Functional Asymmetry of Pelvic Floor Innervation and Its Role in the Pathogenesis of Fecal Incontinence

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Key Words

Fecal incontinence · Pathophysiology · Innervation · Asymmetry

Abstract

While the regular and symmetric innervation of the pelvic floor has been regarded as 'established' for many years, recent data indicate that asymmetry of innervation of the sphincters may exist and may contribute to the occurrence and severity of incontinence symptoms in case of pelvic floor trauma. **Methods:** A systematic review of published papers on asymmetry of sphincter innervation was performed including studies in healthy volunteers and patients with incontinence. 234 consecutive patients with fecal incontinence were investigated by means of side-separated mass surface EMG from the left and right side anal canal, these data were correlated to clinical and anamnestic findings. **Results:** The literature survey indicates that asymmetry of sphincter innervation exists in a subgroup of healthy male and female

volunteers, and may be a risk factor to become incontinent in case of trauma. Patients with incontinence in whom asymmetry of sphincter innervation could be shown more frequently reported a history of pelvic floor trauma during childbirth. Childbirth per se but not the number of deliveries predicted sphincter asymmetry. Asymmetrically innervated sphincters show a compromised sphincter function in routine anorectal manometry. **Conclusion:** Assessment of sphincter innervation asymmetry may be of value in clinical routine testing of patients with incontinence. However, a new technology is needed to replace mass surface EMG by multi-electrode arrays on a sphincter probe. This is one of the goals of the EU-sponsored research project OASIS.

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Assessing the Physiology of Continence and Pathophysiology of Incontinence

Incontinence to urine and/or stool can derive from a variety of clinical conditions, some of which are primary events where incontinence is an unavoidable consequence of the disease, such as bladder and/or anal/rectal cancer or inflammation of the respective storage organs. In many systemic disorders, incontinence occurs as the conse-

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quence of direct involvement of neural pathways to and from the bladder and anorectum, such as in multiple sclerosis, diabetes mellitus, and other diseases. Finally, if injury of the continence organs occurs with surgery (e.g. episiotomy) or trauma (e.g. delivery), incontinence may be the consequence [1]. In many cases however, incontinence appears to be 'idiopathic', that is without an immediate preceding event, and is usually attributed to age-related degeneration of the neuromuscular apparatus maintaining continence, or to traumatic events in the past (e.g. childbirth). As neurophysiological diagnostic testing has revealed pathologic findings in many of these patients, ideopathic incontinence is frequently also labelled 'neurogenic' [2].

Except for the determination of the terminal motor latency of the pudendal nerve (PNTML) by a less invasive technique [2] where a glove-mounted electrode is used to stimulate the pudendal nerve through the rectal wall, and evoked responses are recorded from the anal sphincter by another pair of electrodes at the finger base, neurophysiology of pelvic floor functions [as discussed in the paper by Vodusek, this issue] has never been a clinical routine tool used by many investigators and in many patients. This is due to the fact that needle EMG is an invasive and painful procedure for the patient, and requires lots of experience on the side of the clinician.

Other applications of surface EMG have only been used for assessment of the latencies of cortico-anal afferent and efferent pathways – for the whole pathway as well as for fractions thereof – via recordings of somatosensory and motor-evoked potentials [3], and mainly for research purposes only.

Consequently, very little is known about the normal neurophysiology of pelvic floor innervation in healthy volunteers, and contribution of its neuropathology to the pathogenesis of fecal and/or urinary incontinence. This is especially true for the question, whether innervation of the pelvic floor sphincters is symmetrical or asymmetrical in nature even in healthy volunteers, and whether this can be a contributing factor to the occurrence of incontinence symptoms.

Does 'Unilateral Pudendal Neuropathy' Truly Exist?

Routine clinical experience with recording of 'pudendal nerve terminal motor latency' (PNTML) [2] will occasionally result in differences of potential amplitudes and latencies, which have been attributed by some authors to

'unilateral pudendal neuropathy' but were assumed to be due to technical difficulties to achieve a good electrode-to-pudendal nerve contact on both sides during rectal digital examination by others.

From 174 patients with pelvic floor problems undergoing PNTML in a study by Sangwan et al. [4], 14 (8%) had no response on both sides, 24 (13.8%) responses from one side only. In the remaining 136 patients 83 (61%) normal latency, 53 (39%) had abnormal PNTML; from 53 patients with abnormal PNTML, 15 (28%) were delayed on both sides, and 38 (71%) on one side only. In total, i.e. $24 + 38 = 62$ (25%) had what the authors called 'unilateral pudendal neuropathy'. In a similar but larger report from another group [5], 153/1026 PNTML investigations (15%) showed delayed or missing response on one side only.

