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Survey of anal sphincter dysfunction using anal manometry in patients with fecal incontinence: a possible guide to therapy

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Abstract

Background Despite the surge of new medical and surgical approaches to treat fecal incontinence, the types of sphincter abnormalities in patients with incontinence have not been well characterized. We aimed to categorize anal sphincter dysfunction using anorectal manometry in patients with fecal incontinence as a potential guide for improved treatment.

Methods A retrospective review of 162 consecutive patients with fecal incontinence referred for anorectal manometry was performed. Resting anal pressure and maximal squeeze pressure were considered as measures of internal anal sphincter and external anal sphincter function respectively.

Results Mean age of the patients was 63 years (13-89); females (81.5%) and males (18.5%). 74% of the patients had sphincter dysfunction on anorectal manometry. Internal anal sphincter dysfunction was present in 62% patients vs. external anal sphincter dysfunction present in 44% patients. 80% females had abnormal manometry vs. 44% in males (P<0.0001). Internal anal sphincter dysfunction was present in 68% females vs. 37% in males (P=0.0026).

Conclusions Overall, abnormal anorectal manometry studies revealed that internal anal sphincter dysfunction is the most common finding, alone or in combination with external anal sphincter dysfunction. We suggest that anorectal manometry may be important to delineate anal sphincter function prior to using newer therapeutic mechanical devices. Future studies using pharmacological agents to increase internal anal sphincter tone may be of clinical importance. Finally, the classification of fecal incontinence based on the type of sphincter dysfunction may be an improved guide in the selection of newer agents in treating fecal incontinence.

Keywords Fecal incontinence, anorectal manometry, internal anal sphincter

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Introduction

Fecal incontinence (FI) is defined as involuntary passage or the inability to control the discharge of fecal matter through the anus [1]. Based on a recent survey in US (2005-2010), the prevalence of FI among non-institutionalized U.S. adults was 8.39% [2]. Prevalence increased with age from 2.91% among 20-29-year-old participants to 16.16% among participants >70 years. The average total annual cost per FI person is around USD 17,166. The burden of FI is prevalent across the whole world. FI severely reduces the quality of life and also has psychosocial implications. It is relatively more common in women and elderly. Although the symptom is often attributed to obstetric anal sphincter injury among women with FI, the median age of onset is 62 years [3].

A recent National Institute of Health (NIH) consensus meeting held in 2013 to formulate an agenda for future research in FI focused its attention on defining and treating FI because of it major healthcare impact [4]. According to the majority of practical guidelines FI is characterized only clinically; i.e. passive incontinence, urge incontinence and fecal soilage [1]. Most clinical trials evaluating treatment efficacy of various interventions focus on only symptom scores.

FI is multifactorial associated with factors such as dysfunction in the internal anal sphincter (IAS), external anal sphincter (EAS) and recto-anal sensory dysfunction [5]. Anorectal manometry (ARM) provides morphological and physiological assessment of IAS and EAS, as well as recto-anal reflexes. Detailed yet specific

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pathophysiological information on the mechanisms of FI will provide important guidelines in the appropriate treatment of these patients [6]. Data from the past studies regarding ARM was obtained using conventional water perfusion manometry. Herein, we have used solid state manometry which is more sensitive and accurate method of ARM.

There has not been a definitive treatment algorithm of these patients [4]. New mechanical devices have been introduced recently and approved by the Food and Drug Administration (FDA), USA to treat FI; bulking agent injection; sacral nerve stimulation; and external anal electrical stimulation. Their mechanisms of action are unclear. These devices are promoted without guidelines based on diagnostic tests. They have been used without the specific knowledge and the extent of the type of sphincter dysfunction being treated and objective measures of response in each type of sphincter abnormality.

The aim of our study was to categorize anal sphincter dysfunction using high resolution ARM in consecutive patients with FI to determine the specificity of sphincter dysfunction. These studies will then be used as a guide to further therapeutic options; pharmacological agents or mechanical devices.

Patients and methods

Data from 162 consecutive patients with FI referred for ARM to the Gastrointestinal Motility Laboratory of the Division of Gastroenterology at Thomas Jefferson University during five-year period (January 2009 to December 2013) were analyzed in this study retrospectively. The institutional review board of Thomas Jefferson University approved the retrospective review of data.

