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BILATERAL ILIAC ARTERY ENDOTHELIAL INJURY AND HYPERCHOLESTEROLEMIA LEAD TO BLADDER OVERACTIVITY IN THE RAT.

Hypothesis / aims of study
Idiopathic overactive bladder (OAB) is the most common type of OAB and its prevalence increases with age. Recently, vascular risk factors for atherosclerosis were shown to play a role in the development of LUTS including OAB. This suggests that vascular occlusive disease and concomitant chronic ischemia may produce detrusor overactivity. Although several animal models of chronic bladder ischemia have been developed, these models not necessarily show detrusor overactivity (DO). In research of cardiology, epicardial coronary artery endothelial injury is known to induce downstream coronary microvascular remodeling, which may be related to the development of ischemic heart disease. Similarly, we performed balloon endothelial injury of the rat iliac arteries in order to create an adequate model of chronic ischemia-induced DO. Thus, the present study investigated whether balloon endothelial injury of the iliac arteries combined with 2% cholesterol diet induces arterial occlusive disease in the downstream bladder microvessels, and whether this procedure eventually causes DO in the rat.

Study design, materials and methods
Adult (16-week old) male Sprague-Dawley rats were divided into AI, sham and control groups. The AI group underwent balloon endothelial injury of the iliac arteries and received a 2% cholesterol diet (n=10). Sham group that only incised bilateral inguinal region and did not undergo balloon endothelial injury but received a 2% cholesterol diet alone (n=10). A third group was placed on a regular diet was utilized as an age-match control group (n=10). After 8 weeks, voiding behaviour was studied using metabolic cages and parameters were recorded. Then, all rats were performed cystometrograms（CMG）without anesthesia or restraint. Blood was obtained for measurement of the blood levels of glucose, triglycerides and cholesterol. Finally, all rats from each group were sacrificed, bladders and vessels of from aorta to iliac artery were removed, and histological examination was performed.

Results
In the AI group, 24-hr frequency voiding significantly increased and the mean voided volume significantly decreased compared with those in the sham and control groups (Table 2). The CMGs showed that the mean bladder capacity as well as the mean interval between the successive voiding reflex decreased significantly compared with those in the other two groups (Table 3). The base-line pressure and peak pressure were not significantly different among the three groups. Histological study showed a marked vascular occlusive disease with wall thickening in the bladder microvessels in the AI group. Although iliac arteries in the AI group possessed thickening of intima as well as diffuse fibrosis of media, there was no occlusion at the sites of balloon injury (Figure 1).

Interpretation of results
This study clearly shows that vascular occlusive disease occurred in downstream bladder microvessels after iliac artery endothelial injury with cholesterol diet. The mechanisms underlying this microvascular remodeling have remained to be elucidated. As the downstream bladder microvessel artery is never directly damaged during our experimental procedure, abnormal stimulus or stimuli produced in the iliac artery may induce microvascular remodeling.
In addition, DO was demonstrated in our model of chronic bladder ischemia.

Concluding message
Our findings showed that bilateral iliac artery endothelial injury and hypercholesterolemia led to detrusor overactivity in the rat. Therefore, it is suggested from this model that atherosclerosis-induced chronic bladder ischemia may play a role in the development of idiopathic bladder overactivity.

Table 1 Animal and bladder weight, serum of glucose and lipids at 8 weeks in the control, sham and AI groups

Groups	Body weight (g)	Bladder weight (g)	Glucose (mg/dl)	Triglycerides (mg/dl)	Cholesterol (mg/dl)
Control	573.0 ± 11.9	0.39 ± 0.02	188.7 ± 15.9	70 ± 10.4	68.0 ± 4.2
Sham	553.7 ± 11.3	0.45 ± 0.02	189.7 ± 10.1	64.2 ± 9.63	156.7 ± 15.3*
AI	561.0 ± 9.4	0.44 ± 0.02	190.7 ± 26.1	66.8 ± 14.2	159.3 ± 23.3*

Each value represents the mean ± SEM. *P<0.01 versus control.

Table 2 At 8 weeks, micturition parameters in the metabolic cage study

Groups	24-hr water consumption (ml)	24-hr urine production (ml)	24-hr frequency	Mean voided volume (ml)
Control	19.6 ± 3.7	15.0 ± 2.2	11.0 ± 1.4	1.36 ± 0.07
Sham	20.4 ± 4.0	17.1 ± 2.2	13.8 ± 2.4	1.22 ± 0.05
AI	16.2 ± 3.5	14.7 ± 1.2	17.5 ± 0.7*	0.84 ± 0.06**

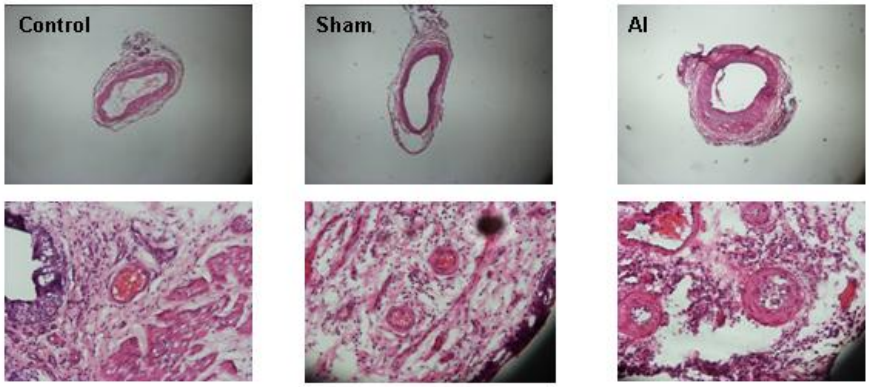
Each value represents the mean ± SEM. *P<0.05 versus Control,
**P<0.01 versus Control and Sham.

Table 3 Bladder capacity, peak pressure and base-line pressure at 8 weeks in cystometrogram

Groups	Bladder capacity (ml)	Peak pressure (cmH_2O)	Base-line pressure (cmH_2O)
Control	1.31 ± 0.11	44.1 ± 2.9	13.9 ± 1.3
Sham	1.28 ± 0.14	51.0 ± 3.2	16.2 ± 2.2
AI	0.78 ± 0.12*	55.0 ± 4.3	13.3 ± 1.0

Each value represents the mean ± SEM. *P<0.05 versus Control and Sham.

Figure 1 H & E staining of cross section of iliac arteries (x40 magnification, upper panel) and downstream bladder microvessels (x200 magnification, lower panel) in animals of control , Sham and AI groups



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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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