However, another explanation of this phenomenon would be that despite its anatomical symmetry, pudendal nerve function may as well be asymmetrical in some subjects, as is the case with other bilaterally innervated organs (e.g. the esophagus) [6]. If this holds true, it may carry significant clinical implications specifically in those subjects with asymmetry of innervation, e.g. in case of unilateral trauma [7]. A research hypothesis based on this assumption is illustrated in figure 1, and was the basis of subsequently conducted research (see below).

Evidence for Functional Asymmetry of Pelvic Floor Innervation

Intraoperative Monitoring of Pudendal Sensory and Motor Pathways

Deletis et al. [8] investigated children in whom individual dorsal root action potentials from the S1-S3 roots were recorded intraoperatively after electrical stimulation of the dorsal penile or clitoral nerves, in preparation for surgery within the cauda equina. In most patients, pudendal afferent activity was present in S2 and S3 bilaterally; in some, the afferent activity was confined to a single root bilaterally, and in one, to a single root on one side. No lesion of the roots or rootlets carrying significant afferent activity was created during the rhizotomy, and no micturition dysfunction resulted. The authors propose that the neurophysiological identification of roots and rootlets carrying significant afferent activity from the penile or clitoral nerves allows for rhizotomy of the S2 roots with the least possible risk of postoperative micturition and sexual dysfunction.

Fig. 1. A research hypothesis of the clinical relevance of functional pudendal nerve asymmetry in case of unilateral trauma.

In a replication study by the same groups [9], 114 children with the diagnosis of cerebral palsy and debilitating spasticity were selected to undergo selective posterior rhizotomies. At the time of surgery, none of the patients had clinically relevant bladder dysfunction. In the majority of these patients (56%), the distribution was asymmetrical. S1 roots contributed 4%, S2 roots 60.5%, and S3 roots 35.5% of the overall pudendal afferent activity. The pudendal afferent distribution was often confined to a single level in 18% of the patients or even to a single root in 7.6%. None of the 105 patients so mapped developed long-term bowel or bladder complications.

Recently, Deletis et al. [10] compared the radicular distribution of anal and penile/clitoral afferents in 22 of these children. A plug electrode was inserted in the anus for stimulation of anal mucosal afferents and surface cup-electrodes were attached to the penis/clitoris for stimulation of the dorsal penile/clitoral nerves. For anal and penile/clitoral afferents, S2 or S3 roots were the main carriers. S1 was never the main carrier. In more than half of the patients, the main carrier was identical, while in 41% the main carrier of anal afferents was caudal to that of penile/clitoral afferents. In 9% the main and only carrier of anal afferents was a single root. Dissociation of fecal and urinary incontinence could be explained by different primary sacral carrier roots for anal and penile/clitoral afferents.

Sacral spinal root pacemaker implantation is a new technique in treatment of fecal incontinence but requires intraoperative decision which two of the six potentially functional sacral spinal nerves should carry the electrodes. Matzel et al. [11] investigated 6 incontinent patients undergoing evaluation for chronic sacral spinal nerve stimulation and in 7 continent patients undergoing

testing for treatment of neurogenic bladder, concentric needle EMG was recorded bilaterally from the external anal sphincter during percutaneous stimulation of the left and right S2 to S4 roots with varying intensities. In all but one incontinent patient, and in 3/7 continent patients the dominant side was on the left. In both patient groups ipsilateral EMG responses were always to identify, while contralateral EMG was only found in some cases. Both in continent as well as in incontinent patients, the dominant level (S2, S3, S4) was often not symmetrical and in many cases, the highest responses obtained from left and right side root stimulation were not on the same level.

Central Mapping of Motor and Sensory Representation of the Pelvic Floor

Topographic cortical mapping of both cerebral hemispheres was performed by Turnbull et al. [12] in 9 healthy subjects by applying suprathreshold transcranial magnetic stimulation (TMS) to individual points on a scalp grid centered over the vertex and then recording the electromyographic responses from the external anal sphincter, rectum, and tibialis anterior muscles. Cortical mapping showed that the anal responses were bilaterally represented on the superior motor cortex of both cerebral hemispheres; a similar topography was found for the rectal responses. By comparison, the tibialis responses showed predominantly contralateral medial motor cortex representation. Subtle but consistent differences in the degree of bilateral hemispheric representation were also apparent both between and within individuals for the anal responses and to a lesser extent for the rectal responses. In conclusions, the anorectal musculature has bilateral motor cortex representation with similar topography, but there is intersubject variation in the degree of symmetry.

