

## THE INFLUENCE OF A PHOSPHODIESTERASE 5 INHIBITOR (SILDENAFIL) ON BLADDER FUNCTION AND BLOOD OXYGEN SATURATION AFTER BLADDER OUTLET OBSTRUCTION

### Hypothesis / aims of study

There is growing evidence that ischemia of the bladder wall contribute to the initiation of bladder dysfunction. Several studies have shown effects in obstructed bladder that can be interpreted as long term results of hypoxia [1]. Furthermore, there is an increasing interest in the nitric oxide (NO) pathway as a potential pharmacological target to treat lower urinary tract symptoms. Phosphodiesterase 5 (PDE5) is involved in the NO pathway and it has been immunolocalized both in the detrusor muscle cells and in the vascular endothelium [2]. PDE5 inhibitors were found to improve several functional aspects of the obstructed bladder in human and animal studies [3]. The mechanisms behind this are not exactly defined yet but it can be assumed that PDE5 inhibitors may influence detrusor muscle cell action direct but also indirect through enhancing the tissue microcirculation of the bladder.

The objective of this study is to determine the effect of the PDE5 inhibitor Sildenafil citrate (SC), which enhances tissue microcirculation, on bladder function and blood oxygen saturation (BOS) in vivo in an animal model of bladder outlet obstruction.

### Study design, materials and methods

32 guinea pigs were studied and divided in four groups; urethrally obstructed receiving either daily SC (n=8) or saline (n=8), and sham operated plus SC (n=8) or plus saline (n=8). SC or saline was given orally just before obstructive / sham surgery and was continued during an 8 week period. BOS of the bladder wall was measured in real-time and in vivo by differential path-length spectroscopy (DPS) before the obstructive / sham procedure (day 0) and at the day of sacrifice (week 8). Urodynamic measurements were performed before surgery and on a regular basis during the 8 week period to provided data on bladder function.

### Results

#### Before operation (day 0)

All measured urodynamic parameters were comparable and considered as normal. No detrusor overactivity (DO) was found. The BOS of the bladder during filling averaged between 88% and 95% in the four groups. The differences between the groups were statistically not significant. During voiding the average value was 84% to 87% in the 4 groups.

#### After sham operation

In the sham + saline and sham + SC group the maximum voiding pressure (MVP), compliance, contractility and DO did not change during the 8 week follow-up. At week 8 BOS was comparable between both groups and comparable with the initial values at day 0.

#### After obstruction

In the obstruction + **saline** group bladder compliance was significantly lower compared to both day 0 and to the corresponding value in the sham + saline group from week 2 - 8. MVP and contractility were also significantly increased. DO appeared at week 2 and remained present during the whole study period. The average BOS decreased significantly both in the filling phase and in the voiding phase. During voiding individual BOS values were as low as 12%.

In the obstruction + **SC** group the compliance and the MVP remained unchanged compared to day 0 and to both sham groups. Compared to the obstruction + saline group both parameter were significantly higher from week 2-8. DO was found throughout the 8 week follow-up but was significantly lower as compared to the obstruction + saline group.

BOS was not decreased after 8 weeks of obstruction and was significantly higher as compared to the obstruction + saline group. The lowest individual value was 71%.

### Interpretation of results

In a normal bladder BOS is high in the filling phase and drops slightly during voiding. In an obstructed bladder the loss of bladder function is accompanied by a significant decrease in BOS during voiding and filling. Treatment of obstructed bladder with SC maintains high BOS during filling and voiding resulting in high bladder compliance and less DO. We hypothesize that maintaining good working conditions (i.e. enhancing tissue microcirculation) enables the bladder to perform its increased duties without the usual complications.

### Concluding message

Treatment of obstructed bladder with SC maintains normal BOS during filling and voiding, high bladder compliance and reduces DO. This supports the hypothesis that maintaining the microcirculation of the bladder wall results in better bladder performance without significant loss of bladder function. Measurement of BOS and interventions focussing on tissue microcirculation may have a place in the evaluation / treatment of bladder dysfunction.

#### References

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2. Filippi S, Morelli A, Sandner P, et al: Characterization and functional role of an androgen-dependent phosphodiesterase-5 activity in bladder. Endocrinology 2007, 148: 1019-1029.
3. Speakman MJ: PDE5 inhibitors in the treatment of LUTS. Curr Pharm Des. 2009;15(30):3502-5.

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<i>Is this a clinical trial?</i>	No
<i>What were the subjects in the study?</i>	ANIMAL
<i>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</i>	Yes
<i>Name of ethics committee</i>	The animal experiments were approved by the animal ethics committee of the ErasmusMC, Rotterdam, The Netherlands.