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THE EFFECT OF SILODOSIN ON THE PROSTATIC MICROCIRCULATION IN A PROSTATITIS RAT MODEL INDUCED BY URINE REFLUX

Hypothesis / aims of study
Alpha-1 adrenoreceptor antagonists are effective for some patients with chronic prostatitis. Although the mechanism has not been elucidated, one possible mechanism is improved prostatic microcirculation. Abacterial prostatitis is partly caused by urine reflux due to high-pressure urination secondary to benign prostate hyperplasia. In this study, we established a novel rat model of prostatitis induced by urine reflux into the prostate and evaluated the effect of silodosin on the prostatic microcirculation.

Study design, materials and methods
Experiment 1: Male SD rats were anesthetized with isoflurane and injected with 500 µL 2.5% Evans Blue through the urethral orifice. The intravesical pressure was measured and the prostate was excised to evaluate histology.
Experiment 2: Rats were anesthetized with isoflurane and the bladder was exposed to collect 500 µL urine sample. The rats were injected with urine or saline (control) from the urethral orifice. Using subcutaneous osmolality pumps, silodosin (200 µg/kg/day) was administered to the silodosin group of rats. We evaluated histopathology and proinflammatory cytokine expression of the prostate of day 7, after assessing the prostatic microcirculation and cystometrogram.

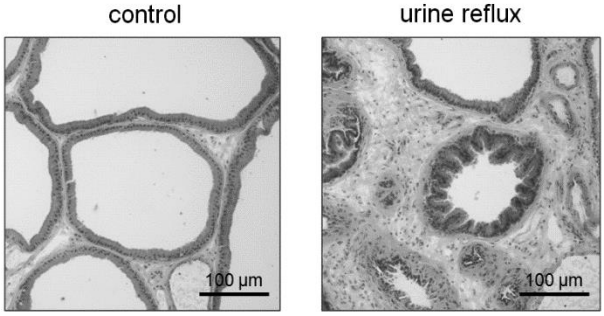
Results
Experiment 1: The histopathology showed that Evans Blue instilled through the urethral orifice inflew into the prostatic ducts. The intravesical pressure during Evans Blue instillation was 47.7 ± 1.6 cmH_2O (mean ± standard error).
Experiment 2: Histopathologically, there was inflammatory cell infiltration in the prostate after instilling urine (Fig. 1). Inflammation-associated proteins were upregulated in the urine reflux rats, but suppressed in the silodosin group (Fig. 2). Erythrocyte speed on the prostatic surface was 158.9 ± 10.4 µm/s in the control, 142.9 ± 3.0 µm/s in the urine reflux group, and 148.6 ± 4.2 µm/s in the silodosin group. Cystometrogram revealed a shorter intercontraction interval in the urine reflux rats compared to the controls, which was prolonged in the silodosin group (Fig. 3).

Interpretation of results
Urine refluxes into the prostatic ducts during micturition in humans and can cause chemical irritation and inflammation. Our results demonstrate that urine instilled through the urethra entered the prostatic duct, and induced abacterial prostatic inflammation. This novel prostatitis model resulted in a disturbed prostatic microcirculation and frequent micturition. Silodosin treatment increased the prostatic blood flow and relieved the bladder overactivity.
A limitation of this study was that we did not identify which urine ingredient was the irritant. Uric acid crystals is reported to result in the development of chronic prostatic inflammation via activation of the NALP3 inflammasome and normalization of uric acid level improves prostatitis symptom. Proton ions, potassium ions, and ammonium in the urine are other candidates.

Concluding message
We developed a novel abacterial prostatitis rat model by instilling urine through the urethral orifice. This model shares some common characteristics with human abacterial prostatitis. Silodosin relieved the bladder overactivity by increasing the microcirculation in the prostate.

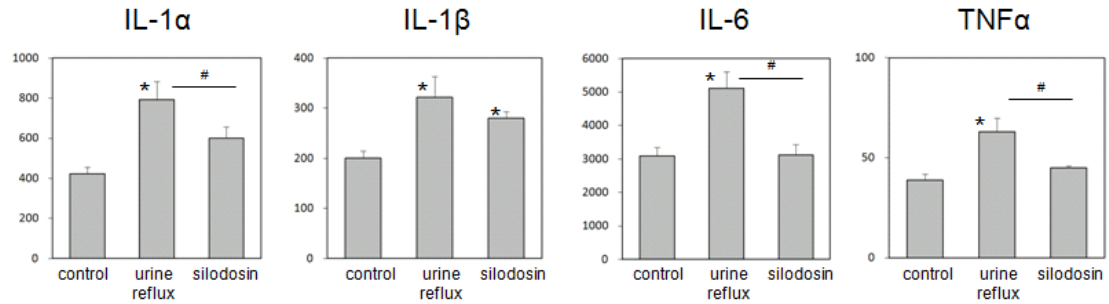
Figures

Fig. 1 Histological findings



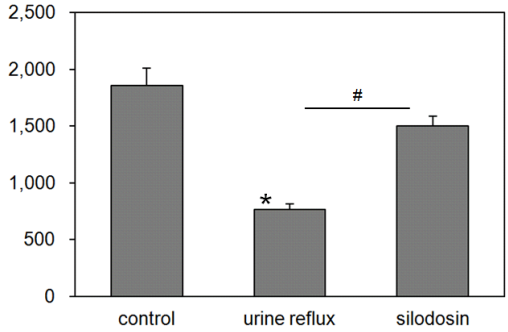
Polymorphological inflammatory cell infiltrated in the stoma in the urine-refluxed rats.

Fig. 2 ELISA for proinflammatory cytokines



All values are expressed as pg/ml (mean ± standard error).
*; $p < 0.05$ compared to the control. #; $p < 0.05$ between groups.

Fig. 3 Intercontraction intervals (sec)



The interconctraction interval was significantly shorter in the urine reflux group, but not in the silodosin groups.

Disclosures
Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Nagoya University Institutional Animal Care and Use Committee