All patients with fecal soilage referred to our motility center were included. Fecal soilage was defined as any episodes of involuntary passage of stool in liquid or solid form that was severe enough to seek medical care. This included urge and passive incontinence. We did not categorize patients based on urge or passive incontinence as this classification may not be widely used and our aim was to evaluate the type of sphincter abnormalities in patients with FI. Patients with prior anorectal surgery, scleroderma, inflammatory bowel diseases, spinal cord injury and rectal prolapse were excluded.

The resting anal pressure was considered as a measure of internal anal sphincter function while the squeeze pressure was considered as a measure of external anal sphincter function. It has been shown in various studies that resting anal pressures and squeeze pressures correlate well with internal anal sphincter and external anal sphincter function respectively [7-9].

Each patient underwent ARM after informed consent using a solid state manometry system (Konigsberg Anorectal Solid State Catheter, Medtronic, Minnesota, USA) using a standard technique. The same catheter system was used throughout the study patients. A solid state manometry catheter with 2 ports with sensors at 7 cm and 8 cm from the distal end of the catheter placed circumferentially was used. The manometry catheter was inserted deep inside the rectum with the patient in the left lateral position. The catheter was withdrawn slowly by 1 cm at a time so that the high pressure zone of the sphincter is reached and then it was pulled 0.5 cm at a time till it came out of the high pressure zone. The highest value obtained in the high pressure zone was considered as the resting anal pressure was recorded as the measure of IAS function. The evaluation of the EAS function was performed by measuring the squeeze sphincter pressure. For this, the manometry catheter was placed at the same position and the patient was asked to squeeze the anal sphincter as hard as possible for 5-10 sec. This was repeated twice and the highest value obtained from both the sensors was used to measure the squeeze sphincter pressure. A resting pressure (a measure of IAS function) of <20 mmHg and squeeze pressure of <25 mmHg were considered abnormal based on company settings. The rectal volume sensory function was also tested. For this, the probe was inserted to position the sensors 3 cm above the anal verge. Gradually 10 mL of air was inflated into rectal balloon over 5 sec and recordings of the patient's sensory response to the balloon distension were made. In the absence of any sensation to the balloon distension, balloon was emptied and inflated with 20 mL of air. A lack of sensation to 30 mL of balloon distension was considered positive for having impaired sensation to rectal distension.

Statistical analysis

The data were calculated for distribution using Shapiro-Wilk test. The data were normally distributed. Categorical data were analyzed by chi-squared test and Fisher's exact test as applicable. P value less than 0.05 was considered significant.

Results

The mean age of the patients was 63 years (range 13-89 years); females 81.5% (132/162) compared to males 18.5% (30/162). 74% (119/162) of the patients had sphincter dysfunction on manometric study, 17% (27/162) patients had impaired rectal sensation while 21% of the patients revealed no abnormality (Fig. 1). Abnormal manometry with sphincter

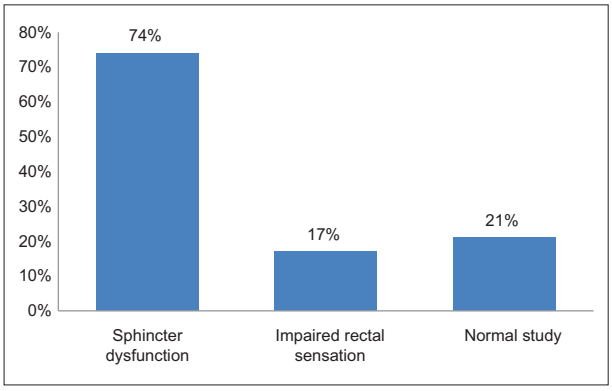

Figure 1 Distribution of patients having normal and abnormal manometry
Note that 21% of the patients did not have any sphincter or sensory dysfunction

dysfunction was further characterized based on the type of sphincter dysfunction present. Of 119 patients with sphincter dysfunction on manometry, only 15% (18) of the patients had isolated EAS dysfunction, while 40% (48) of the patients had isolated IAS dysfunction. 45% (53/119) of the patients had combined internal and external anal sphincter dysfunction (Fig. 2). Considering the overall involvement, EAS was involved in 44% of the total patients while IAS was involved in 62% patients.

