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THE ROLE OF NITRIC OXIDE IN THE ORIGIN OF LOWER URINARY TRACT SYMPTOMS AND THE POTENTIAL OF PDE5 INHIBITORS FOR TREATMENT OF VOID DYSFUNCTION

Hypothesis / aims of study
The aims of this study were to determine if the inhibition of nitric oxide synthesis, with inhibition of nitric oxide synthase, would lead to voiding dysfunction in rats and to evaluate if the action of sildenafil potentiating the effect of nitric oxide would revert the urodynamic alterations caused by N-Nitro-L-Arginine Methyl Ester.

Study design, materials and methods
The rats were separated into four groups: nine in the untreated group (Group 1), eight rats treated with N-Nitro-L-Arginine Methyl Ester (L-NAME) during 30 days (Group 2), four rats acutely treated with sildenafil (Group 3) and six rats treated with L-NAME during 30 days and submitted to acute systemic administration of sildenafil (Group 4). All animals were evaluated by urodynamic study under anesthesia.

Results
The chronic and systemic administration of L-NAME resulted in a significant increase in non voiding contractions, volume threshold and frequency of micturition cycles. The others parameters were not differences (Table 1).
The intravenous administration of sildenafil to control animals did not significantly alter the frequency or amplitude of micturition cycles. A significant difference was found between the groups in relation to: void cycles after administration of sildenafil (lower in Group 4). The amplitude before administration was large in Group 4, however become similar to that of the control animals (post-sildenafil) (Fig. 1).

Table 1. Descriptive and comparative analyses of continuous variables between Groups 1 and 2.

Control group							Treated group						
Variable	N	Mean	DP	Min	Median	Max	Variable	N	Mean	DP	Min	Median	Max	P*
NVC	9	1.17	0.75	0.5	0.98	3.04	FDC	8	2.62	0.89	1.13	2.71	3.60	P=0.004
VT	9	1.18	0.38	0.53	1.26	1.80	TV	8	2.83	1.64	0.80	2.80	6.00	P=0.012
PT	9	19.14	3.02	16.20	17.60	25.20	PT	8	19.13	2.90	15.20	19.20	22.40	P=0.860
PP	9	21.14	3.06	16.20	20.80	26.50	PP	8	20.05	2.93	16.20	20.55	23.40	P=0.555
FM	9	1.08	0.65	0.17	1.2	1.84	FM	8	1.97	0.78	1.15	1.79	3.45	P=0.05
BP	9	11.69	6.77	2.7	12.30	20.30	BP	8	13.73	3.35	7.00	15.05	15.70	P=0.906
Weight	9	332.56	7.75	321.00	332.00	345.00	Weight	8	334.77	7.95	319.15	335.00	347.00	P=0.336

p-values refer to Mann-Whitney test for comparison between the control and treated groups.
NVC – Non voiding contractions; VT – volume threshold; PT – pressure threshold; PP – peak pressure; FM – frequency of the micturition cycles; BP – baseline pressure during micturition

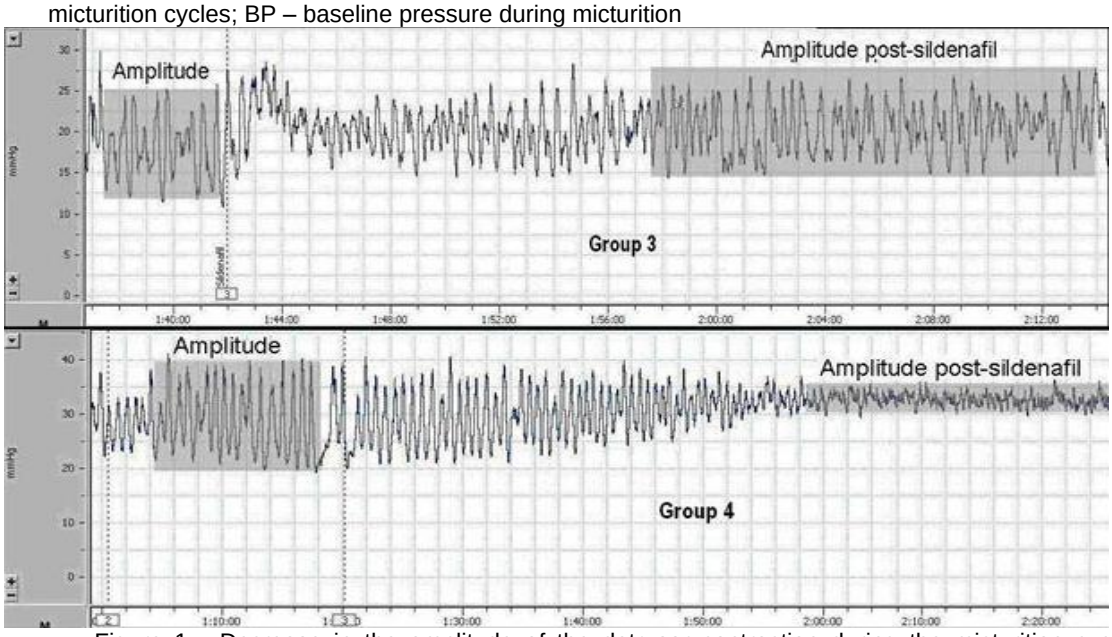

Figure 1 - Decrease in the amplitude of the detrusor contraction during the micturition cycles after administration of sildenafil in a rat treated with L-NAME (Group 4)

Interpretation of results

In the present study, the role of nitric oxide on the lower urinary tract of rats was experimentally assessed in vivo. Initially, a systemic decrease of nitric oxide by L-NAME was developed. Compared to the Group 1, the Group 2 (L-NAME) had a higher number of NVC during the filling phase and an increase in the number of micturition cycles. The volume threshold was also higher than in the Group 1. In this way, a higher volume becomes necessary to initiate micturition. There are two theories that could explain this fact, a lack of urethral relaxation or detrusor hypocontractility. However, as micturition of the Group 2 rats had detrusor pressures similar to Group 1, it suggests a lack of urethral relaxation. These results suggest that nitric oxide has a muscular contraction inhibitory effect both in the bladder and in the urethra of animals treated in a chronic and systemic manner with L-NAME. Concluding, the systemic reduction of nitric oxide causes detrusor hyperactivity with a decrease in the functional relaxation of the urethra conditions similar to functional BOO and DO secondary.

Sildenafil reverted the detrusor alterations, with a decrease in the number of micturition cycles and also in the contractions amplitude in the Group 4 animals, but did not alter the cystometric parameters of the Group 3 animals. The PDE5 inhibition increased the cGMP concentration, resulting in a relaxation of the detrusor smooth muscles, potentiating the effect of available nitric oxide. This study reveals that not only the cholinergic and adrenergic pathways are involved in the physiology of the lower urinary tract. There is also a participation of non-adrenergic and non-cholinergic pathway (NANC), formed by nerves containing NO, that might be involved in the origin of LUTS.

Concluding message

The non-adrenergic non-cholinergic neurotransmission involving nitric oxide has a role in the pathophysiology of the lower urinary tract.

The systemic reduction of nitric oxide causes detrusor overactivity and sildenafil decreases the number of micturition cycles as well as the contractions amplitude.

Specify source of funding or grant	**none**
Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Committee on Animal Research and Ethics of the Universidade Estadual de Campinas**