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Can an Algorithm Predict a Voiding Contraction in Unconscious Rats?

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Abstract—**Urinary incontinence (UI) is a very common and serious disorder which can be classified in stress and urge incontinence, the latter mainly caused by an overactive bladder (OAB). A definitive treatment for OAB does not exist yet due to its complex nature. Therefore, more attention must be focused on improving the patient's quality of life. A device able to alert the patient to development of a voiding contraction would be highly desirable, enabling actions to avoid incontinence. The main hypothesis of this work is that a voiding contraction is preceded by a consistent change in the pattern of intravesical pressure (p_{ves}). We developed an algorithm based on frequency analysis of p_{ves} recordings of two strains of rats whose bladders were first filled with saline (S fillings) and then with acetic acid (AA fillings); the latter was used as model for OAB in rats. The algorithm was designed to provide an alarm when an increase in the range 0.2-0.6Hz of the amplitude spectrum was detected. The accuracy of the algorithm has been tested and quantified, successful alarms were those taking place within fifty seconds before the start of voiding. Although the results are still very preliminary, due to the low number of tested animals, they seem encouraging since, in five rats, only one showed a percentage of success lower than 50%, with one rat reaching 100%. The accuracy of the algorithm is affected by the choice of the values for the controlling parameters, which have been set the same for all rats; future developments might include individual values for each rat.**

I. Introduction

The process of urinary bladder filling and the subsequent urine elimination (micturition) involves a coordination of the urinary bladder (the reservoir) and urethra (bladder outlet). A complex neural circuitry controls this process, involving pathways at many levels of the central nervous system (brain, the spinal cord) and the peripheral nervous system [1]. Three phases can be identified during a normal micturition cycle. The first phase is the bladder filling with the detrusor (bladder muscle) relaxed and the bladder outlet closed, to prevent leakage of urine. The second phase is the sensation of first desire to void, due to the activity of nerves sending signals to the central nervous system (afferent nerve activity). The third phase is the voiding where nerve signals from the central nervous system (efferent nerve activity) cause a contraction of the detrusor and a relaxation of the bladder outlet. In healthy conditions the voiding is voluntary, enabling one to void at a desired time and place. In young children (up to 3-5 years old) urination occurs as an involuntary reflex which may reappear in some elderly people or in the presence of neurologic diseases or injuries (spinal cord injuries), leading to urinary incontinence (UI) [1]. UI is a very common and serious disorder; its incidence is increasing due to the aging population. UI can be classified in stress incontinence, which is generally caused by a deficient urinary sphincter, and urge incontinence of which the common cause is an overactive bladder (OAB). OAB has an overall estimated prevalence, in European individuals aged >40 years, of 16.6% [2]. The OAB mechanism is still poorly understood due to its complex nature, involving many distinct components (nervous system, interstitial cells, smooth muscle cells and the epithelium lining the surface of the urinary bladder). For this reason attention must be given to techniques which may help to improve the patient's quality of life addressing their main complaints (i.e. leakage, smell). In this respect a wetness sensor, attached to the underwear, has recently been introduced by Fernandes et al. [3] to monitor urine loss. The sensor provides a vibration in the presence of wet pad detection. The main limitation of the wetness sensor is that the warning occurs after the urine has already been expelled. In anaesthetized rats, small rapid transients in the intravesical pressure (p_{ves}) have been shown shortly before a voiding contraction [4]. A device able to predict involuntary voidings in advance would be highly desirable so that the patient would be able to take action to avoid the incontinence. The aim of our work is to develop an algorithm to identify the pattern of p_{ves} changes just before a voiding contraction which may be different from other bladder contractions. This preliminary study was conducted in anaesthetized rats.