Table 1 shows the sphincter dysfunction based on gender distribution. As shown, 80% of the females had sphincter dysfunction on manometry compared to 44% in males (Chi Square test, P<0.0001). IAS dysfunction was present in 68% of the females compared to 37% in males (chi-square test, P=0.0026). Of the total sphincter dysfunction in males, IAS was most commonly affected (85%) while EAS was affected in 15% of the patients having sphincter dysfunction. Of the females with sphincter dysfunction, IAS was also most commonly affected 85%, 90/109 while EAS was affected in 63% (69/109) of the patients. Twenty-seven of 162 (17%) patients had impaired rectal sensation on ARM. Eight of 27 patients had isolated rectal sensory impairment without any sphincter dysfunction. Thus, about 5% patients had isolated impaired rectal sensation without sphincter dysfunction, 12% patients having impaired rectal sensation in combination with one or other sphincter dysfunction.

Table 1 Manometric characteristics based on gender

Parameter	Total	Females (%)	Males (%)	P value (difference between females and males)
Total	162	132/162 (81.5)	30/162 (18.5)	
Abnormal manometry based on sphincter dysfunction	119	106/132 (80)	13/30 (44)	P<0.0001
IAS dysfunction	101	90/132 (68)	11/30 (37)	P=0.002
EAS dysfunction	71	69/132 (52)	2/30 (7)	P=0.001

IAS, internal anal sphincter; EAS, external anal sphincter

Discussion

The current study demonstrated four types of patients based on manometry: 1) isolated IAS dysfunction (30%); 2) isolated EAS dysfunction (11%); 3) combined IAS and EAS dysfunction (33%); and 4) normal sphincter function (26%).

The anal sphincter is composed of two sphincters, i.e. internal and external. Both sphincters are heterogeneously different in their properties. The IAS is made of smooth muscle that maintains sustained tone in the basal state, and is fatigue resistant [10-12]. The EAS on the other hand is made of skeletal muscles, is under voluntary control, and is fatigable [10-12]. Importantly, IAS contributes to 70-85% of the resting sphincter pressure and is chiefly responsible for anal continence at rest [10-12]. The puborectalis is a U-shaped component of the levator ani complex that helps maintain the rectoanal angle at rest. Maintenance of continence depends on the function of these sphincters, rectal sensation, and compliance.

In our study, the IAS was significantly more commonly involved in females. Studies show that anal sphincter dysfunction after vaginal delivery is a major risk factor for FI. Many studies imply the sole involvement of EAS in obstetric trauma [13-15]. However, only a few studies show that IAS may be equally involved as EAS in vaginal delivery [16,17]. A study by Sultan *et al* in women post vaginal delivery, 13% of the women had isolated IAS dysfunction compared to 5% having EAS dysfunction; 10% had combined dysfunction [16]. In another study by Richter *et al* in women post vaginal delivery 35% of the women had IAS dysfunction compared to 51% having EAS dysfunction; 27% had combined dysfunction [17]. The above studies in support of the present study show that IAS dysfunction is frequently present in women with FI. This dysfunction

