[Frontiers in Bioscience 9, 995-999, January 1, 2004]

VESICAL PACING: PACING PARAMETERS REQUIRED FOR NORMALIZATION OF VESICAL ELECTRIC ACTIVITY IN PATIENTS WITH OVERACTIVE BLADDER

Ahmed Shafik[1] , Olfat El Sibai[2] , Ali A. Shafik [3], Ismail Ahmed [4], and Randa M. Mostafa [5]

[1] Department of Surgery and Experimental Research, Faculty of Medicine, Cairo University, Cairo, [2] Department of Surgery, Faculty of Medicine, Menoufia University, Shebin El-Kom, [3] Department of Surgery and Experimental Research, Faculty of Medicine, Cairo University, Cairo,[4] Department of Surgery and Experimental Research, Faculty of Medicine, Cairo University, Cairo, [5] Department of Physiology, Faculty of Medicine, Benha University, Egypt

TABLE OF CONTENTS

1. ABSTRACT

There are several modalities for the treatment of the overactive bladder (OAB), but the results may not be satisfactory. A recent study has demonstrated that the OAB has a dysrhythmic electric activity that seems to result from a disordered vesical pacemaker. We hypothesized that vesical pacing may correct the irregularities of the vesical electric waves and consequently normalize the vesical contractility. In this communication, we primarily defined the adequate pacing parameters required for correction of the vesical dysrhythmia. 36 patients with OAB were divided into a study group (22; 13 women; mean age 40.2 years) and a control group (14; 8 women; mean age 41.8 years). Ten healthy volunteers (6 women; mean age 39.8 years) were included in the study. Three 28-gauge cardiac pacing electrodes were hooked to the vesical mucosa: one (pacing) to the vault, and two (recording) to the lateral wall. Electric activity at rest and during stimulation of the pacing electrode was recorded in the study group and the healthy volunteers. In the control group, recording was done without pacing. Reproducible regular triphasic SWs were recorded from the 2 electrodes of the healthy volunteers with a similar pattern from the 2 electrodes of each individual subject. The optimal pacing parameters we determined were: an amplitude of 5 mA, a pulse width of 200 ms and a frequency of 20% higher than the frequency of the basal vesical waves.Vesical pacing effected a significant increase of waves' variables. The OAB patients exhibited a "dysrhythmic" wave pattern which was normalized during vesical pacing using the aforementioned pacing parameters. The optimal parameters required for vesical pacing of the dysrhythmic waves of the OAB were determined and succeeded in normalization of the vesical electric activity. Vesical pacing is suggested to be used as a therapeutic tool for the treatment of the OAB.

2. INTRODUCTION

Overactive bladder (OAB) is a common disorder worldwide. It is a symptom syndrome suggestive of lower urinary tract dysfunction and is characterized by urgency with or without urge incontinence (1). OAB is usually associated with frequency and nocturia with no proven infection or other obvious pathology (1).

In the OAB, the neurologic or myogenic activity of the urinary bladder is affected by a variety of conditions including neurologic illness or injury, bladder outlet obstruction and urethral weakness (2); there is, however, an idiopathic type of OAB which has a hitherto unknown etiology. Denervation is commonly found in biopsy specimens of patients with OAB, suggesting that muscle abnormalities may be a cause of the condition (3). Investigators (4,5) proposed that a change in the smooth muscle properties seems to be a prerequisite for OAB.

Electric activity in the form of slow waves (SWs) and action potentials (APs) have been recorded from the urinary bladder (6-10). It is claimed that the waves in the gut are generated by the interstitial cells of Cajal (ICC) (11-15), and are responsible for the contractile activity of the smooth musculature (16-18). A disorder of the electric activity presumably leads to deranged contractility of the organ (19,20). Previous studies could demonstrate the presence of ICCs in the urinary bladder (21).

A recent study has revealed that the electric activity in the OAB was "dysrhyrthmic"(22). The electric waves exhibited irregular frequency, amplitude and conduction velocity from the electrodes applied to the urinary bladder of the same individual. The cause of this dysrhythmic pattern was related to disordered

Table 1. The causes of the overactive bladder in 22 patients

Disease	No. patients
Cerebral palsy	5
Spinal canal stenosis	6
Cerebellar ataxia	3
Parkinson's disease	3
Idiopathic	5

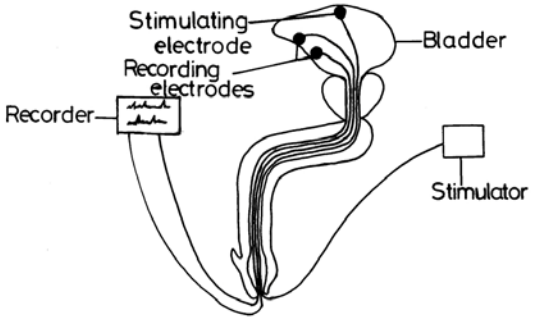

Figure 1. The location of the electrodes in the urinary bladder.

pacemaker(22) which is presumably located in the bladder vault (6). We assumed that the irregular electric waves of the OAB are generated by this dysfunctioning pacemaker.

