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Evaluation of Lower Urinary Tract Sensory Evoked Potentials in patients with Overactive Bladder

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Resumo

Introdução: A Bexiga Hiperativa (BH) define-se como urgência urinária, normalmente associada ao aumento da frequência e/ ou noctúria. Apenas metade da população com BH apresenta aumento da atividade do músculo detrusor da bexiga, o que realça a necessidade de investigar outras etiologias, entre as quais anomalias da via neurológica aferente do Trato Urinário Inferior (TUI). Contudo, devido à ausência de meios complementares de diagnóstico bem estabelecidos, é difícil detetar alterações na condução sensitiva do TUI. Os Potenciais Evocados Sensitivos (PESs) têm vindo a ganhar importância na avaliação neuro-urológica, embora insuficiente de modo a permitir uma melhor compreensão de algumas patologias do TUI.

Objetivos: Descrever um protocolo preliminar de avaliação dos PESs do trato urinário inferior, e respetivos resultados, num grupo de 4 doentes com bexiga hiperativa, assim como compará-los com estudos internacionais prévios realizados em participantes saudáveis.

Metodologia: Recrutamos quatro doentes seguidos na consulta de urologia do Centro Hospitalar Universitário do Porto (CHUPorto) com diagnóstico de bexiga hiperativa sem resposta à terapêutica médica otimizada. Recolhemos a história clínica, exame físico e dados do estudo urodinâmico. Estímulos elétricos (3Hz/ 0.2ms) foram aplicados no Esfíncter Uretral Externo (EUE). Em seguida, registamos e analisamos as latências dos PESs do nervo tibial posterior e do EUE, este último com volume vesical de 50 mL e o correspondente a 80% da Capacidade Vesical Máxima (CVM).

Resultados: Estudamos 4 participantes, 1 do sexo masculino e os restantes do sexo feminino. A média de idades foi de 55 anos, com média de peso e altura de 79 kg e 169 cm, respetivamente. Os participantes foram nomeados S1, S2, S3 e S4. S1, do sexo masculino com bexiga hiperativa de etiologia neurogénica (esclerose múltipla), enquanto os restantes 3 eram do sexo feminino com bexiga hiperativa não neurogénica. A média da CVM foi de 428,2 ± 32,1 mL. Com volume vesical de 50 mL, obteve-se uma média de latências de 37,6 ± 4,6 ms. Com volume vesical a corresponder a 80% da CVM, verificou-se uma média de latências de 40,4 ± 10,0 ms. Não se verificou diferença significativa entre as latências dos PESs com os diferentes volumes vesicais.

Conclusões: Foi possível replicar os PESs do trato urinário inferior em doentes com bexiga hiperativa, como anteriormente demonstrado em populações saudáveis. Porém não identificamos nenhuma característica definidora dos PESs em doentes com esta síndrome, eventualmente devido à nossa amostra reduzida e heterogénea.

Palavras-chave: lower urinary tract, neurophysiology, evoked potentials, overactive bladder.

Abstract

***Introduction**:* Overactive Bladder (OAB) Syndrome is defined as urinary urgency, usually accompanied by increased daytime frequency and/or nocturia. Only half of the patients who have urinary urgency present with urodynamic detrusor overactivity which demonstrates the need to search for other aetiologies such as improper signalling of the bladder afferent pathways. Nevertheless, it is currently difficult to detect alterations in afferent conduction due to the lack of an established objective and reliable clinical assessment tool. The use of Sensory Evoked Potentials (SEPs) in neuro-urological evaluation has recently been gaining support though it has not yet progressed sufficiently to enable a better understanding of Lower Urinary Tract (LUT) dysfunctions.

Objectives: We aim to describe a preliminary LUT SEPs evaluation protocol and its results in a group of four patients with OAB. Furthermore, we seek to compare our participants' data to the results of healthy populations described in previous international studies.

Methods: We recruited four patients followed in the urology medical consultation of Centro Hospitalar Universitário do Porto (CHUPorto) with a diagnosis of OAB syndrome unresponsive to optimal medical treatment. We collected the complete medical history, physical examination, and urodynamic parameters. Electric stimulation (3Hz/0.2 ms) was applied at the External Urethral Sphincter (EUS). Then, we recorded and analysed the SEPs latencies of the posterior tibial nerve, and of the EUS with a bladder volume of 50 mL and at 80% of Maximum Bladder Capacity (MBC).