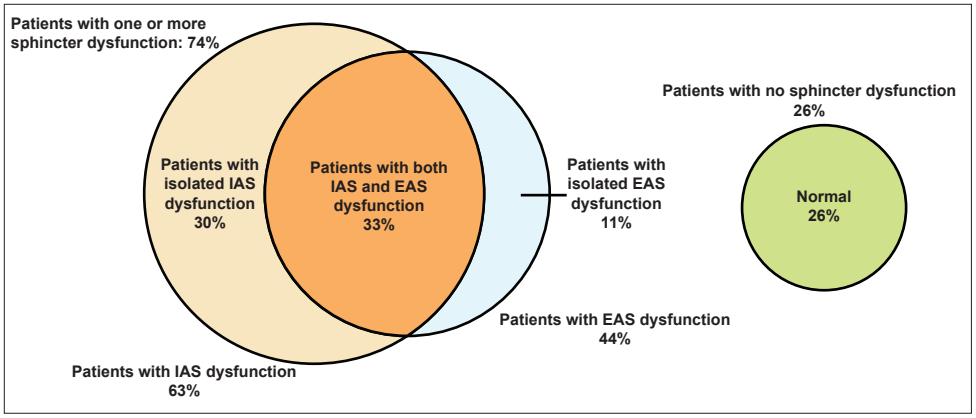

Figure 2 Quantitative Venn diagram showing the characteristics of the sphincter dysfunction involved in patients with abnormal sphincter function on manometry

IAS, internal anal sphincter; EAS, external anal sphincter

Note that there is a significantly higher number of patients with isolated IAS dysfunction compared to isolated EAS dysfunction

is manifested at a later stage of life. It is possible that age-related reduction in basal tone of internal anal sphincter may unmask the sphincter dysfunction causing FI.

In our study, 26% of the patients did not have any sphincter dysfunction. 5% of these patients had impaired rectal sensation probably leading to FI. FI in patients without anal sphincter dysfunction may suggest: 1) failure to maintain anal pressure during rectal distension; and 2) blunted sensation of bowel wall to rectal filling. Siproudhis in a prospective study in patients with FI with normal anal canal pressures demonstrated that a decrease in rectal adaptation could be involved in fecal leakage in patients without any rectoanal manometric abnormality [18]. However, an exact mechanism for the remaining 21% of the patients with FI that had normal anal pressures and rectal sensation is not presently understood.

A treatment algorithm for FI using anal manometry is not available. New agents are being introduced most of which are based only on clinical scores. Anal bulking agent injection, sacral nerve stimulation and external anal electrical stimulation are being used for the treatment of FI without objective evidence of pre or post procedural findings. The mechanisms of action are unclear and the cause of treatment failure is not known. Bulking agents are injected into the internal anal sphincter with the idea of thickening internal anal sphincter and prevent leakage of stool [19]. Sacral nerve stimulation seems to act by enhancing external anal sphincter activity as well as neuromodulation of sacral reflexes that regulate rectal sensitivity and contractility based on direct observations [20]. Direct anal electrical stimulation possibly acts by sensitization of the patient to the anal area and not by sphincter contraction based on a recent randomized controlled trial [21]. Also, it is unclear about the role of these devices in patients without any sphincter dysfunction. Anorectal manometry may be important to characterize sphincter dysfunction in patients with FI prior to considering these therapies.

The finding on anorectal manometry can further guide the therapy either pharmacological or mechanical. A novel classification of FI based on the precise characterization of sphincteric involvement or lack of this involvement is critical in selecting targeted therapy for FI with long-term outcomes that are free of side effects. This will also facilitate to objectively monitor and calibrate the improvement in sphincter dysfunction after a selected targeted treatment.

In contrast to urinary incontinence, there is no widely accepted classification system of FI. Currently, FI is classified based on type of leakage (urge, passive or soilage), etiology, pathophysiology (bowel disturbances or anorectal dysfunction) or symptom severity scale [4]. A recent NIH consensus meeting for guiding future research in FI to overcome the barriers in diagnosis and treatment of FI, mentioned the need to further develop this classification [4]. As demonstrated in this study, internal anal sphincter was the most commonly affected sphincter in patients with FI.

Presently, there are no systematic studies in humans examining the effects of pharmacological agents in the IAS function. Such data is expected to provide non invasive novel and rationale therapeutic approaches as compared to mechanical devices in patients with specific dysfunction of the IAS. Currently, there are no effective clinical guidelines for the gastroenterologists dealing with the selection of drug therapies for FI. A recent Cochrane database review of the drug therapies for the treatment of FI identified small trials that assessed different drugs in diverse population [22]. The focus of most of the trials included treatment of diarrhea rather than FI. There are potential pharmacological targets that can augment the tone of the internal anal sphincter. The IAS is innervated by the extrinsic (sympathetic and parasympathetic nerves), and the intrinsic or enteric nervous system. Stimulation of sympathetic nerves produces variable changes in the intraluminal pressures [23]. Table 2 lists pharmacological agents shown to augment IAS tone in humans and animals. This leads to an opportunity to pursue some of these agents to alleviate FI especially associated with IAS dysfunction.