Several treatment modalities are being practiced for OAB. These include~~s~~ behavioral therapy (23), pelvic floor exercises (24), electrical stimulation (25), biofeedback (26), muscarinic receptor antagonists (27), intravesical agents that block cholinergic transmission (28), bladder denervation procedures (29), and sacral neuromodulation (30). However, the results may not be satisfactory in some patients.

We hypothesized that vesical pacing may correct the irregularities of the vesical electric waves of the OAB, and consequently normalize the vesical contractility. This hypothesis was investigated in the current communication aiming primarily at defining the adequate pacing parameters that are required for correction of the vesical dysrhythmia of the OAB.

3. MATERIAL and METHODS

3.1. Subjects

36 patients with OAB were divided into a study group of 22 patients (13 women, 9 men; mean age of 40.2±10.7 SD years; range 32–62) and a control group of 14 patients (8 women, 6 men; mean age 41.8±10.9 SD years; range 34–60). Table 1 shows the causes of the OAB as diagnosed on the basis of urodynamic examination including uroflowmetry and pressure flow studies.

The study comprised also 10 healthy volunteers who matched the patients in age and gender (6 women, 4 men, mean age of 39.8±10.2 SD years; range 30–58). The subjects had no genitourinary manifestations in the past or at the time of enroll~~l~~ment. Physical examination including neurologic assessment was normal. Urinalysis and sonography of the urinary tract were also normal.

All the studied subjects were informed about the tests to be done and their role in the study, and gave an informed consent. The study was approved by the Review Board and Ethics Committee of the Cairo University Faculty of Medicine.

3.2. Methods

The subjects were asked to evacuate their bladder. Three 28-gauge cardiac pacing electrodes (Prevail, Medtronic, NC Kerkrade, The Netherlands) were used for the experiment. The electrodes were introduced cystoscopically into the urinary bladder per urethram and under videoscopic control; they were hooked to the vesical mucosa. One electrode (stimulating) was applied to the vesical vault and two electrodes (recording) to the lateral wall of the bladder with a distance of 3-4 cm between them (Figure 1). The wires were brought out through the urethral orifice. Twenty minutes were allowed before recording was started so that the urinary bladder would have adapted to the hooked electrodes. Thereafter the basal electric activity was registered from the 2 recording electrodes for 20 minutes. This was followed in the study group and in the healthy volunteers by a 20-minute recording during electrical stimulation of the vault electrode (pacing) using an electrical stimulator (Mode A310, World Precision Instruments, Sarasota, FL). The stimulator delivered a series of constant electric currents. The optimal pacing parameters were defined after performing multiple sessions with different pacing parameters. The latency, which is the time lapse from the onset of pacing to the onset of response, was calculated. As regards the 14 patients of the control group, the recordings were made without activation of the pacemaker.

The waves registered from the two recording electrodes were amplified using an ac amplifier with a frequency response within ± 3 dB from 0.016Hz to 1 KHz, and were displayed on a UV recorder at a sensitivity level of 1 mV/cm.

To assess reproducibility of the results, the recordings~~s~~ sessions were repeated at least twice in the individual subject and the mean value was calculated. The results were analyzed statistically using the Student's t test and the values were given as the mean ± standard deviation (SD). Differences assumed significance at $p<0.05$.

4. RESULTS and DISCUSSION

No adverse side effects were encountered during or after performance of the tests and all the subjects were evaluated.