Table 1. Cortical representation of the anal canal during MEG recording after end stimulation

Subjects	S1 source	S2 source
AF	left	bilateral
RP	right	bilateral
PM	bilateral	bilateral
MR	left	bilateral
KS	right	bilateral
SU	left	bilateral
PE	bilateral	bilateral

A similar study by another group was undertaken [13] in ten healthy volunteers (8 right-handed, 2 left-handed). A plug electrode located in the anal canal recorded anal sphincter EMG responses. TMS was performed using a figure-of-eight-shaped coil with the stimulus intensity set separately for each hemisphere at $1.1 \times$ motor threshold, over the whole area of representation. Across all subjects, latencies and motor thresholds were similar between the dominant and the non-dominant hemisphere. The area over the non-dominant hemisphere was significantly larger compared to the dominant one. However, in 2/10 cases the intraindividual left:right area of activation was asymmetric ($>30\%$ difference), in one case each the left or the right side was dominant. This distribution was not related to handedness.

To compare cortical responses following electrical stimulation of the human anal canal to responses after stimulation of median and tibial nerves, Stottrop et al. [14] employed magneto-encephalography (MEG). Electrical stimuli were applied to the anal canal, and to median and tibial nerves at different repetition rates, using below-pain-threshold intensities. Magnetic brain responses were averaged time-locked to the stimuli. Magnetic responses to stimulation of the anal canal were explained by unilateral (5 subjects) or bilateral (2 subjects) sources located in SI between hand and foot area, peaking at 100–190 ms, and bilateral sources near the Sylvian fissure peaking at 120–190 ms, most probably representing SII activation. At least in a subgroup of volunteers this representation is asymmetrical (table 1).

Peripheral Nerve Stimulation and Recording

To explore the individual effects of left and right pudendal nerve stimulation on the corticofugal pathways to the human external anal sphincter and thus assess evidence for functional asymmetric pelvic innervation,

Hamdy et al. [15], after finding evidence for pudendal asymmetry in an earlier study, investigated healthy subjects, in whom anal sphincter electromyographic responses, evoked by transcranial magnetic stimulation (RMS) of the motor cortex, were recorded 5–500 ms after digital transrectal electrical conditioning stimuli applied to each pudendal nerve [16]. Right or left pudendal nerve stimulation evoked anal responses of similar latencies but asymmetric amplitudes in six subjects: dominant responses ($>50\%$ contralateral side) from the right pudendal in four subjects and from the left in two. Cortical stimulation preceded by pudendal nerve stimulation facilitated the response, but induced greater facilitation on the dominant side than on the non-dominant side.

To explore whether muscular function of the external anal sphincter (EAS) is symmetrical or asymmetrical in healthy volunteer, 17 healthy volunteers were investigated by needle EMG of the anal sphincter muscle [17]. At least 20 evoked muscle action potentials (EMAP) at a minimum of 5 different insertion sites were recorded for each side of the muscle. In 14/17 subjects (82%) the mean left ($n = 11$) or right side ($n = 3$) amplitude exceeded the other side by more than 10%. In 6/17 subjects (35%), significant intraindividual asymmetries of EMAP amplitudes were found (fig. 2a, b). None of the differences found were directly related to gender and age of the subjects.

In summary, there is sufficient empirical evidence to assume that the left-to-right ratio of pelvic floor functions is asymmetrical in a subgroup of volunteers and/or patients; based on the preliminary data cited above, this fraction may be about 20%, while in the remaining, the function may be symmetrical. It is currently open to discussion, whether this asymmetry is cortical in nature, or whether any cortical sign of asymmetry is only reflecting peripheral dominance of pudendal pathway utilization.

Clinical Relevance of Asymmetry in Patients with Incontinence

Left- and right-side anal surface EMG (S-EMG) recordings by means of a modified anal plug with a pair of electrodes on each side and a conventional S-EMG system was used to assess the innervation of the external anal sphincter at both sides in the anal canal separately [18]. Three cohorts were studied: 40 nulliparous women in the third trimester (study 1), 15 primiparae within 6 months after non-traumatic vaginal delivery (study 2), and 50 women after childbirth-related 3rd or 4th degree perineal

Fig. 2. a Example of needle-EMG recordings in the left and right anal sphincter muscle following different needle insertions on each side. Note the difference in EMG amplitude for all recorded potentials. This is the recording in a young and healthy male volunteer with our previous sphincter trauma. **b** Distribution of left/right side difference among 17 healthy male and female volunteers. In 6/17 subjects the difference reached significance levels either on the left or right side.