II. Methodology

Approval for the animal experiments was obtained from the local Erasmus MC Animal Experiment Committee. All laboratory and experimental procedures were conducted in accordance with institutional guidelines. Three male Wistar rats (Charles River, US) A, B, C (weight: 425±27g) and two Athymic nude HS (ANHS) rats (Harlan, US) I and II (weight: 366±13g), were anaesthetized with urethane (1 g/kg) and the bladder and postganglionic bladder nerves, presumably branches of the pelvic nerve, were exposed through an abdominal incision. Paraffin oil was poured into the abdomen and one of the aforementioned nerves was

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mounted on a bipolar platinum-iridium electrode to record nerve activity, amplified using a DISA 15C01 EMG amplifier (gain: 10^5) and band-pass filtered with a Krohn-Hite 3944 filter (Bessel, 4th order, 200-2000 Hz). Bladder filling (0.11 ml/min) and measurement of p_{ves} was performed by inserting a 23G needle at the top of the bladder, the other end of the needle was connected to a disposable pressure transducer, connected to a Statham SP1400 blood pressure monitor. p_{ves} and nerve activity were both sampled at 25 kHz for a duration T=300s. The rats were euthanized at the end of the experiment with an overdose of KCl, injected in the heart.

A. S and AA fillings

In all rats the bladder was first repeatedly filled with saline (0.9% NaCl), which mimics normal urine (S fillings); then (except Rat C) with a solution of acetic acid in the range 0.25-1% (AA fillings). Acetic acid is known to cause irritation of the bladder, the range 0.25-1% is commonly used as a model of OAB in rats [5].

B. Description of the algorithm

The main hypothesis for developing an algorithm which may predict the occurrence of voiding, is that a voiding is preceded by a recurrent change in the pattern of p_{ves} with increased oscillations in a narrow range of frequencies. The algorithm, custom written in Matlab (Mathworks, US), divides the p_{ves} recordings in N windows of the same size (Fig 1a) specified by the parameter D (in seconds). For each window an amplitude spectrum of the pressure is derived and the area under the curve (AUC) is calculated in the specified range of frequencies (f_1-f_2), as shown in Fig.1b. In this way N values of AUC are obtained from which N-1 values of derivatives are calculated (diff(AUC)). The algorithm provides an alarm when the value of the *i-th* derivative overcomes a specified threshold ($diff(AUC)_i>ST$) (Fig. 1c).

C. Criteria for testing the algorithm's accuracy

To test the accuracy of the algorithm in predicting a voiding, recordings with at least one voiding event were considered. The occurrence and duration of voiding was identified by the start (t_1) and the end (t_2) point of the high frequency voiding oscillations in p_{ves}, which are normal in the male rat urination and are caused by rapid contractions of the urinary sphincter [6]. Three main regions were identified in each recording (Fig 2a):

<u>*The voiding region X*</u> ($t_1< t <t_2+D$): this region was discarded because the high frequency voiding oscillations may interfere with the results of the algorithm; t_2+D (not t_2) is considered as the end point of this region to allow a certain time for the resetting of AUC values to normal. Because actual voiding is taking place any alarm would be too late and is therefore discarded. In the presence of multiple voidings in the same recording (Fig. 2b), the time between the start of a voiding and the start of the following one (Δt) is taken into account: if Δt < 30s only one voiding is considered and the discarded area is extended until the end of the last voiding +D (Fig. 2b), if Δt>30s, the voidings are considered separately.