4.1. Pacing parameters

The optimal pacing parameters comprised an amplitude of 5m A, a pulse width of 200 ms and a frequency that was 20% higher than the frequency of the basal vesical waves already recorded. We found that pacing with an amplitude less than 5 mA did not effect normalization of the dysrhythmic electric pattern. Similarly, the pulse width of the pacing stimulus had an effect on vesical myoelectric activity. Vesical pacing with

Table 2. Frequency, amplitude and velocity of conduction of the slow waves recorded from 10 healthy volunteers at rest and during vesical pacing [1]

Slow Waves						
	Frequency (cpm)		**Amplitude (mV)**		**Conduction velocity (cm/s)**	
	Mean	**Range**	**Mean**	**Range**	**Mean**	**Range**
At rest	4.3 ± 0.9	3 - 6	1.1 ± 0.2	.08 – 1.3	4.2 ± 0.9	3.2 – 4.7
During pacing	10.2 ± 2.3 [3]	7 - 12	1.5 ± 0.4 [2]	1.2 – 1.8	5.3 ± 1.1 [2]	4.3 – 6.2

[1] Values were given as the mean ± standard deviation (SD), [2] $p<0.05$, [3] $p<0.01$ cpm = cycle per minute, *p* values during pacing were compared to those at rest

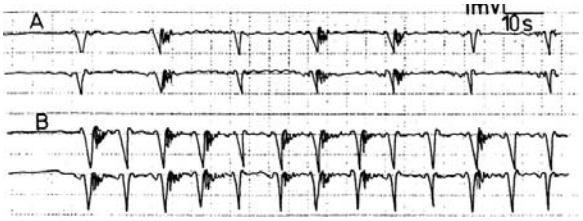

Figure 2. Electrovesicogram of a healthy volunteer: (a) before vesical pacing, (b) during pacing.

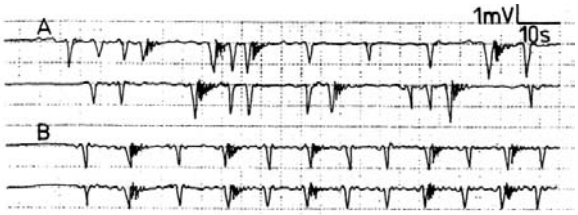

Figure 3. Electrovesicogram of a patient with overactive bladder: (a) before vesical pacing, (b) during pacing.

pulse widths of less than 200 ms produced occasional wave recordings, or none.

4.2. Vesical pacing of the healthy volunteers

Slow waves were registered from the 2 recording electrodes under basal conditions. The waves from the 2 electrodes of the same subject had a regular rhythm and the same frequency, amplitude and velocity of conduction (Figure 2); the values of these variables are displayed in table 2. The SWs were followed by bursts of action potentials (APs) represented by negative deflections (Figure 2). The APs were inconsistent and occurred randomly; they had the same pattern from the 2 electrodes of the same subject (Figure 2).

Vesical pacing with the aforementioned pacing parameters effected an increase in frequency, amplitude, and conduction velocity of the SWs ($p<0.01$, $p<0.05$, $p<0.05$, respectively; table 2, Figure 2) and also increased the APs. The mean latency was 0.9±0.2 min (range 0.5–1.2). The SWs had a regular rhythm and were similar from the 2 electrodes in the same subject. When pacing was terminated, its effect on the vesical myoelectric activity disappeared within 5–10 s (mean ~~9~~7.3±1.1).

4.3. Vesical pacing of the OAB

The resting electric activity of both the study and control patients showed a dysrhythmic pattern; the SWs exhibited irregular frequency, amplitude and conduction velocity from the 2 electrodes of the individual subject (Figure 3). These variables differed from one electrode to the other in the same subject. The APs also occurred randomly and did not show the same pattern from the 2 electrodes of the individual subject (Figure 3).

Upon vesical pacing of the study group, using the aforementioned defined pacing parameters, the SWs exhibited a regular rhythm with occasional irregularities during the 20 min recording period (Figure 3). The frequency, amplitude, and conduction velocity were similar from the 2 electrodes of the same patient. The values of these variables are listed in table 3. APs were also recorded, occurred randomly and showed similar pattern from the 2 electrodes of the individual subject. The mean latency was 1.7±0.6 min (range 1.2–2.6) and the effect of vesical pacing disappeared after pacing was ceased by a mean of 9.3±1.35 (range 6-12).

The OAB patients of the control group in whom the electrodes were applied to the urinary bladder but not activated did not show any change of the dysrhythmic electric activity.

We obtained reproducibility of the results with no significant difference when the recordings were repeated in the same subject.

The OAB is a common disorder which affects the quality of life of many patients. There are many treatment modalities but none is entirely satisfactory. For this reason new methods are still being developed with the aim of finding a cure of this condition.

The current study presents a novel method for the treatment of the OAB. It has been shown in previous (22) and the current study that the OAB exhibits a dysrhythmic pattern of electric activity. Furthermore, it is reported that the electric waves control the contractile activity of the smooth musculature of the different organs (16-18). Thus, a disordered electric activity would disturb the motile activity whereas its correction would presumably improve the contractility.