Results: We studied 4 subjects, 3 women and 1 man. The patient's average age was 55 years, with a mean body weight and height of 79 kg and 169 cm, respectively. We named our subjects as S1, S2, S3 and S4. S1 was a man who had a neurological OAB (Multiple Sclerosis) while S2, S3 and S4 were all women with non-neurological OAB. The MBC average was 428,2 ± 32,1 mL. We obtained a latency mean of 37,6 ± 4,6 ms with 50 mL of bladder volume. With a bladder volume corresponding to 80% of MBC, the latency mean was 40,4 ± 10,0 ms. SEPs latencies were not significantly different between bladder volumes.

Conclusions: It was possible to replicate LUT SEPs in OAB patients as had been previously reported in healthy subjects in international studies. However, we could not detect any defining characteristic of OAB LUT SEPs possibly due to our narrow and heterogeneous sample.

Keywords: lower urinary tract, neurophysiology, evoked potentials, overactive bladder.

Lista de abreviaturas

BMI – Body Mass Index

CHUPorto - Centro Hospitalar Universitário do Porto

ES – Electrical Stimulation

EUS - External Urethral Sphincter

ICIQ-OAB - International Consultation on Incontinence Questionnaire - Overactive Bladder

LUT - Lower Urinary Tract

LUTS - Lower Urinary Tract Symptoms

MBC - Maximum Bladder Capacity

MS - Multiple Sclerosis

OAB - Overactive Bladder

SEPs - Sensory Evoked Potentials

Índice

Introduction

Lower Urinary Tract Symptoms (LUTS) encompass storage, voiding and post-micturition symptoms [1] and are highly prevalent in the worldwide population. Overactive Bladder (OAB) Syndrome is defined by the International Continence Society as urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with or without incontinence.[2] Current literature suggests that several pathophysiological factors and neurogenic and non-neurogenic mechanisms might be responsible for the nonspecific symptom complex of OAB. [3,4]

OAB syndrome definition is still being challenged as it focuses more on overt bladder contractions rather than the main problem, which is an altered and heightened urge sensation. In other words, just half of the patients who have urinary urgency present with urodynamic detrusor involuntary contractions, while the remainder have the same symptoms but no such activity.[5] This demonstrates the paramount need to search for other aetiologies such as the improper signalling of the bladder afferent pathways.

Since the beginning of this millennium, it has become clear that the afferent nervous system plays an important role in the regulation of Lower Urinary Tract (LUT) function.[6] Nevertheless, it is currently difficult to detect alterations of the human afferent bladder pathways due to the lack of an established objective and reliable clinical assessment tool. Consequently, this hypothetical pathological mechanism behind OAB remains unclear. [7]

Bladder afferent pathways start from the urothelium, and sensory nerves (primary bladder afferents) reach the dorsal root ganglia and then travel through the spinal cord to reach the pons, midbrain, and higher brain. Afferent information from the LUT is carried in three sets of nerves: the pudendal, pelvic and hypogastric.[8] In general, information from the external sphincter is carried in the pudendal nerve while signals from the urethra, bladder neck and body ascend through the pelvic and hypogastric nerves.[9] It is also likely that each major nerve contains afferent fibres of different types, and fibres associated with the different reflexes. Thus, there are many inputs travelling in different nerves contributing to different physiological systems that permanently need to be interpreted by the human central nervous system. The problem is to unravel this complexity and dissect this “afferent noise” to better understand OAB syndrome pathophysiology.[10]

Urodynamic testing refers to a group of tests used to measure various aspects of urine storage and evacuation, providing a comprehensive analysis of LUT function. However, these studies largely rely on subjective or semi-objective criteria based on intravesical and intra-abdominal

pressures. [11] Most urodynamic parameters show variability within the same session and over time, and this may limit clinical interpretation. One promising alternative is the assessment of Sensory Evoked Potentials (SEPs). Electrical stimulation of a nerve or dermatome is typically followed by an evoked potential, evaluated according to latency and amplitude, which can be measured along the spinal cord or at the cortex. SEPs has become a well-established method to assess afferent nerve fibre function.[7,12] The use of SEPs in neuro-urological evaluation is currently gaining support as a reliable clinical tool.[13,14] In other words, cortical SEPs could be used to objectively assess the functionality of the afferent fibres from lower urinary tract to the cortex and represent the electrical activity of the brain in response to electrical stimulation.[15] However, while tibial and pudendal nerve stimulation are well established in clinical practice, the measurement of lower urinary tract SEPs have not yet progressed so far as to enable a better understanding of LUT dysfunctions.