Table 2. Patients investigated by S-EMG for asymmetry of EMG amplitudes on each side of the anal canal

EMG of the external anal sphincter muscle							Symptoms incontinence yes/no
patient No.	right			left			
1	12	12	12	12	12	12	no
2	5	5	5	5	5	5	no
3	10	10	9	9	10	9	no
4	3	3	3	6	6	5	yes
5	6	6	5	6	5	5	no
6	8	8	8	11	11	10	no
7	10	10	10	7	6	7	yes
8	9	9	9	9	9	9	no
9	8	8	8	8	8	8	yes
10	10	9	10	11	11	11	yes
11	6	6	7	8	8	7	yes
12	6	6	6	10	10	9	yes
13	6	6	6	9	9	9	yes
14	6	6	6	9	9	9	yes
15	10	10	10	9	9	9	no
16	3	3	3	6	6	6	yes
17	9	8	8	11	11	11	yes
18	6	7	6	11	11	11	yes
19	8	8	8	9	9	9	yes
20	7	7	7	8	8	8	no
21	7	8	7	9	9	9	no

Correlation between symptoms and symmetry: $\chi^2 = 4.385$, $p < 0.05$.

tear 6–12 months postpartum (study 3). Sixteen of the 40 nulliparous reported signs of mild fecal incontinence; however, relative asymmetry was neither correlated to symptom severity nor to manometric measures (study 1). In study 2, 6/15 women had an episiotomy performed of which two developed severe incontinence; 2 more women without episiotomies had incontinence signs postpartum. The association between asymmetry and incontinence did not reach significance level; however, comparison of pre- and postpartal measures of S-EMG showed high reproducibility within subjects. In study 3, 19/50 women reported moderate to severe incontinence. Asymmetry and symptom severity were significantly correlated (table 2). Manometry revealed a significant negative correlation between relative asymmetry and squeeze pressure but not with resting pressure. It was concluded that functional asymmetry of anal sphincter innervation is associated with incontinence symptoms, but only after childbirth-related injuries (trauma).

With the same technique, a large series of patients with fecal incontinence were investigated during routine diagnostic work-up [19] in 234 consecutive patients of an incontinence outpatient clinic to assess the functional

innervation of the left and right side external anal sphincter (EAS). Patients were predominantly women (83%), average age was 70.7 (18–87) (men: 57.1, women: 61.4) years. Besides being investigated by mass surface EMG, all patients underwent conventional clinical diagnostic work-up including anorectal manometry, endoanal ultrasound, defecography, and other routines.

Surface EMG was repeated three times per side to assure reproducibility. A symmetry index was computed according to the formula $SI = \text{mean (left-right)} / \text{max (left, right)}$ of the EMG amplitude; it defined the relative S-EMG amplitude symmetry of both sides between 0 (symmetric) and ± 1 (asymmetric). The overall distribution of the SI was normally distributed around ‘zero’, as shown in figure 3. To define a subgroup of patients with asymmetry, the total range was split based on normal values collected in healthy subjects, and patients with a $SI < -0.5$ or $> +0.5$ were regarded as asymmetric. This left 164 of 234 patients (70%) as symmetric (131:33 female:male), and 70 (30%) (63:7 female:male) as asymmetric. More women than men were identified as asymmetric, the association between female gender and asymmetry status was significant ($\chi^2 = 4.1$, $p = 0.03$).

Fig. 3. Distribution of S-EMG amplitude side differences among 234 consecutive patients with fecal incontinence. Note the nearly normal distribution of values.

Among the (female) patients with asymmetric innervation, 54 (77%) had a history of deliveries, while in the symmetric group, this were 109 (83%). The SI between women with childbirth was significantly higher than in those without (0.23 ± 0.03 vs. 0.31 ± 0.015 ; *t* test, $p = 0.024$). The degree of asymmetry was not related to the number of childbirths.

Asymmetry degree was correlated to the results of diagnostic work-up to identify major determinants and consequences of relative asymmetry, but without the investigators knowing the results of symmetry assessment. In both men and women, it was also significantly and negatively correlated to the EAS squeeze pressure when registered digitally ($p = 0.035$) or manometrically ($p = 0.001$ for maximal and $p = 0.001$ for sustained EAS contraction) (fig. 4), and with a positive result for sphincter defects in endosonography ($p = 0.024$). Association with EAS squeeze pressure was stronger in men than in women, but in men, it was also correlated positively to resting pressure.