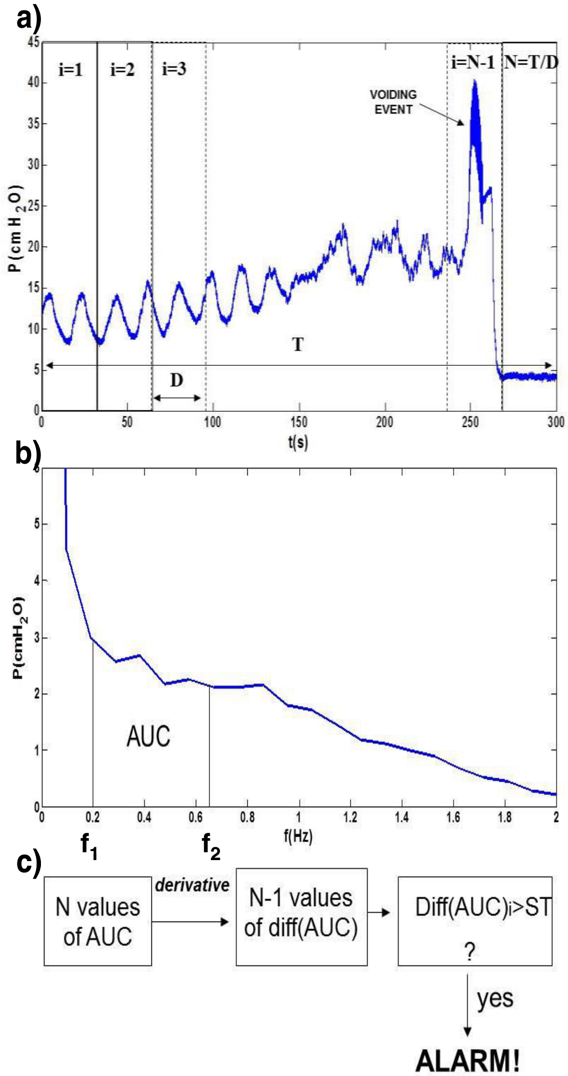

Figure 1 Schematic of the algorithm working principles. a) The intravesical pressure (p_{ves}) recording is first divided in N windows. b) For each window the area under the curve (AUC) is calculated in the specified range of frequencies (f_1-f_2). c) The algorithm provides an alarm if the value of the derivative of AUC overcomes a specified threshold (ST).

<u>*True Positive region (TP):*</u> the region starting from 50s before the start of the voiding: $t_1-50\leq t\leq t_1$. The choice of 50s seconds is arbitrary. All the alarms provided by the algorithm in this region are considered successful since they indicate that a voiding event will happen within 50 seconds.

<u>*False Positive region (FP):*</u> defined as the remaining region. All alarms provided by the algorithm in this period of time are considered false positive events. Considering that for all the recordings T and TP are constant (T=300s, TP=50s), the minimum duration of the FP region (FP_{min}) depends on the maximum duration of the X region.

Additionally we define:
<u>*False negative event (FN):*</u> the case in which the algorithm does not provide any alarms or an alarm is provided after t_1.

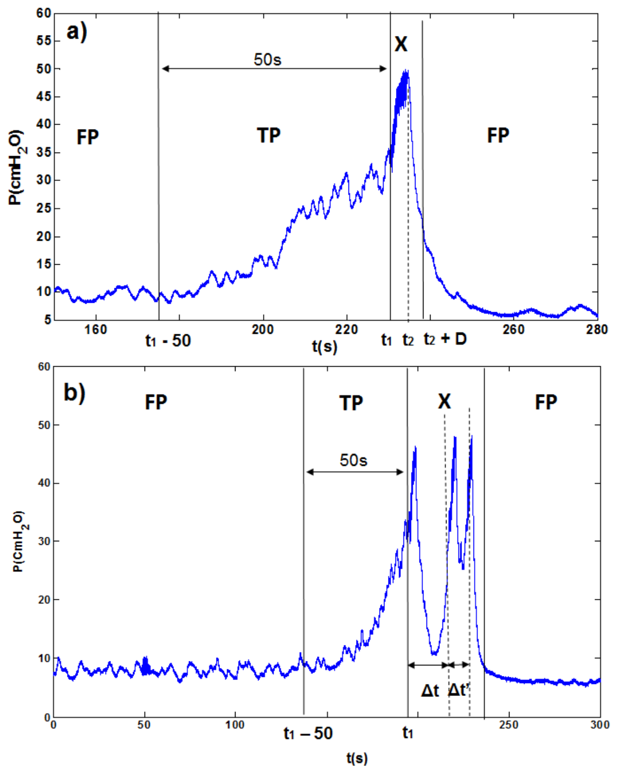

Figure 2 To test the algorithm accuracy in predicting voiding event, three regions have been arbitrarily defined (for details see text). TP is the true positive region (t_1-50≤t≤t_1), FP is the false positive region and X is the discarded region. a) example of division in regions used to test the algorithm, the figure is only a part of the T=300s recordings showing a voiding event. b) Example of multiple voidings during a single recording with the interval between the start of two subsequent voidings (Δt and Δt') <30s.