With this study, we aim to describe a preliminary LUT SEPs evaluation protocol and its results in a group of patients with OAB. Furthermore, we seek to compare our participants' data to the results of healthy populations described in previous international studies.

Methods

Subjects

We started by recruiting four patients followed in the urology medical consultation of Centro Hospitalar Universitário do Porto (CHUPorto) with a diagnosis of OAB syndrome unresponsive to optimal medical treatment. Exclusion criteria were age over 75 years and under 18 years, urinary tract infection, pregnancy, breastfeeding, radiation exposure or urinary tract surgery in the previous 12 months. All subjects provided written informed consent prior to inclusion in this study. We collected the complete medical history, physical examination, free uroflowmetry, post voiding residual and other urodynamic findings (maximum bladder capacity, compliance, vesical overactivity, detrusor pressions, maximum flow). Additionally, we applied the International Consultation on Incontinence Questionnaire - Overactive Bladder (ICIQ-OAB)[16], a urological standardised questionnaire validated for the Portuguese language in which the higher the score the greater the impact in a patient's life. This study was approved by the Administration Board, direction of the Department of Education, Formation and Research and Ethics Committee of CHUPorto/ICBAS with the reference number 2021.320 (265-DEFI/ 273-CE).

Electrical Stimulation

Using a sterile and disposable urethral catheter electrode 10 Fr (manufactured by Spes Medica S.r.l.) (figure 1), bipolar electric stimulation was applied at the External Urethral Sphincter (EUS). The exposed electrodes of the urethral catheter contacted with the mucosal lining of the urethra at the EUS. To ensure that the electrode is positioned correctly, gentle traction was used on the catheter to maintain the balloon against the bladder neck. The electrical stimulation in the posterior urethra was determined by a gradually increasing current strength with a stimulus frequency of 3 Hz and a stimulus duration of 0.2 ms, reaching the highest tolerable level for each stimulation series.

The electrical current was generated using an electromyograph with the Keypoint. NET v2.40 software. As a methodological standard reference, tibial SEPs (left side only) were also measured in all patients, adopting a previously described technique.[17] During the exam, subjects were supine and had their eyes closed. Neuromonitoring was supervised by a neurophysiologist (Márcio Cardoso) and performed by two board-certified neurophysiology technicians (Mónica Freitas and Ana Lopes).

Sensory Evoked Potentials (SEPs)

Three cortical electrodes were located with the active electrode at Cz and the reference at Fz, according to the 10-20 international system.[18] The ground electrode was placed at the superior crest of the ilium. Impedance was kept below 5 kΩ for entire electrodes. We recorded the SEPs of the posterior tibial nerve (T), and of the external urethral sphincter with a bladder volume of 50 mL and at 80% of Maximum Bladder Capacity (MBC) (V1 and V2, respectively). Evoked potential signals were continuously recorded using Dantec Dynamics/ Keypoint 2.4. All data were filtered from 10 Hz to 3 kHz. Conforming to the direction of detected SEPs deflections, the 1 negative and 2 positive peaks were named N1, P1 and P2, respectively. After measuring the averages of each measurement, the N1 latencies of the SEPs were calculated semi-automatically through Keypoint.NET 2.4. The study protocol is systematised in figure 2.

Statistical Analysis

Data was analysed with IBM® SPSS® Statistics 27 for Windows. For categorical variables, absolute frequencies (n) and percentages (%) were calculated. We also performed the two-sample t-test.

Results

We reviewed the medical files of 4 patients, 3 women and 1 man, with a diagnosis of OAB syndrome unresponsive to optimal medical treatment. The patient's average age was 55 years, with a mean body weight of 79 kg and a mean body height of 169 cm. The participants' urodynamic parameters are listed in table I.

All participants performed the procedure to completion despite all reporting transitory urinary discomfort. No subject experienced adverse events. We named our subjects as S1, S2, S3 and S4. Subject number 1 (S1) was a man who had an OAB of neurological aetiology, in particular Multiple Sclerosis (MS), while S2, S3 and S4 were all women with non-neurological OAB.

