

## FUNCTIONAL AND STRUCTURAL CHANGES IN THE CHRONIC ISCHEMIC BLADDER AND THE PROTECTIVE EFFECT OF ALPHA ADRENERGIC RECEPTOR BLOCKER: IN VIVO / IN VITRO STUDY

### Hypothesis / aims of study

To assess the effects of atherosclerosis and chronic ischemia on bladder structure and function and the protective effect of alpha adrenergic receptor blockers of the structural and functional changes in the chronic ischemic bladder.

### Study design, materials and methods

Male Sprague-Dawley rats were divided into three groups. The atherosclerosis-induced chronic bladder ischemia group (n=15) and doxazosin group (n=10) underwent balloon endothelial injury of the bilateral iliac arteries and received a 0.25% cholesterol diet for 16 weeks. Doxazosin group was administered doxazosin (30mg/kg dissolved in 30% DMSO) for 4 weeks. The control group (n=13) underwent sham operation and was followed with regular diet. After 16 weeks of procedure, cystometrograms were obtained and bladder tissues were processed for the contractility and spontaneous relaxation course in the organ bath and for histological evaluation in all groups.

### Results

At 16 weeks, basal intravesical pressure and voiding frequency were increased and bladder capacity and compliance were decreased in the atherosclerosis-induced chronic bladder ischemia group compared with the control group (table 1). In the doxazosin group, intravesical pressure and voiding frequency were decreased and bladder capacity and compliance were increased than the atherosclerosis-induced chronic bladder ischemia group and showed no significant differences to the control group. In the organ bath study, bladder strips from the atherosclerosis-induced chronic bladder ischemia rats demonstrated decreased contractile response to carbachol and delayed spontaneous relaxation course while bladder strips from the doxazosin group showed increased contractility and more rapid relaxation than the atherosclerosis-induced chronic bladder ischemia group (Fig 2, 3). Histological examination of bladder strips from the atherosclerosis-induced chronic bladder ischemia group showed the structural damage in urothelium causing disruption of mucosa and vacuolation compared with control group while these structural changes were not observed in the doxazosin group.

### Interpretation of results

Our results suggest that chronic ischemia of bladder causes detrusor overactivity, impaired function of bladder smooth muscle and structural damage of bladder tissue. It is suggested that alpha adrenergic receptor blocker reduces the severity of the response to the atherosclerosis-induced chronic bladder ischemia. These beneficial effects would be due to pharmacological effects on alpha adrenergic system in the bladder which include effect on blood flow to the bladder.

### Concluding message

Alpha adrenergic receptor blocker had the protective effects on the chronic ischemic bladder as recovering the function of bladder smooth muscle and reducing the structural changes of bladder tissue. Additional study will be needed to clarify the mechanism of these effects of alpha adrenergic receptor blocker on the bladder.

Table 1. Urodynamic parameters of two groups; normal control group and atherosclerosis-induced chronic ischemia group.

	BP	TP	TP-BP	MP	MP-TP	MF	BCap	BCom
<b>Control</b>	0.12±0.07	7.40±0.86	7.28±0.91	27.04±5.53	19.64±5.31	10.44±4.76	1.17±0.60	0.17±0.11
<b>Chronic ischemia</b>	0.57±0.23	9.04±1.18	8.47±1.34	25.93±6.15	16.89±5.75	30.34±19.35	0.47±0.30	0.06±0.04
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<b>Doxazosin</b>	0.15±0.06	7.96±2.11	7.80±2.08	27.85±10.0	19.90±8.25	12.36±2.51	0.84±0.18	0.12±0.05
<b>P value</b>	0.003	0.095	0.242	0.832	0.701	0.022	0.022	0.012

BP, TP, TP-BP, MP, MP-TP, cmH<sub>2</sub>O; BCom, ml/cmH<sub>2</sub>O; MF, /hr

MP; micturition pressure, maximum bladder pressure during micturition

TP; threshold pressure, bladder pressure at onset of micturition

BP; basal pressure, minimum bladder pressure between two micturitions

MP-TP; change of bladder pressure from baseline during contraction

MF; micturition frequency

BCap; bladder capacity, infusion rate divided by MF

BCom; bladder compliance, BCap/(TP - BP)

Kruskal-Wallis test used

Figure 1. Carbachol concentration-response curves of bladder strips. Strips of bladder smooth muscle from control rats, atherosclerosis-induced chronic ischemia rats and doxazosin rats to the cumulative addition of carbachol.

