Protective effect of tadalafil on endothelial function of bladder microvessels in a rat model of chronic bladder ischemia

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Hypothesis / aims of study
Vascular endothelial dysfunction and atherosclerosis, a common clinical problem in the elderly population, may lead to impaired lower urinary tract perfusion and have an important role in the development of lower urinary tract symptoms (LUTS) (1, 2). In male LUTS, the therapeutic effects of PDE5 inhibitors, such as tadalafil, sildenafil and vardenafil have been well documented. It has been suggested that the reduction of LUTS by PDE5 inhibitors is due in part to improvement of vascular endothelial function, resulting in increased bladder perfusion (1, 2). However, despite intensive clinical studies, it has not been established that PDE5 inhibitors can improve endothelial dysfunction of bladder microvessels. Thus, we used a previously described rat model of chronic bladder ischemia (3) to investigate whether chronic ischemia-induced bladder hyperactivity and change of eNOS expression in bladder microvessels can be prevented by chronic treatment with tadalafil.

Results
Iliaic arteries from AI and AI-tadalafil rats displayed neo-intimal formation and luminal occlusion. Average wall thickness of the common iliac arteries in the AI and AI-tadalafil groups was significantly greater than in controls (Fig.1). In the AI group, the micrturition interval was significantly shorter (5.4± 0.5 vs 11.1± 1.1 min), and bladder capacity and voided volume were less than in controls (Table 1, Fig 4). The AI bladders showed significantly increased collagen ratio and decreased eNOS expression in the microvessels compared with the controls (Fig 2). In the AI-tadalafil group, tadalafil significantly improved collagen ratio and eNOS expression, and there were significant improvements in cystometric parameters compared with the AI group (Table 1, Fig 2,3,4).

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Study design, materials and methods
Adult male Sprague-Dawley rats were divided into control, arterial endothelial injury (AI), and AI with tadalafil treatment (AI-tadalafil). AI and AI-tadalafil groups underwent endothelial injury of the iliac arteries and received a 2% cholesterol diet following AI. AI-tadalafil rats received tadalafil (2mg/kg/day) orally for 8 weeks after AI. The control group received a regular diet. After 8 weeks, urodynamic investigation was performed. Bladder tissues and iliac arteries were processed for histological and immunohistochemical examination.

Possible mechanisms for LUTS induced by chronic bladder ischemia

Concluding message
Chronic bladder ischemia may be an important factor contributing to the development of LUTS. Our findings suggest that protection of vascular endothelial function and improvement of LUT perfusion as therapeutic strategies for LUTS may have beneficial effects on chronic ischemia-related bladder dysfunction in the elderly population.