The dysrhythmic vesical electric activity in the OAB patients of the current study seems to be a sequence of the neuropathic condition of the urinary bladder. The source of the electric waves in the gut and urinary bladder is believed to be the ICCs (11-15,21). The electric waves generated from the ICCs appear to be delivered to the smooth muscle or nerve fibers. The ICCs could thus be considered as the pacemakers which pace the vesical motor activity. Previous studies have suggested that the vesical

Table 3. Frequency, amplitude and velocity of conduction of the slow waves recorded from the 22 patients with overactive bladder [1]

Slow Waves						
	Frequency (cpm)		**Amplitude (mV)**		**Conduction velocity (cm/s)**	
	Mean	**Range**	**Mean**	**Range**	**Mean**	**Range**
At rest	irregular		irregular		Irregular	
During pacing	4.8 ± 0.8	4 - 6	1.2 ± 0.3	0.7 – 1.4	4.8 ± 0.7	4.1 – 6.2

[1] Values were given as the mean ± standard deviation (SD) cpm = cycle per minute

pacemaker exists at the bladder vault and delivers the electric waves to the rest of the vesical wall (6). We postulated that this pacemaker is deranged in the OAB and may need to be paced. We therefore applied the pacing electrode at the vesical vault presuming that this is the site of the deranged pacemaker.

The electric activity of the healthy volunteers was regular and exhibited a significant increase on pacing due probably to stimulation of the vesical pacemaker. In the OAB, pacing corrected the dysrhythmic electric pattern. The disturbed wave rhythm became regular except for occasional periods of irregularities. We postulate that the regular wave rhythm would regulate the vesical contractility and inhibit the bladder overactivity. Normalization of the electric activity has been achieved using optimal pacing parameters that had been selected after repeated trials with different variables. We found that pacing with parameters at a lower level failed to correct the dysrhythmic electric activity of the OAB.

An alternative concept of the effect of pacing on OAB could be related to the denervation of the vesical musculature. Vesical muscle denervation was reported by investigators to occur in the OAB as shown in biopsy specimens (3). We believe that in such cases, the vesical pacemaker discharges normal electric waves which are, however, improperly transmitted to the muscle fibers through the impaired innervation. Therefore, the disorder in such cases seems to be related to the wave transmission and not to the pacemaker itself. With this concept in mind, and with the correction of the dysrhythmic pattern of the electric activity in the OAB by vesical pacing, we suggest that pacing may correct not only a disordered vesical pacemaker, but also improper nerve transmission of the electric waves, not unlike sacral neurostimulation in the treatment of urinary control disorders.

In conclusion, the optimal parameters required for vesical pacing of the dysrhythmic electric activity pattern of the OAB were determined and succeeded in normalization of the dysrhythmic electric waves. Accordingly, vesical pacing is suggested to be used as a therapeutic method for the treatment of the OAB.

5. ACKNOWLEDGMENT

Margot Yehia assisted in preparing the manuscript.

6. REFERENCES

1. Mills, I.W., J.E. Greenland, G. Mcmurray, M. Gordon, M. Rachel, H. Kossen, N, Jeremy, A, Brading & F, Alison: The standardization of terminology of lower urinary tract function: report from the standardization subcommittee of the International Continence Society. *Neurourol Urodyn* 21, 167-178 (2002)

2. Mostwin, J.L: Pathophysiology: the variety of bladder overactivity. *Urology* 60, 22-27 (2002)

3. Mills, I.W., J.E. Greenland, & G. McMurray, et al: Studies of the pathophysiology of idiopathic detrusor instability: the physiological properties of the detrusor smooth musce and its pattern of innervations. *J Urol* 163, 646-651 (2000)

4. Brading, A.F.: A myogenic basis for the overactive bladder. *Urology* 50, 57-67 (1997)

5. Brading, A.F., & W.H. Turner: The unstable bladder: towards a common mechanism. *Br J Urol* 73, 3-8 (1994)

6. Shafik, A.: Study of the electromechanical activity of the urinary bladder. Experimental study. *World J Urol* 12, 316-318 (1994)

