dyssynergic defecation. Dyssynergic defecation is the paradoxical contraction of the external anal sphincter and puborectal muscle while trying to defecate, and can lead to overflow incontinence. In some cases we found that treating dyssynergic defecation resulted in fecal continence, and overall improvement of incontinence complaints in most cases. We recommend performing anorectal function tests to examine the presence of the fecal continence reflexes and to investigate whether the patient suffers from dyssynergic defecation. By so doing we can help these patients to become continent.

**Fecal continence outcomes in patients after ileal pouch-anal anastomosis**

In contrast to patients with CARMs, patients who undergo proctocolectomy with ileal pouch-anal anastomosis (IPAA) are usually born with a properly developed anorectum. As with patients with CARMs, patients with IPAA are prone to accidental damage of the fecal continence mechanisms during surgical intervention. Moreover, because the colon is removed, it does not extract any remaining water from the stool anymore, hence patients with an IPAA have a more watery stool compared to healthy individuals. As we found that there is only one reflex for liquid stool, it makes them even more prone to incontinence. Indeed, with the study presented in Chapter 8, we observed that more than one-third of the patients experienced fecal incontinence and most suffered from liquid stool incontinence that drastically decreased their quality of life. It is, therefore, important to decrease fecal incontinence in this group of patients. In this study we found a way of helping: the more proximal the IPAA, the better the fecal continence outcomes. This information is of crucial importance for surgeons, who should be aware to not place the anastomosis too close to the anal canal, if at all possible. Previous research already addressed the difference in fecal continence outcomes between stapled and hand-sewn anastomosis in favor of the stapled anastomosis, possibly thanks to better preservation of the anal canal and/or anal transition zone.20-24 We postulate that with the more proximal anastomosis the fecal continence reflexes remain intact. Further research on patients with IPAA, involving anorectal manometry and investigating the fecal continence reflexes, should elaborate on the findings reported in this study. In addition, such experiments could enable us to explain how the height of anastomosis affects the voluntary and involuntary contractions. This proposed study might also provide additional insight into the localization of the neural pathways of the fecal continence reflexes. Possibly, there is a cut-off point at some height of the anastomosis beyond which these
reflexes are still functional. In the light of such knowledge surgeons could, where possible, adjust their dissection plane to prevent damage of the neural pathways, and in so doing protect these patients from becoming incontinent.

Future perspectives

The studies presented in this thesis provide the foundation for future fundamental and clinical research. We identified the puborectal continence reflex and described how it functions in healthy subjects and patients, but the exact neural pathway to this reflex remains unknown. In order to identify which nerve belongs to the afferent and which to the efferent pathways of this reflex, we propose to inactivate, one by one, some nerves in the pelvic floor to investigate their effect on the puborectal continence reflex. At first sight, this would seem to be unethical. There is, however, a cohort of patients who undergo temporary inactivation of certain nerves, as a treatment, because they suffer from unbearable pain in the pelvic floor. On account of the fact that the origin of the pain is usually unclear and standard use of painkillers does not eliminate the pain, blockages are placed on certain nerves. This group of patients constitutes invaluable cohort to investigate the association between certain nerve blockages and the presence and absence of the fecal continence reflexes. To prove such an association, these patients should undergo anorectal function tests before and after placing the blockage, in order to enable us to provide direct proof that inactivation of a certain nerve also renders the reflex inactive. Moreover, a double blind randomized controlled trial whereby both the investigator and the patient are unaware whether and where a blockage is placed, would be the most objective study design.

Identifying the exact neural pathways responsible for the fecal continence reflexes would help to prevent accidental damage to these important nerves during surgery. Reflexes, however, do not consist of nerves only, but also of receptors. Identifying the receptors might pose a challenge, but could be performed by studying cadavers.

We observed that neither of the fecal continence reflexes diminished with age. This finding was based on cross-sectional studies, but a longitudinal study with an extended follow-up would be required to confirm this finding. In this way it would be possible to investigate the vitality of the various fecal continence mechanisms, including the voluntary and involuntary contractions of the external anal sphincter and the puborectal muscle.

We obtained information regarding fecal continence of patients with congenital anorectal malformations (CARM) from their medical files as recorded by pediatric surgeons during consultations. Ideally, we would use the Groningen Defecation and Fecal Continence (DeFeC) Questionnaire and compare the outcomes of the questionnaire before and after pelvic physical therapy.

In this thesis, we showed that surgical interventions in both patients with CARMs and with IPAA might result in an alteration of the fecal continence reflexes. It seems possible therefore
that other types of surgery performed in the pelvic floor region might also damage the reflexes. Therefore, investigation of the fecal continence outcomes and status of the fecal continence reflexes in patients subjected to other types of surgery would be of value to prevent more patients from developing postoperative fecal incontinence. For example, transanal minimally invasive surgery performed in patients with rectal carcinoma. During this surgery the incision is localized distally, and one can imagine that dissection performed up to the peritoneal reflection could also alter the fecal continence reflexes. Alteration of the reflex can happen as a result of damage to the neural pathway but also if, for example, the receptor has become dysfunctional. The second issue might be relevant in case of patients who undergo hemorrhoidal repair surgery or surgery for anal fissures. During these two types of surgery anal mucosa is subjected to relatively severe intervention. As we discussed in this thesis, it is most likely that the receptors belonging to the AESCR are located superficially, in the anal mucosa, or in the submucosa. The procedure might thus inactivate the receptors and impair the AESCR. Confirmation of this hypothesis would indicate the need for innovation in the field of surgery and development of less invasive treatment procedures. We postulate that surgery involving anal mucosa has less effect on the functionality of the puborectal continence reflex. Our hypothesis that it is activated through a stretch receptor, probably located deeper than the mucosa. This stresses the importance of investigating the functionality of both reflexes after such surgery.

In summary, fecal incontinence is a devastating condition. By presenting the studies contained in this thesis we hope to improve the fundamental knowledge regarding the mechanisms controlling fecal continence and the possible factors underlying fecal incontinence. Additionally, the studies in this thesis contribute toward improving diagnosis and treatment of patients with colorectal diseases undergoing either conservative treatment or colorectal surgery.
REFERENCES