III. Results

Fig.3 shows, as an example, the nerve activity, intravesical pressure and the calculated distributions of AUC and derivative of AUC in rat A; alarms are represented by squares (FP region) and black circles (TP region) (Fig.3b). An initial increase of nerve activity is visible before the beginning of the TP region (Fig. 3a). This may justify an extension of this region. Many combinations of variables can be selected for the algorithm under investigation: window size (D), range of frequencies (f_1-f_2) for calculating AUC, threshold for the alarm (ST) and also the size of the interval chosen as the TP region (50s). For the current analysis we optimized the parameters according to the available p_{ves} recordings; we selected D=10s, T=0.05 cmH_2O/s , f_1=0.2Hz and f_2=0.6Hz (five equidistant points are included in this range of the spectrum). The frequency range was chosen according to the period of the small and high frequency transients (before the micturition) [4] similarly to the ones occurring at t=150s, shown in Fig 1a (lasting from 1.5 up to 5 seconds). The maximum duration of the discarded region in our recordings was 44s therefore the percentage of duration for the two regions is: TP/(T-44s)=20% and FP_{min}/(T-44s)=80%. Table I shows the results for the three Wistar rats in the measurements conducted using saline and the three concentrations of acetic acid as filling fluid. A percentage of successful events is provided, calculated as 'TP·100/N. alarms'. The maximum percentage of success (100%) was obtained in rat B with all the filling fluids while the minimum was reached in rat C (54%) for which only values associated with saline fillings are provided. The total percentage of success for the three Wistar rats is 68%, no FN events were recorded for these rats. Moreover an effect of the filling fluid on the algorithm's success rate is visible only in rat A which shows better results for the S filling than the AA ones. Values for the two ANHS rats are shown in Table II. The percentage of successful alarms provided by the algorithm in ANHS rats was in general lower than in Wistar rats with a total value of 49%. The algorithm was less successful in rat II even if in Rat I the software completely failed twice (FN) with 0.5% AA.

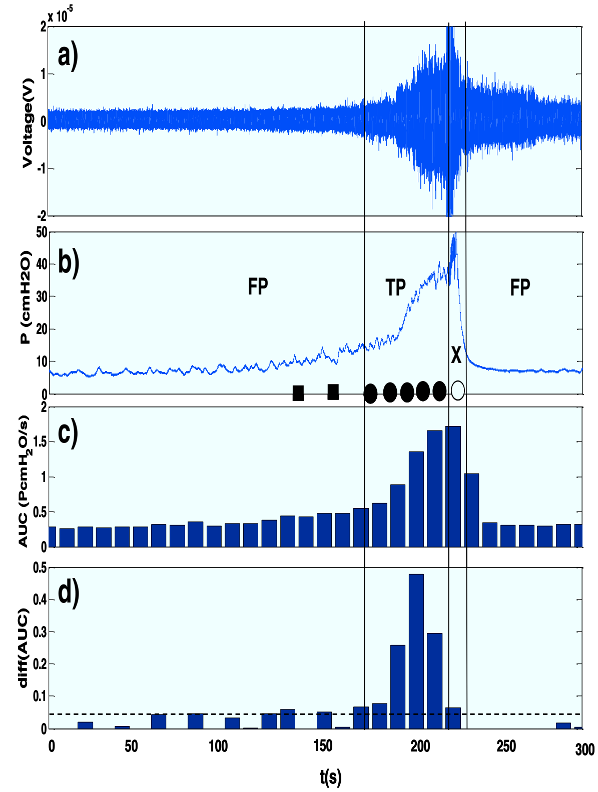

Figure 3 Example of data analysis in Rat A (saline filling) conducted using the algorithm. a) Nerve activity recording from a branch of the pelvic nerve. b) p_{ves} recording and associated c) amplitude distributions of the AUC values and d) derivative diff(AUC) values. The dashed line defines the threshold (ST=0.05 cmH2O/s). For all the rectangles with height>ST (panel d) an alarm is generated in panel b: black square are FP alarms, black circle are TP alarms while the white circle is the alarm that is discarded.

