or following ovariectomy (OVX) and implantation of E2 or vehicle (V). Injured vessels were examined 28 days after carotid ligation injury for cross-sectional media and neointima areas.

Results: There was a marked sexual dimorphism in neointima formation in the OPN-/- mice with INT females having a >70% reduction in neointima formation compared to INT males (see graph). The sexually dimorphic response was attenuated by OVX, with V treated females having no significant difference in neointima formation compared to INT males. E2 replacement in OVX females restored the sexually dimorphic response with a 58% reduction in neointima formation compared to OVX+V females. There was no difference in media area among the groups.

Conclusions: These results demonstrate that E2 has vasoprotective effects following vascular injury that are independent of osteopontin expression.

Key Words: Hormones, Vasculature, Osteopontin

P-539
EFFECTS OF INFLAMMATION ON A MODEL OF CYTOCHROME P450 DEPENDENT VERSUS INDEPENDENT ANTIHYPTERTENSIVES: LOSARTAN VERSUS VALSARTAN
Richard Z. Lewanczuk, Noriko Daneshrooz, Anthony S. Russell, Fahkredin Jamali. Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; Faculty of Pharmacy, University of Alberta, Edmonton, Alberta, Canada.

Previous studies have demonstrated that the pharmacokinetics of cytochrome P450 (CYP450) metabolized drugs may be altered in inflammation. The objective of this study was to determine whether the pharmacokinetics and associated pharmacodynamics of a CYP450-activated drug (losartan) would be affected by inflammation when compared to a non-CYP450 metabolized drug (valsartan).

Fourteen patients with acute rheumatoid arthritis, 12 patients with rheumatoid arthritis in remission and 8 healthy controls took part in this study. Losartan 100 mg or valsartan 160 mg were administered as a single oral dose in a double-blind, randomized order to study subjects. At specified intervals after dosing, blood was sampled for measurement of valsartan, losartan and losartan active metabolite, EXP3174, levels. Pharmacodynamic measurements were carried out at the same time as pharmacokinetic measurements using an HDI Pulsewave monitor. Results were assessed based on clinical categorization as well as continuously based on inflammatory mediator levels.

When assessed by clinical status, conversion of losartan to EXP3174 when assessed continuously based on baseline C-reactive protein level (CRP), the AUC ratio for EXP3174:losartan was inversely related to CRP (r=-.49, p=.004). Similar correlations were seen when tendon swollen joints or total serum nitrites were used as dependent variables.

In terms of pharmacodynamics, the Cmax of EXP3174 and the Cmax ratio of EXP3174:losartan correlated with maximum changes in mean arterial pressure and with area under the effect curves for mean arterial pressure and a number of other clinical variables. In multiple regression models, Cmax of EXP3174 was the strongest predictor of clinical effect for losartan. No pharmacodynamic differences were seen for valsartan when analyzed categorically by clinical status or continuously by various inflammatory markers.

We conclude that in the presence of inflammation the activation or metabolism of CYP450-dependent angiotensin II receptor blockers such as losartan may be altered leading to changes in pharmacokinetics and hence, clinical effect. Non-CYP450 dependent ARBs such as valsartan seem to be unaffected by inflammation.

Key Words: Inflammation, Cytochrome P450, Angiotensin Receptor Blockers

P-540
OLMESARTAN AND TEMOCAPRILAT SUPPRESS IL-1ß-INDUCED IL-6 EXPRESSION VIA A DECREASE IN mRNA STABILITY IN VASCULAR SMOOTH MUSCLE CELLS
Zhao-Hui Yang, Yutaka Kitami, Yasunori Takata, Michitsugu Nakamura, Sanae Watanabe, Takafumi Okura, Kunio Hiwada. The 2nd Department of Internal Medicine, Ehime University School of Medicine, Onsen-gun, Ehime, Japan.

Angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (ARB) have been well known to decrease mortality and morbidity of cardiovascular disease in hypertensive patients. Vascular inflammation is thought to be implicated to pathogenesis and progression of cardiovascular disease, and IL-6 is one of important proinflammatory cytokines initiating vascular inflammation and remodeling. Since both ACE-I and ARB are supposed to suppress vascular inflammation through modulation of several inflammatory genes expression, we investigated, in the present study, the effect of ACE-I and ARB on IL-6 expression in vascular smooth muscle cells (VSMCs) and elucidated the underlying mechanism.

Protein and mRNA expression levels of IL-6 were determined in the presence and absence of temocaprilat (10⁻⁷ mol/L) or olmesartan (10⁻⁷ mol/L) after treatment with IL-1ß (0.5 ng/mL). Electromobility shift assay (EMSA) was carried out using an NF-κB probe. Effect of ACE-I or ARB on IL-6 mRNA stability was determined by Northern blotting after treatment with actinomycin D (5 µg/mL).

IL-6 production into culture medium was markedly increased by stimulation of IL-1ß, and this induction was significantly reduced by preincubation with either temocaprilat or olmesartan. IL-6 mRNA levels were slightly reduced, and IL-1ß-induced NF-κB binding activity was also suppressed by pretreatment with these drugs. On the other hand, IL-6 mRNA stability was significantly decreased by the pretreatment.

In conclusions, both ARB and ACE-I can modulate IL-6 gene expression mainly by a decrease in its mRNA stability, and partially by a reduction of mRNA transcription, suggesting that these drugs have a beneficial effect to prevent vascular inflammation.

Key Words: ACE Inhibitor, Angiotensin II Receptor Blocker, IL-6 Expression