

## ANGIOTENSIN II TYPE I (AT-1) RECEPTOR INHIBITION PREVENTS THE URODYNAMIC AND DETRUSOR CHANGES ASSOCIATED WITH BLADDER OUTLET OBSTRUCTION – A MOUSE MODEL

### Hypothesis / aims of study

Bladder outlet obstruction (BOO) can result in bothersome storage and voiding symptoms. Storage symptoms are often associated with urodynamic changes (detrusor overactivity) and/or histological changes (detrusor muscular hypertrophy and/or collagen deposition). Treatment of patients with LUTS associated with benign prostatic hyperplasia (BPH), however, is typically focused on reducing bladder outlet resistance. Recently, detrusor-directed therapy with antimuscarinics has proven safe and efficacious in men with BPH. The lower urinary tract has been shown to have a functional local rennin-angiotensin system, similar to the vascular system. We investigate whether treatment with the angiotensin receptor blocker (ARB) losartan can prevent the structural and functional changes that occur with BOO in a mouse model.

### Study design, materials and methods

We partially obstructed the urethra in twenty Balb/CAN mice. Mice were anesthetized with ketamine (60 mg/kg), xylazine (5 mg/kg), and acepromazine (5 mg/kg) via intraperitoneal injection. Through a midline abdominal incision, a 4-0 nylon suture was tied around the proximal urethra using PE-50 tubing as a guide to partially obstruct. Mice were survived for 6 weeks. Half of the mice (n=10) were given the AT-1 inhibitor losartan daily (10 mg/kg) via gastric gavage, starting at the time of obstruction, until 6 weeks, and half of the mice (n=10) were not. An additional 6 mice were used as untreated, unobstructed controls. Urodynamics were performed at a filling rate of 25 ul per min via suprapubic PE 50 tubing, at baseline, and after 6 weeks. Capacity (C), detrusor voiding pressure (Pdet) and volume at first non-voiding contraction as a percentage of bladder capacity (NVC1) were recorded. After urodynamics, the bladder was harvested, fixed in 10% formalin, processed for histological evaluation, and stained with trichrome (for collagen deposition) and hematoxylin and eosin (for detrusor hypertrophy). Trichrome scoring was performed. Scores were given of 1 for decreased staining, 2 for normal staining, and 3 for increased staining of collagen when compared to our control group. Hematoxylin and eosin scoring was done in a similar fashion, with a score of 1 for atrophy, 2 for normal appearing muscle thickness, and 3 for hypertrophy, compared to control bladders. Histological scoring was performed in blinded fashion by 2 pathologists and 2 urologists. Consensus for each specimen was recorded as a single value.

### Results

BOO was associated with urodynamic and histological changes. Compared to controls, BOO mediated an increase in bladder capacity ( $154 \pm 20.9$  ul vs.  $57.5 \pm 7.4$  ul,  $p < 0.01$ ), an increase in Pdet ( $28.8 \pm 2.1$  mm Hg vs  $12.1 \pm 1.9$  mm Hg) a decrease in NVC1 (median = 24% vs. 54%  $p = 0.03$ ). BOO mediated an increase in detrusor muscle hypertrophy (median score = 3.0 vs. 2.0,  $p = 0.02$ ), and in fibrosis (median score = 3.0 vs 2.0,  $p = 0.01$ ) compared to controls. Compared to untreated BOO mice, treatment of BOO mice with 6 weeks of losartan mediated an increase in bladder capacity ( $249 \pm 28.9$  ul vs.  $154 \pm 20.9$  ul,  $p = 0.01$ ), no significant change in Pdet ( $24.7 \pm 1.6$  mm Hg vs  $28.8 \pm 2.1$  mm Hg,  $p = 0.2$ ) an increase in NVC1 (47% vs 24%,  $p = 0.02$ ). Structural changes were also noted. Compared to untreated BOO mice, treatment with losartan mediated a reduction in detrusor hypertrophy (median score = 2.0 vs 3.0,  $p = 0.02$ ), as well as a reduction in fibrosis (median score = 1.0 vs 3.0,  $p < 0.01$ .)

### Interpretation of results

Detrusor-directed therapy can ameliorate urodynamic and histological changes than can result from BOO. The lower urinary tract indeed has a functional rennin-angiotensin system, similar to the vascular system. In addition to its vital role in smooth muscle contraction, angiotensin II has also been shown to provide a means by which the tissue responds to increased work loads. Similar to the heart, the bladder contains receptors for angiotensin II and blockade of these receptors during outflow obstruction results in a blunted compensatory response, notably muscle hypertrophy and collagen deposition. The mechanism of action may be two-fold. The partial inhibition of non-voiding contractions likely prevents detrusor hypertrophy by reducing the frequency of isovolumetric detrusor contractions. In addition, AT-1 antagonism may also directly blunt the angiotensin II-induced muscular response to increased resistance/work load.

### Concluding message

In a mouse model of BOO, treatment with six weeks of oral losartan, an AT-1 receptor antagonist, appeared to prevent some of the urodynamic and histological changes that occur with untreated BOO. BOO was associated with urodynamic changes, including a significant increase in bladder capacity, voiding pressure, and detrusor overactivity, as well as histological changes, including increased hypertrophy of the detrusor muscle, and increased collagen deposition in the lamina propria and detrusor muscular layer. Treatment with losartan resulted in a further increase in bladder capacity, improvement in detrusor overactivity, but did not adversely affect bladder contractility. AT-1 antagonism also partially inhibited detrusor hypertrophy and collagen deposition. Long-term studies regarding the use of ARBs would be helpful to determine the ultimate safety and efficacy of this class of medications in the setting of BOO.

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<b>What were the subjects in the study?</b>	ANIMAL
<b>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</b>	Yes