The symmetry status (SI) also correlated with the degree of incontinence, as assessed by the Wexner score: Patients with severe incontinence (Wexner >5) were significantly more frequent asymmetric than those with Wexner scores ≤ 5 (table 3) ($\chi^2 = 3.22$, $p = 0.035$).

Functional asymmetry of EAS innervation appears to be varying from physiological to pathophysiological grades, and in the latter case, is resulting in decreased

Fig. 4. Difference in EAS maximum contraction amplitude (in mm Hg) in patients with and without asymmetric sphincter innervation. The difference is statistically significant (71.5 ± 6.2 vs. 113.21 ± 5.0 mm Hg, $p < 0.001$).

squeeze pressures of the EAS. However, overall moderate to weak correlations indicate other important factors contributing to symptom development and severity on the one hand and asymmetry of sphincter innervation on the other.

Fig. 5. Original recording of surface EMG from the anal sphincter muscle (top). Enlargements of parts of the tracing to show different motor units travelling along the muscle fibre across all 5 channels (bottom).

Table 3. Association between symmetry and severity of incontinence

	Wexner score		Σ
	≤ 5	> 5	
Symmetric	49	115	164
Not symmetric	13	57	70
Σ	62	172	234

The Project OASIS (On ASymmetry In Sphincters)

While the above-cited literature gives first evidence to the clinical relevance of functional asymmetry of sphincter innervation, important questions remain and can only be resolved with a new technology that allows screening of the pelvic floor innervation is large patient and volunteer

cohorts. This – per se – excludes conventional neurophysiological techniques based on needle EMG from this task. On the other hand, surface EMG has so far only been used to evaluated within-subject changes of pelvic floor function with therapy, e.g. after biofeedback training [20], or latencies of somatosensory and somatomotoric responses following central, spinal, or peripheral stimulation of the pathways [2, 4, 21, 22]; it is not regarded as appropriate technique to diagnose pelvic floor innervation and its dysfunctions [23; see paper by Vodusek, this issue].

A recently described new technology using multi-electrode arrays (MEA) to study individual motor unit action potentials (MUAP) from large muscle in the body's periphery [24, 25] was the starting point of the European-community-sponsored research project who's first results are reported with this special issue. It is named OASIS (On ASymmetry In Sphincters – The role of functional asymmetry in sphincter innervation for incontinence, QLRT-2001-00218) and includes 4 clinical partners (from gastroenterology, surgery, gynecology, and urology),

Fig. 6. Three multi-electrode arrays with 16 electrodes each on an anal probe (diameter: 1.4 cm) (prototype, developed by Prof. Merletti, Torino) [see paper by Merletti, this issue].

an academic partner with expertise in biomedical engineering and two small-size companies.

The first application of this technique to the study of the anal sphincter innervation and a first recording of MUAPs from the anal and urethral sphincters marked the beginning of this project (fig. 5). A new probe (fig. 6) with 16 surface-EMG electrodes was tested in a series of healthy volunteers without signs of clinical incontinence to record the origin and propagation of MUAP circumfer-

entially along the muscle fibers from the external anal sphincter muscle at three levels (at the anal orifice and 1 and 2 cm proximal) in healthy volunteers [26; see paper by Enck et al., this issue].

It was shown that MUAPs were reliably recorded during maximum contractions; occasional MUAPs were detectable under resting conditions. Characterization of MUAPs by means of multi-electrode arrays reveals individual as well as general patterns of innervation of the external anal sphincter that can and should be used for evaluation in pelvic floor disorders.

Meanwhile, these findings have been replicated in many more subjects, and first data have been recorded from the urethral sphincter as well. Automated signal detection and analysis by a 'pattern recognition program' has revealed the potential of this technique to detect not only individual MUAP within subjects but also individual patterns of asymmetry of sphincter innervation. Data from patients with both urinary and fecal incontinence are currently collected in all clinical centers and will allow to answer the question of the relevance of asymmetry of sphincter innervation in the near future. Thus, pelvic floor neurophysiology has opened a new chapter, irrespective of the importance of its symmetry and asymmetry of innervation. It will have to be shown, however, in the future whether the new technique will confirm the clinical relevance of asymmetry in case of pelvic floor trauma and incontinence.

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