The mean of ICIQ-OAB was 6 (maximum of 16). The MBC average was 428,2 ± 32,1 mL during urodynamic studies. The mean of posterior tibial SEPs intensity and latencies were 15,6 **±** 5,0 mA and 46,3 ± 8,8 ms, respectively. After recording external urethral sphincter evoked potentials with 50,0 mL of bladder volume, at a mean intensity of 25,0 ± 15,3 mA, we obtained a latency mean of 37,6 ± 4,6 ms. With a bladder volume corresponding to 80% of MBC (strongest desire), the latency mean was 40,4 ± 10,0 ms to an intensity average of 25,0 ± 15,9 mA. SEPs intensities and latencies are exposed in table II. Figure 3 illustrates an example of the graphics of the results of SEPs intensities and latencies with two different volumes, V1 and V2. SEPs latencies were not significantly different between bladder volumes (50 mL vs 80% of MBC).

Subject 1 (S1)

Subject 1 was a 49 years-old man, 85 kg and 185 cm (BMI 24,8) with a history of multiple sclerosis. His OAB was characterised by urgency, weak stream, intermittence, urinary hesitancy, and feeling of incomplete emptying and dripping. Bulbocavernosus and cremasteric reflex on the physical exam were normal. His MBC was 403,0 mL with no urodynamic detrusor overactivity registered and normal bladder compliance. The subject scored 5/16 in the ICIQ-OAB questionnaire, with an urgency qualitative measure of 3/4. The V1 and V2 latencies were 43,7 and 57,0 ms, respectively.

Subject 2 (S2)

Subject 2 was a 59 years-old woman, with 81 kg and 161 cm (BMI 31,2), diagnosed with non-neurogenic OAB, arterial hypertension, dyslipidemia, and clinical depression. Her OAB symptoms were nocturia, increased voiding frequency (1/1h), urgency and urge incontinence. Her MBC was 480 mL. Urodynamic study revealed bladder overactivity with a normal bladder compliance. She scored 8/16 in the ICIQ-OAB, with an urgency qualitative measure of 3/4. The V1 and V2 latencies were 39,6 and 38,3 ms, respectively.

Subject 3 (S3)

Subject number 3 was a 53 years-old female, with 79 kg and 164 cm (BMI 29,4), diagnosed with non-neurogenic OAB and arterial hypertension. Her OAB symptoms consisted of nocturia, increased voiding frequency (3/3h), urgency, urge incontinence and feeling of incomplete emptying. Her MBC was 430 mL. Urodynamic study revealed bladder overactivity with a normal bladder compliance. She scored 2/16 in the ICIQ-OAB, with an urgency qualitative measure of 1/4. The V1 and V2 latencies were 35,9 and 35,8 ms, respectively.

Subject 4 (S4)

Subject 4 was a 59 years-old female, with 71 kg and 166 cm (BMI 25,8), diagnosed with non-neurogenic OAB and osteoporosis. Her OAB symptoms consisted of nocturia, increased voiding frequency (30 minutes intervals), urgency and feeling of incomplete voiding. Her MBC was 400 mL. On the urodynamic study, bladder compliance was normal with no involuntary detrusor contractions. She scored 9/16 in the ICIQ-OAB, with an urgency qualitative measure of 4/4. The V1 and V2 latencies were 31,1 and 30,5 ms, respectively.

Discussion

The brain´s electrical response to ascending sensory input from the LUT conveys important knowledge about the processing of afferent information. This is crucial for the control of LUT function considering that impaired afferent nerve signalling to the brain could be involved in urinary frequency, urgency and urge-incontinence. [19,20] Previous studies showed that lower urinary tract SEPs evaluation is feasible in healthy subjects[12, 13, 21] however, its application in pathological dysfunctions is still under investigation and needs to be further defined.

With this preliminary study, we aimed to adapt to clinical practice the LUT SEPs evaluation in patients with urological pathology, namely OAB. Owing to our short sample size, we decided to discuss individually each subject's results.