Kruskal-Wallis test used

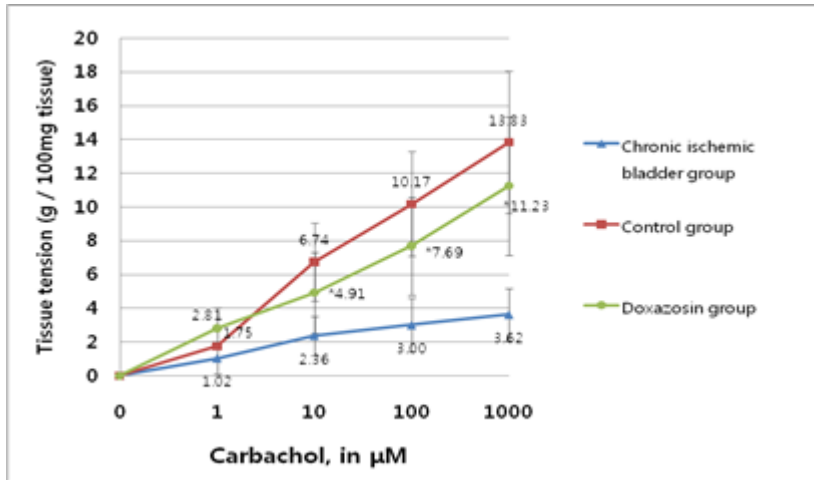
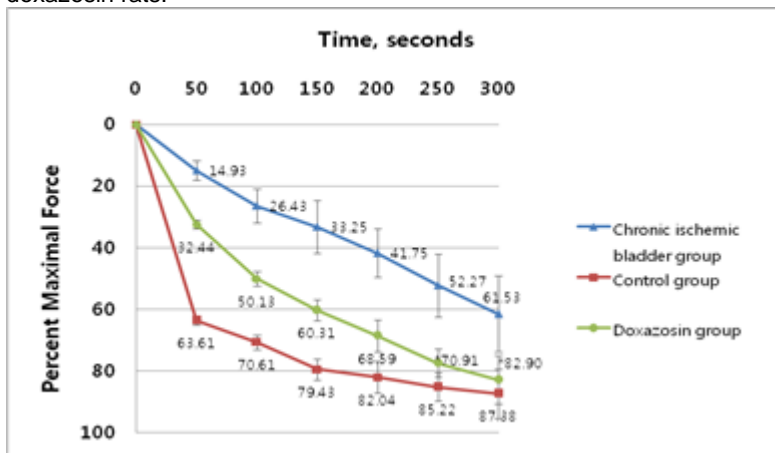


Figure 2. Time course of bladder smooth muscle in strips from control rats, atherosclerosis-induced chronic ischemia rats and doxazosin rats.



Kruskal-Wallis test used

#### References

1. Azadzi KM, Tarcan T, Siroky MB, Krane RJ. Atherosclerosis-induced chronic ischemia causes bladder fibrosis and non-compliance in the rabbit. *J Urol.* 1999 May;161(5):1626-35.
2. Pinggera GM, Mitterberger M, Steiner E, Pallwein L, Frauscher F, Aigner F, et al. Association of lower urinary tract symptoms and chronic ischaemia of the lower urinary tract in elderly women and men: assessment using colour Doppler ultrasonography. *BJU Int.* 2008 Aug;102(4):470-4.
3. Pinggera GM, Mitterberger M, Pallwein L, Schuster A, Herwig R, Frauscher F, et al. alpha-Blockers improve chronic ischaemia of the lower urinary tract in patients with lower urinary tract symptoms. *BJU Int.* 2008 Feb;101(3):319-24

#### Disclosures

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