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CAN MODELIZED ANALYSIS OF PRESSURE-FLOW STUDIES IMPROVE THE KNOWLEDGE OF THE NERVOUS CONTROL OF BOTH BLADDER AND URETHRA?

Hypothesis / aims of study

Each year, physiological studies on men and animals bring new results on the neuronal system governing bladder and urethra. Higher brain takes the deliberate decision to void and triggers micturition. Brain stem and spinal cord use afferent sensory inputs to shape the excitations of the motoneurones controlling detrusor and sphincters activity.

A number of excitatory and inhibitory reflexes have been described. But their relative physiological weights and many crucial mechanisms are still unknown. The goal of this paper is to show that the accurate analysis of pressure-flow (PFs) recordings (flow and detrusor pressure curves) using a mathematical model of micturition supplies us with additional information and allows to improve modelling of the nervous control of both storage and voiding.

Study design, materials and methods

The mathematical model:

The VBN model [1] was used for modelled analysis of the recordings. The goal of this model is, starting from the initial bladder volume V_{ini} and from the nervous excitations of detrusor E_{det} and sphincter E_{sph} (which vary during the micturition) to compute the flow rate Q and the detrusor pressure p_{det} vs time. The excitations E_{det} and E_{sph} (contractile fibers) depend on the normalized concentration of free calcium ions in the muscular cell which governs the regulatory proteins function and so the muscular force (thus, detrusor and sphincter pressures are sigmoid functions of E). The excitation of motoneurons, and more generally, of afferent and efferent neurons is quantified by the firing rate of the cell or/and the number of recruited parallel neurons.

The initial VBN model of nervous control assumed empirical hyperbolic laws for both detrusor and striated sphincter. In this study, exponentially increasing signals were tested and results compared with the published knowledge on the nervous circuitry implied in voiding.

The database:

It comprised of urodynamic recordings obtained from 71 men [24-86 years old] complaining of lower urinary tract symptoms (LUTS) due to benign prostatic enlargement (BPE) and from 102 women [24-86 years old] with urinary incontinence. A total of 112 PFs of men and 147 PFs of women were analyzed. Exclusion criteria were neurological disease, diabetes mellitus, grade > 2 pelvic organ prolapse.

Data were obtained from 4 urodynamic laboratories.

Results

1- Detrusor excitation E_{det}

a- Normal voiding: the best shape for $E_{det}(t)$ is an exponential function with an asymptotic value E_{max} and a time constant T_{det}; E_{max} and T_{det} have the same values for all the voidings of any patient of our data bank: E_{max}=5 and T_{det}=6 s.

b- Micturition with fading of detrusor excitation

Fading of detrusor excitation occurs early (t_{break} = 2±1 s after the onset of flow) in 125 male (72%) and 220 female (61%) voidings. Before the break, excitation is standard. At t_{break}, the slope of $E_{det}(t)$ changes briskly; after t_{break}, E_{det} is still an exponential with the same time constant T_{det} but a weaker asymptotic value $\Gamma.E_{max}$ [Γ range 0-1] (Figure).

2- Striated sphincter excitation E_{sph} (Figure)

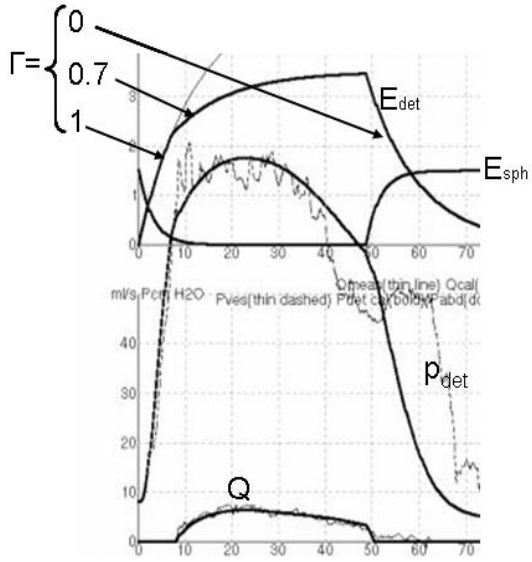
In the standard case, E_{sph} decreases briskly just before the increase of the E_{det} [range 1-5 s]. The law is exponential with a time constant T_{sph} = 3 s. But, in 7% of cases, a delayed decrease of E_{sph} has been observed.

3- Excitations at the end of voiding

a- Without significant post void residual (PVR) (Figure)When the bladder volume V is < 50 mL a progressive closure of the striated sphincter occurs: E_{sph} returns exponentially to the storage value with the time constant T_{sph} = 3 s and E_{det} exponentially decreases to zero with a time constant T_{end} = 11 s.

b- With significant PVR

High PVR results from a decrease of E_{det} later than the usually observed t_{break}.



PFs of a male patient suspected of BPE.

V_{ini} = 255 mL; PVR = 0

Top: Excitations E_{det} and E_{sph}

Bottom: flow and detrusor pressure

4- Phasic detrusor overactivity (DO)

All the non inhibited detrusor contractions (NIDC) follow the same scheme: first E_{det} increases and second it decreases following exponential laws which have the time constant T_{det} and respective asymptotic values Γ=1, and 0.

Interpretation of results

The detrusor excitation $E_{det}(t)$ appears as a sequence of exponentials which have always the same time constants T_{det} (same remark for the sphincter excitation and its time constant $T_{sph.}$). This property is characteristic of a linearly delayed transmission. We assume that all the efferent excitations combine to excite a bladder pre-ganglionic parasympathetic first efferent neurone and that this neurone excites the second efferent and the detrusor motoneurones through slow synapses (using for instance G proteins) with a synaptic time constant T_{det}.

Occurrence of breaks of detrusor excitation (fading) shows that voiding is compounded of two periods. We assume that the first one is driven by a triggering signal sent by the pons M center, the second by the well known positive bladder-bladder feedback.

Delayed opening of the sphincter confirms a well known fact: the pons L center is not rigidly connected to the M center. A recurrent inhibition of the bladder-bladder reflex has been described in cats [2]. It is induced by the activity of the parasympathetic pre-ganglionic neurones, takes about 20s to build up and inhibits both Aδ and C bladder reflexes for seconds and even minutes. Such a reflex in men would explain the delayed break of the detrusor excitation. We concluded that urethral sensors trigger the process.

Phasic DO: The finding of a normal time constant and of Γ=1 command signals shows that NIDC are due to the normal working of the efferent pathway (and not to a spontaneous activity of the motoneurones). The sequences of Γ=1 and Γ=0 periods suggest the working of a delayed inhibiting feedback.

Concluding message

Animal studies have described some reflexes during the micturition course, but their relative physiological weights are still unknown. Functional imagery of the brain in human [3] has shown what are the specific brain areas working during filling and a general map of the main connecting pathways is suggested, but at a scale which does not allow to follow the signal processing. On the contrary, the analysis of recordings of pressure-flow studies gives some light on the signal processing, but is not concerned by brain localizations. Thus, the method described in this study appears as a complement to the previous ones.

References

1. NAU 2000; 19:153-176
2. J Physiol 2006; 575(Pt 2): 603-15
3. NAU 2008; 27: 466-474

Specify source of funding or grant	**None**
Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**No**
This study did not require eithics committee approval because	**Theoretical study involving a retrospective analysis of urodynamic studies from a database.**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**No**