Latest research showing that ROCKII siRNA by silencing Rho kinase gene decreasing IAS tone demonstrated specific role of Rho kinase in the molecular control of the basal tone in the IAS [35]. It is of interest that there is a large number of studies now that show the presence of noncoding small RNAs or miRNA (miR) that silence a number of genes within the smooth muscle cells and may work similar to the siRNAs, and

Table 2 Pharmacological agents that augment the IAS tone in animals and in humans

Agent	Mechanism of action	IAS pressure change	References
Phenylephrine	Alpha 1 receptor activator	Increase	24,25,26
A61603 –Experimental drug. (63.2 times potent than Phenylephrine)	Alpha1 receptor A/L subgroup activator	Increase	27
Imidazoline (Clonidine)	Alpha 2 receptor activator	Mixed (Increase or decrease)	28,29
Angiotensinogen	$AT_{1\text{-receptor}}$ activator	Increase	30
Prostaglandin	PGF2α activator	Increase	31,32
Thromboxane A_2 analog, U46619	Thromboxane receptor activator	Increase	32
5 HT agonist	5 HT receptor activator	Increase	31
Neuropeptide Y	Direct action on smooth muscle	Increase	33
Rho-kinase	Rho/ROCK pathway	Increase	34

IAS, internal anal sphincter; 5 HT, 5-hydroxytryptamine

for that reason they may be known as endogenous siRNAs [36]. Therefore, such miRNAs by targeting RhoA/ROCK may lower the basal IAS tone, and may contribute to the hypotensive IAS and thus to the pathogenesis of the IAS-associated FI [35]. It follows therefore that, once such siRNAs are identified in the specific cases of FI patients, it is possible to custom design an approach to specifically suppress the production of such siRNAs using specific anti-miR or antagomir. Such an approach may lead to targeted therapy in augmenting the IAS tone. Thus future novel research avenues studying the pharmacological agents to increase IAS tone is highly important.

This was a non-randomized study with a retrospective review of patients referred to a tertiary referral center for evaluation of FI. Due to the small sample size of the study (n=162) it is subject to the risk of Type II error. This study should be followed up with a large multicenter randomized control study to increase the statistical power for better significance.

Summary Box

What is already known:

- The burden of fecal incontinence (FI) is prevalent worldwide
- There is a lack of data regarding the frequency of specific type of sphincter involvement in FI
- According to the majority of practical guidelines FI is characterized only clinically; i.e. passive incontinence, urge incontinence and fecal soilage
- A recent National Institute of Health consensus meeting for guiding future research in FI to overcome the barriers in diagnosis and treatment of FI, mentioned the need to further develop this classification
- There is a lack of research in development of pharmacological agents that augment internal anal sphincter tone as there is a scarcity of data about the prevalence of internal anal sphincter dysfunction in patients with FI

What the new findings are:

- In patients with FI, internal anal sphincter dysfunction is the most common finding, alone or in combination with external anal sphincter dysfunction
- A novel classification of FI based on the precise characterization of sphincteric involvement or lack of this involvement is critical in selecting targeted therapy for FI with long-term outcomes that are free of side effects
- Future studies using pharmacological agents to target internal anal sphincter dysfunction by increasing the tone will be of clinical importance

The present study demonstrated several important findings that will further guide the current management of FI as well as guide further research in demonstrating pharmacological agents that augment IAS sphincter. 1) The IAS dysfunction is the most common finding, alone or in combination with EAS dysfunction. 2) Despite a history of incontinence, 26% of patients had no measurable sphincter abnormality, thus suggesting a non-muscular disease mechanism. 3) We suggest that anal manometry is important to delineate anal sphincter function prior to using newer interventional mechanical devices for therapy. 4) Future studies using pharmacological agents to target IAS dysfunction by increasing the tone will be of clinical importance. 5) Finally, the classification of FI based on the type of sphincter dysfunction may be a better guide in the selection of newer agents in treating FI.

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