Subject 1 (S1) presented with a neurological OAB (MS). Bladder sensation and compliance were normal with no evidence of detrusor overactivity during urodynamics. This patient had the greatest bladder capacity and post-voiding volume. This high post-voiding residual volume was symptomatically reported by the patient on daily routine and could indicate chronic urinary retention, a medical condition frequent in patients with multiple sclerosis.[22] SEPs results demonstrated increased posterior tibial latencies when compared with a healthy population[23], as well as increased external urethral sphincter latencies. This could be justified by his neurological pathology since multiple sclerosis disrupts myelin in the central nervous system and consequently produces alterations in saltatory conduction, slowed conduction velocity and propensity to conduction block.[24] Eardley et al demonstrated a correlation between detrusor overactivity and delayed SEPs latency in multiple sclerosis. [25]

Besides that, the latency values regarding different bladder filling volumes (50 ml vs. 80% of MBC) and, inherently bladder filling sensations, were substantially different in this neurogenic patient (43,7 vs. 57,0 ms). Sensations from the bladder are mainly carried through parasympathetic nerve fibres: afferent signals arising from bladder filling originate in the bladder and proximal urethra, and travel to the pelvic plexus.[26] The parasympathetic fibres join the pudendal nerves and enter the spinal cord at levels S2-S4. Some sensory information may also travel through sympathetic fibres in the hypogastric nerves, which enter the central nervous system at spinal cord levels T11-L2. Centrally, bladder filling sensations are transmitted mainly by the spinothalamic tract,[27] however, old studies already demonstrated that these bladder filling sensations could also travel in the dorsal column.[28] Bladder sensory information relays in the periaqueductal grey and enters the pontine micturition centre (M-region).[29] At this level a

monosynaptic excitatory pathway can activate sacral bladder motor neurons which also might be responsible for involuntary detrusor contractions and trigger urge sensation in some OAB patients.

These viscerosensory pathways can be evaluated subjectively with cystometry bladder sensation during urodynamic studies but, possibly, even with more precision through electrical perception thresholds measurements and/or through SEPs evaluation, namely, latencies determination. Neuroanatomically, these three methods seem to evaluate the same nerve pathways.

As a preliminary study we did not register the electrical perception thresholds which might have enriched our protocol. In the patient with MS, latencies were abnormally delayed as expected. However, bladder sensation clinically and during urodynamics studies was normal which probably means that bladder filling sensations and LUT sensory evoked potentials can be separately disturbed and modulated. The discrepancy between bladder filling sensations and LUT sensory signals is probably related to a difference in stimulation mechanisms and/or in nerve fibres used to transport the information. In other words, the complexity of the LUT nervous innervation turns the central nervous system constantly inundated by "afferent noise"[10] where a small part of these signals contributes to sensation, while the other components contribute to reflex control of the LUT.

Normal filling sensations are presumably conducted by small myelinated Aδ fibres[30], whereas electrical stimulation activates Aδ fibres and unmyelinated C fibres.[31] In patients with multiple sclerosis, bladder dysfunction occurs in over two-thirds of patients at some time during their illness[32] largely due to disruption in myelinated spinal cord pathways. It is accepted that these tracts are the main pathway for detrusor and sphincter control and, when affected, are responsible for OAB and voiding dysfunction, as in our neurogenic patient (S1). Small myelinated fibres and unmyelinated fibres are less affected and may justify why bladder sensation is preserved in multiple sclerosis patients but, with just one neurogenic patient, we were not able to understand how different bladder filling volumes can alter SEPs and latencies, as happened with S1, and its clinical meaning.

Regarding the other three participants (S2, S3 and S4), all are post-menopausal women with non-neurogenic OAB. These subjects reported nocturia, increased voiding frequency and urgency, classical symptoms of OAB.[33] Urodynamic studies revealed a negligible post-voiding residual volume, which corroborates a non-neurological origin to their OAB. The latencies of

posterior tibial SEPs are within the normal range, which supports a normal afferent nerve conduction. There was no significant difference between the two distinct bladder volumes (V1 and V2) in LUT SEPs latencies, suggesting that there isn't a conduction delay in patients with non-neurological OAB. Previous SEPs studies among healthy post-menopausal women demonstrated that N1 latencies were lower when compared with younger subjects[21], proposing that stimuli hypersensitivity increases with age. In fact, with increasing age, pelvic floor disorders rise, particularly overactive bladder and urinary incontinence.[34]

Despite our narrow sample, LUT SEPs latencies in the non-neurogenic patients showed no significant differences when comparing distinct bladder volumes which could suggest that afferent information conduction is independent of bladder volume as well as distension in non-neurogenic OAB patients. However, further evidence is needed to confirm this hypothesis and to improve research in this area.

