Introduction: The physiologic response to hypotension involves catecholamine-mediated contraction of vascular smooth muscle. During sepsis, this process is impaired and the response to catecholamines is blunted. Current evidence suggests that this is in part due to the over-production of nitric oxide by inducible nitric oxide synthase (iNOS) as well as the opening of K-ATP channel in vascular smooth muscle. In this study, we have examined the effects of propofol (a putative scavenger of peroxynitrite radicals) and bupivacaine (a K-ATP channel blocker) on concentration-response curves generated with phenylephrine (an α1-adrenergic agonist) in isolated rat aortic (thoracic) rings, ex vivo, obtained from animals 4 hours post-treatment with either saline (1.0 mL/kg) or lipopolysaccharide (LPS; 1.0 mg/kg).

Methods: All procedures on animals were carried out in accordance with the guidelines and approval of the Animal Care Committee at our institution. Aortic rings were suspended on stainless steel wire in 20 mL tissue baths containing physiological salt solution gassed with O2:CO2 95%:5% at temperature 37°C and pH 7.4. Isometric contractions were recorded using force transducers connected to a polygraph. The effects of propofol (10 µM and 30 µM), bupivacaine (30 µM) and propofol (30 µM) combined, N-nitro-L-arginine methyl ester (L-NAME; 10 µM) and NaOH (1.0 M; 20 µL) were investigated on phenylephrine-induced contractions.

Results: Injection of LPS compared to saline resulted in a significant reduction in the systolic blood pressure (108 ± 4.0 vs. 122 ± 4.0 mmHg) (mean ± S.E.M.), an increase in heart rate (410 ± 10 vs. 347 ± 9.0 bpm), and elevation in plasma concentrations of NO2-/NO3- (90.4 ± 8.8 vs. <3.0 µM), respectively. Mechanical responses of aortic rings to phenylephrine were diminished in tissues obtained from animals treated with LPS compared to saline. Maximal force of contraction induced by phenylephrine was 8.2 ± 1.4 mN and 6.5 ± 1.4 mN (n=12; mean ± S.D., p<0.05) in saline- and LPS-treated rats, respectively. The presence of propofol (10 and 30 µM) increased potency and efficacy of phenylephrine in tissue from animals treated with LPS. Bupivacaine (30 µM) alone also reversed the inhibitory effects of LPS-treatment on phenylephrine-induced contractions. A combination of propofol (30 µM) and bupivacaine (30 µM) produced an increase in phenylephrine-elicited contractions in aortic rings, however, the effect was less than with either agent alone. L-NAME potentiated phenylephrine-mediated contractions increasing the maximal response in aortic rings obtained from saline- and LPS-treated animals.

Discussion: It is possible that propofol-mediated sensitization to phenylephrine was due to (a) reduction of peroxynitrite radicals, (b) inhibition of iNOS or a combination of (a) and (b). The impact of bupivacaine may have been via the inhibition of K-ATP channels but it is evident that this effect was not synergistic with propofol.

Further research is needed to elaborate on these findings. Though clinicians may be reluctant to use propofol in hypotensive patients, its properties may be beneficial in patients with sepsis. Whether local anesthetics with better safety profiles than bupivacaine will show the same properties observed here has yet to be determined.