IV. Discussion

The idea of detecting the onset of a bladder voiding contraction through bladder associated signals is not new; attempts were made for example by analyzing signals from the pudental nerve [7] or EMG of the external anal sphincter [8]. However none of the methods, mentioned above, have appeared in clinical practice yet probably due to the complexity of the recordings. The possibility of accessing directly the intravesical pressure through an implantable pressure transducer appears a promising and easier solution

[9]. To the best knowledge of the authors the present work represents the first attempt of predicting a voiding contraction through an algorithm, based on frequency analysis of p_{ves}. Only one rat (Rat II) has shown a percentage of correct predictions lower than 50%; a percentage of 100% success was reached in Rat B in which all the predictions were in the true positive region. Better results were reached with Wistar rats but the small number of animals used does not allow us to draw significant conclusions about the effects of the strain. No conclusions could be drawn on the effects of the filling fluid either. The success rate of the algorithm decreased (from Saline to Acetic Acid) in rat A, it did not show variations in rat B and rat I while it increased in rat II.

TABLE I:

Success rate of the algorithm in Wistar rats: number of voidings 'N. voidings', number of alarms from the algorithm (N. alarms), not in the X region, number of true positive (TP), false positive (FP) and false negative (FP) alarms.

Wistar rats	**Rat A**			**Rat B**			**Rat C**	**Tot**
	S	**AA %**		**S**	**AA %**		**S**	**all**
		0.25	**0.5**		**0.5**	**1**		
N. voidings	4	5	5	1	4	4	2	25
N. alarms	24	31	28	2	5	5	13	108
TP	18	17	19	2	5	5	7	73
FP	6	14	9	0	0	0	6	35
FN	0	0	0	0	0	0	0	0
% TP/ N. alarms	**75**	**55**	**68**	**100**	**100**	**100**	**54**	**68**

TABLE II:

Success rate of the algorithm in ANHS rats: number of voidings 'N. voidings', number of alarms from the algorithm (N. alarms), not in the X region, number of true positive (TP), false positive (FP) and false negative (FP) alarms.

	Rat I			**Rat II**			**Tot**
	S	**AA %**		**S**	**AA %**		**All**
		0.5	**1**		**0.5**	**1**	
N. voidings	2	2	2	4	3	3	16
N. alarms	4	0	8	14	4	5	35
TP	3	0	6	4	1	3	17
FP	1	0	2	10	3	2	18
FN	0	2	0	0	0	0	2
% TP/ N. alarms	**75**	**Null**	**75**	**29**	**25**	**60**	***49***

As the False Positive region occupied 80% of the recording time, the expected success rate would have been around 20% if the alarm from the algorithm had been just randomly generated. By simply doubling the size of the TP region (TP=100s, FP_{min}/T-44=61%) we have calculated that the success rate of the algorithm would increase from 68 to 85% in Wistar rats and from 49 to 69 % in ANHS rats. This shows that the success rate of the algorithm is related to the values selected for its parameters. In this regard the use of an adaptive thresholding may constitute further improvement of the algorithm. The Matlab program is a prototype which, using frequency analysis, may provide a better alternative to the existing techniques for conditional electrical stimulation [10] which are exclusively based on pressure values (e.g. p_{ves}>8-12cmH2O). The program can be easily modified to generate a real time alarm and stimulation to suppress the voiding contraction (e.g. using Labview (National Instrument Corporation, US)).

V. LIMITATIONS

The preliminary results shown on five rats appear encouraging however the algorithm needs to be tested on a larger number of animals to reach statistical significance. Although there is a large difference between rats and humans, we think that if further studies confirm the accuracy of the algorithm in more rats, future investigation may focus on identifying similar changes of intravesical pressure in the human bladder (i.e. in spinal cord injured patients who have lost bladder sensation).

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