

## THE EFFECTS OF L-ARGININE AND L-NAME ON THE RESPONSE TO CHRONIC PARTIAL BLADDER OUTLET OBSTRUCTION IN THE RABBIT

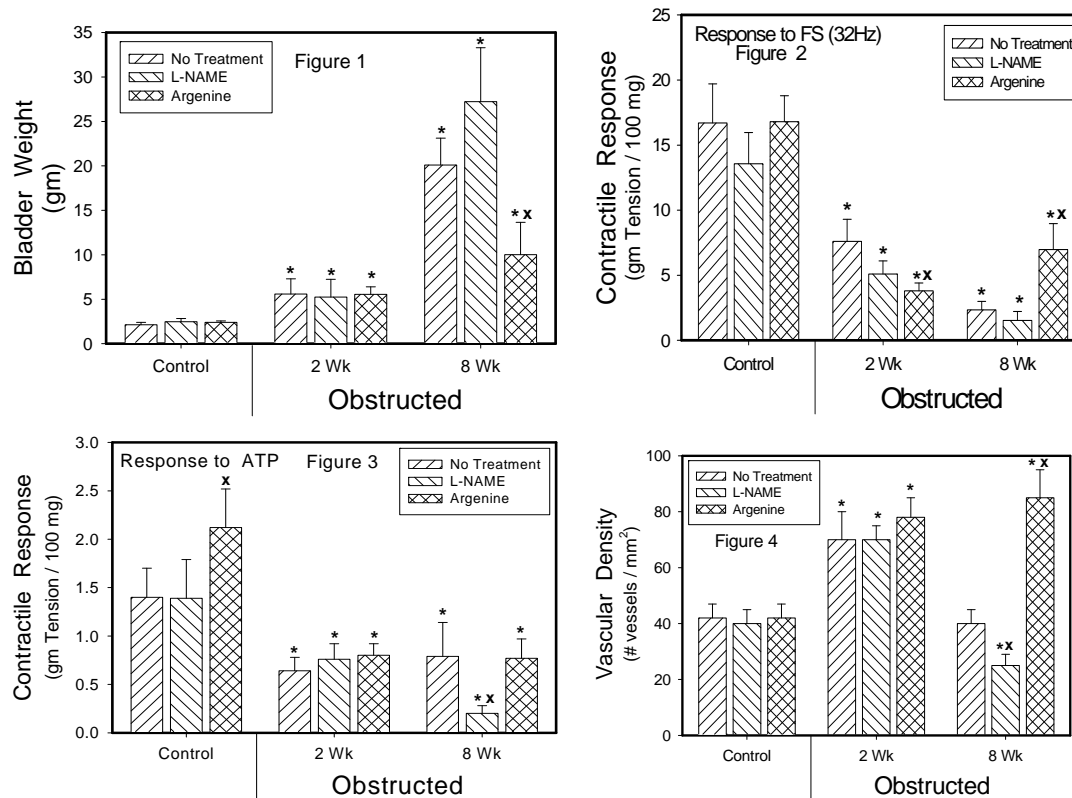
### Hypothesis / aims of study

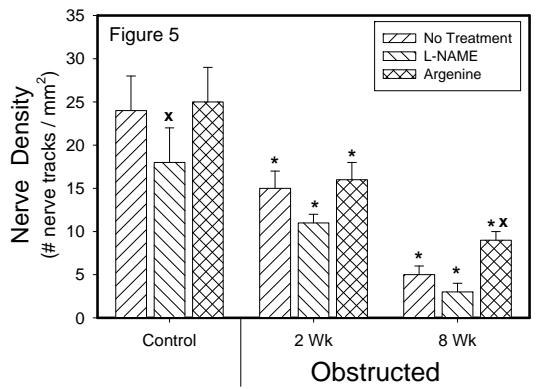
Nitric oxide (NO), a neurotransmitter responsible for relaxation and vascular dilation activities in the lower urinary tract, is synthesized from L-arginine by nitric oxide synthase (NOS). This reaction is inhibited by *N*-G-nitro-L-arginine methyl ester (L-NAME) and increased by L-Arginine (the substrate for NOS). The aim of the study is to investigate the effects of chronic treatments with L-arginine and L-NAME on the response of the rabbit to partial bladder outlet obstruction (PBOO).

### Study design, materials and methods

Thirty-six adult male New Zealand White rabbits (~5 kg) were divided into three equal groups. Each group is composed of 3 subgroups with 4 rabbits each. Subgroups included no-treatment, L-arginine, and L-NAME treatment. Rabbits in groups 1 and 2 were subjected to 2 and 8 weeks of PBOO. The remaining group underwent sham surgery (controls). The bladders were then removed, weighed, and the tissues used for contractile, histological and molecular studies. Western blotting was performed to determine the level of carbonylation and nitrotyrosination at the protein level.

### Results





#### Interpretation of results

There was a progressive increase in bladder weight among all groups at 2 weeks obstruction. At 8 weeks obstruction, there was a substantial increase in bladder weight in both the no-treatment and L-NAME groups but only a moderate increase was only seen in the L-arginine group. In general, there was a declining trend in contractile response to all modes of stimulation at 2 weeks of PBOO and a further drop after 8 weeks obstruction. However, at 8 weeks of PBOO, L-arginine group had significantly greater contractile responses to field stimulation and carbachol. The L-NAME group had significantly lower contractile function in response to KCl and ATP compared to both no treatment and L-arginine groups. In morphological studies, after 2 weeks obstruction, all groups showed hyperplasia of the mucosa and hypertrophy of the smooth muscle compartment. However, at 8 weeks obstruction, denudation of mucosa and atrophy of smooth muscle cell were characteristics in both non-treatment and L-NAME groups; whereas in the L-arginine group we observed intact mucosa and hypertrophied smooth muscle cells. Immunostaining with anti-CD 31 antibodies showed transmural angiogenesis among all groups at 2 weeks obstruction. At 8 weeks obstruction, vascularization generally decreased in serosal and muscular layer in the non-treatment and L-NAME groups; whereas transmural angiogenesis was still found in the L-arginine group. The mean number of vessels per unit area was significantly increased among all subgroups at 2 weeks obstruction. However, at 8 weeks obstruction, vessels density decreased to control levels in the no-treatment group and even lower in the L-NAME group; vessel density was still higher than control level in the L-arginine group. In general, there was a declining trend in nerve density at 2 weeks of PBOO and a further drop after 8 weeks obstruction. However, at 8 weeks obstruction, the L-arginine group had a significantly greater nerve density compared with the no treatment and L-NAME groups. There was a significant increase in the level of carbonylation and nitrotyrosination following 2 and 8 weeks obstruction in the no-treatment group. However, at 8 weeks obstruction, in the L-arginine group, the levels of carbonylation and nitrotyrosination was significantly lower than the no-treatment and L-NAME groups.

#### Concluding message

In the 8 week obstructed group, blockade of NOS by L-NAME resulted in decreased contraction, decreased angiogenesis, denervation and an increase of oxidative stress thus resulting in increased bladder dysfunction. Supplementation with L-arginine resulted in a maintenance of angiogenesis, neuroprotection, decreased oxidative stress and improved contractile function after chronic PBOO.

**FUNDING:** no

**ANIMAL SUBJECTS:** This study followed the guidelines for care and use of laboratory animals and was approved by the Institutional Animal Care and Use Committee of the Stratton VAMC