In this experiment, we used fast electrical stimulation (3Hz) despite previous studies demonstrating that fast ES is less reliable, because of fewer fast conduction fibres in the LUT afferent pathway.[12,13] Thus, the electrical stimulation chosen in our study could compromise the validity of our results. Furthermore, the heterogeneous sample and some inconsistencies of measurement settings could also hamper our outcomes.

Previous studies had already proved that LUT electrical stimulation in healthy subjects leads to consistent LUT SEPs.[13,35] and consequently a clinically useful test for the investigation of bladder afferents.[7] Nevertheless, it will be essential to increase the LUT SEPs investigation in populations with urological disorders, for example in OAB.

Finally, our purpose with this study was to outline a LUT SEPs protocol that could assess the afferent activity of the lower urinary tract in OAB patients, that could be subsequently enhanced and improved through a larger sample and more accurate methods.

Conclusions

This study reports the evaluation of lower urinary tract sensory evoked potentials with different bladder volumes in four patients. Thus, it was possible to replicate LUT SEPs of the vesicourethral segment in OAB patients as had been previously reported in healthy subjects in international studies. However, we could not detect and conclude any defining characteristic of OAB LUT SEPs due to our narrow and heterogeneous sample.

Furthermore, this article introduces the LUT SEPs investigation in Portugal, namely in CHUPorto, that hereafter could be implemented in this centre to keep up to international research. Thus, we conclude that LUT SEPs could help improve our understanding of the underlying mechanisms of overactive bladder and other urological pathologies as well as become a clinically relevant and useful tool in this setting.

Appendix

Table I: Subjects 1, 2, 3 and 4 urodynamic parameters (Urodynamic Detrusor Overactivity, MBC, Bladder Capacity, Bladder Contractility Index and post-voiding residue).

	Urodynamic Detrusor Overactivity	MBC (strongest desire) (mL)	Bladder Capacity (mL)	Bladder Contractility Index (BCI)	Post-voiding Residue (mL)
S1	No	403	487	158	203
S2	Yes	480	485	160	0
S3	Yes	430	424	190	8
S4	Yes	400	400	341	0

Table II: SEPs intensities and latencies of subjects 1,2,3 and 4.

	Posterior Tibial SEPs		V1 SEPs (Bladder volume = 50 mL)		V2 SEPs (Bladder volume = 80% of MBC)	
	Intensity (mA)	**Latency (ms)**	**Intensity (mA)**	**Latency (ms)**	**Intensity (mA)**	**Latency (ms)**
S1	22,6	61,5	48,5	43,7	51,3	57,0
S2	17,3	42,8	13,4	39,6	12,9	38,3
S3	12,6	39,6	9,7	35,9	11,6	35,8
S4	9,6	41,3	28,2	31,1	24,2	30,5
Mean	15,6±5,0	46,3±8,8	25,0±15.3	37,6±4,6	25,0±15,9	40,4±10,0