7. Shafik, A.: Electrovesicography in interstitial cystitis. *Urol Int* 54, 66-69 (1995)

8. Shafik, A.: Electrovesicogram in the neurogenic bladder. *J Invest Surg* 9, 481-486 (1996)

9. Shafik, A.: Electrovesicography in benign prostatic hyperplasia. *Arch Androl* 33, 201–207 (1994)

10. Shafik, A.: Electrovesicogram in stress urinary incontinence. *Int Urogynecol J* 7, 203–207 (1996)

11. Thuneberg, L.: Interstitial cells of Cajal: intestinal pacemaker cells? *Adv Anat Embryol Cell Bio* 71, 1-130 (1982)

12. Vanderwinden, J.M., J.J., Rumessen, H. Liu, D., Descamps, M.H., DeLet, & J.J. Vanderhaegen: Interstitial cells of Cajal in human colon and in Hirschsprung's disease. *Gastroenterology* 111, 901-910 (1996)

13. Ward, S.M., & K.M. Sanders: Physiology and pathophysiology of the interstitial cells of Cajal: from bench to bedside. I. Functional development and plasticity of interstitial cells of Cajal networks. *Am J Physiol* 281, 602-611 (2001)

14. Wester, T., L. Eriksson, Y. Olsson & L. Olsen: Interstitial cells of Cajal in the human fetal small bowel as shown by c-kit immunohistochemistry. *Gut* 44, 65-71 (1999)

15. Liu LWC, L. Thuneberg & J.D. Huizinga: Selective lesioning of interstitial cells of Cajal by methylene blue and light leads to loss of slow waves. *Am J Physiol* 266, 485-496 (1983)

16. Durdle, N.G., Y.J. Kingma, K.L. Bowes & M.M. Chambers: Origin of slow waves in the canine colon. *Gastroenterology* 84, 375-382 (1983)

17. Daniel, E.E., J. Thomas, M. Ramnarain, T.J. Bowes & J. Jury: Do gap junctions couple interstitial cells of Cajal pacing and neurotransmission to gastrointestinal smooth muscle? *Neurogastroenterol Motil* 13, 297-307 (2001)

18. Liu, LWC, & J.D. Huizinga: Electrical coupling of circular muscle to longitudinal muscle and interstitial cells of Cajal in canine colon. *J Physiol* (Lond) 470, 445-461 (1993)

19. Aube, A.C., C. Cherbut, M. Barbier, J.H. Xing, C. Roze & J.P. Galmiche: Altered myoelectrical activity in noninflamed ileum of rats with colitis induced by trinitrobenzene sulphonic acid. *Neurogastroenterol Motil* 11, 55-62 (1999)
20. Abo, M., T. Kono, C.L. Lu & J.D. Chen: Effects of caffeine on gastrointestinal myoelectric activity and colonic spike activity in dogs. *Scand J Gastroenterol* 33, 368-374 (2000)
21. Mc, Closky KD & A.M. Gurney: Kit positive cells in the guinea pig bladder. *J Urol* 168, 832-836 (2002)
22. Shafik, A., O. El-Sibai & A.A. Shafik, I. Ahmed: Electrovesicogram in the overactive bladder. Role in pathogenesis and diagnostic significance. Under publication.
23. Payne, C.K.: Behavioral therapy for overactive bladder. *Urology* 55, 3-6 (2000)
24. Bo, K. & L.C.M Berghmans: Non-pharmacologic treatments for overactive bladder- Pelvic floor exercises. *Urology* 55, 7-11 (2000)
25. Primus, G. & G. Kramer: Maximal external electrical stimulation for treatment of neurogenic or non-neurogenic urgency and/or urge incontinence. *Neurourol Urodyn* 15, 187-194 (1996)
26. Cardozo, L.D.: Biofeedback in overactive bladder. *Urology* 55, 24-28 (2000)
27. Yarker, Y., K.L. Goa & A. Fitton: Oxybutynin: a review of its pharmacodynamic and pharmacokinetic properties and its therapeutic use in detrusor instability. *Drugs Aging* 6, 243-262 (1995)
28. Madersbacher, H. & G. Jilg: Control of detrusor hypereflexia by intravesical instillation of oxybutynin hydrochloride. *Paraplegia* 29, 84-90 (1991)
29. Torrens, M. & T. Hald: Bladder denervation procedures. *Urol Clin North Am* 6, 283-293 (1979)
Shaker, H. & M. Hassouna: Sacral nerve root neuromodulation: an effective treatment for refractory urge incontinence. *J Urol 159*, 1516-1519 (1998)

Key Words: Pacing Electrode, Slow Waves, Action Potentials, Dysrhythmia

Send correspondence to : Professor Ahmed Shafik, 2 Talaat Harb Street, Cairo 11121, Egypt, Tel/Fax: +20-2-7498851, E-mail: shafik@ahmed-shafik.org, URL: www.ahmed-shafik.org