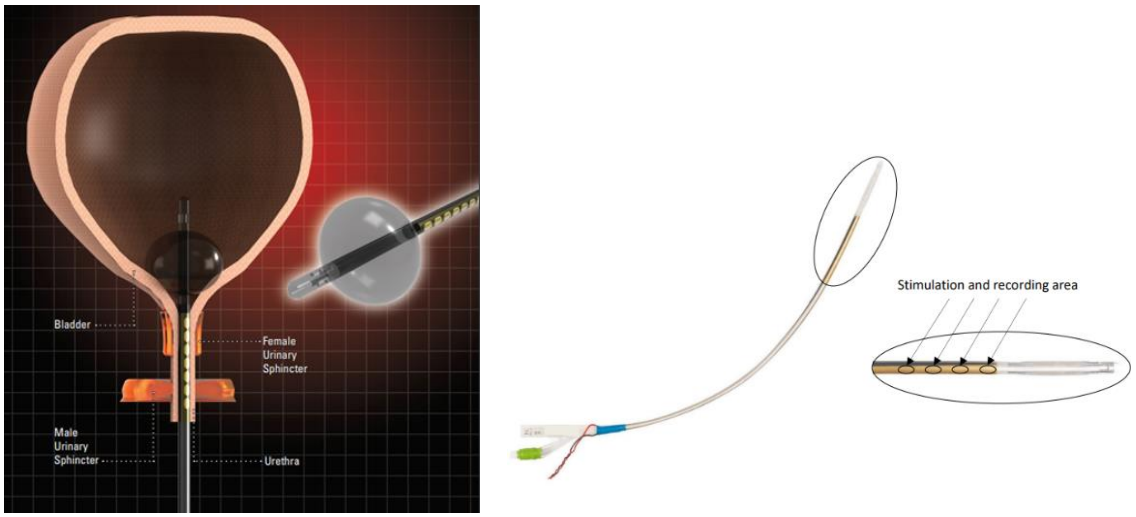

Figure 1: Designed for male and female patients, the disposable urethral catheter electrode 10 Fr (manufactured by Spes Medica S.r.l.) is used to monitor the external urinary sphincter, as well as for recording and electrical stimulation. In *https://www.spesmedica.com/wp-content/uploads/2020/05/UE-Brochure.pdf*

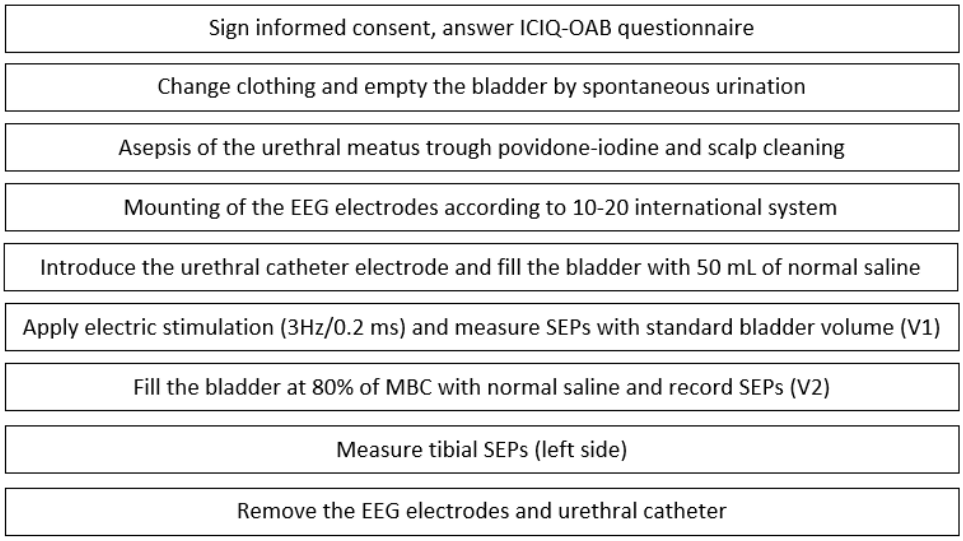

Figure 2: Flowchart of the LUT SEPs study protocol.

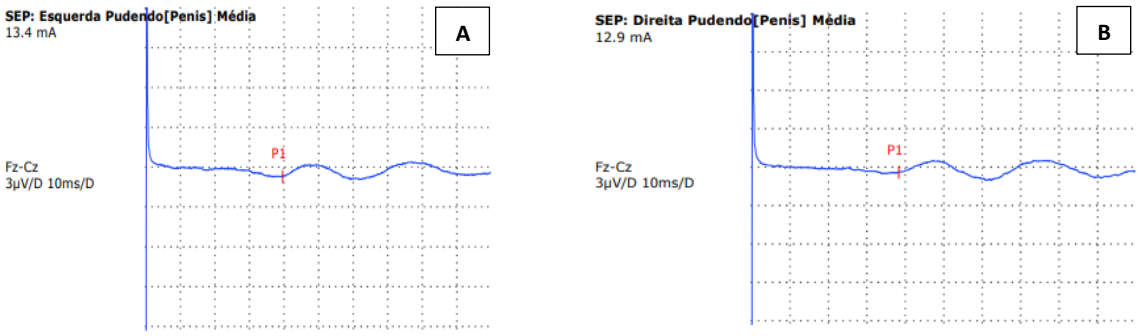

Figure 3: Graphics of the results of subject 2 SEPs intensities and latencies with V1 (50 mL) – figure 3A – and V2 (80% of MBC) – figure 3B.

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