Omapatrilat is a recently developed vasopeptidase inhibitor (VPI) which displays equipotent, highly selective competitive activity against neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE). Previous studies demonstrated that ACE inhibitors or NEP inhibitors increased nitric oxide (NO) production in coronary microvessels. To date, there is no information regarding the effect of VPI on vasorelaxation and NO production. We hypothesized that long-term treatment with omapatrilat will increase generation of nitric oxide and enhance NO-mediated vasorelaxation in hypertensive rat. To test this hypothesis, we performed the current study in spontaneously hypertensive rats (SHR, n=5). Vehicle (NaHCO3, 0.5 ml/day) or omapatrilat (100 nM/kg/day) were administered to SHR once daily by gavage for six months. Mean blood pressure (MBP) was determined by tail cuff method. Omapatrilat significantly decreased MBP from day 1 through end of study. At 6 months, SHR was sacrificed and aortic ring was isolated. The effect of omapatrilat on vasorelaxation in aortic ring was determined by organ chamber study. Omapatrilat caused concentration-dependent vasorelaxation (10-10 to 10-6 M) in aortic rings isolated from SHR which received long-term treatment of omapatrilat. The maximal relaxation to omapatrilat (10-6 M) was 68±1.8%. In contrast, L-NAME (10-4 M) completely blocked omapatrilat-mediated vasorelaxation in aortic rings. This study first time demonstrated that omapatrilat has potent vasorelaxation effect through NO-dependent pathway in hypertensive rats. Therefore, nitric oxide may play an important role on omapatrilat-mediated antihypertensive actions.

Key Words: Vasorelaxation, Nitric oxide, Omapatrilat

In a previous work, we demonstrated that vascular smooth muscle modifies endothelium-independent relaxations in spontaneously hypertensive rats (SHR) by releasing cyclooxygenase-derived contracting factors. On the other hand, angiotensin II (ANG-II) is involved in the vascular function with antihypertensive treatment. Furthermore, the modification of the SNP-induced relaxations appears to be related to a lower production of cyclooxygenase-dependent contracting factors. Firstly, incubation of aortic rings from irbesartan-treated SHR with indomethacin did not significantly alter the relaxations in response to cumulative doses of SNP. Secondly, the dose-response curve to SNP for aortic rings from irbesartan-treated SHR was comparable to that obtained in aortic rings from non-treated SHR incubated in the presence of indomethacin. In conclusion, increased relaxation in response to the nitric oxide donor SNP in aortic rings from irbesartan-treated SHR could be related to a lower ANG-II-dependent production of cyclooxygenase-dependent contracting factors in smooth muscle cells. Further experiments are needed to validate these observations, but our findings open a new line of investigation into the mechanisms involved in improving vascular function with antihypertensive treatment.

Key Words: Irbesartan, Angiotensin II, Indomethacin

---

**P-96**

OMAPATRILAT-MEDIATED VASORELAXATION THROUGH NITRIC OXIDE PATHWAY IN AORTIC RINGS ISOLATED FROM HYPERTENSIVE RATS

Chiming Wei, Ruxin Lin, Li Chen, Yafeng Dong, Joseph S. McLaughlin.

OMapatrilat, a recently developed vasopeptidase inhibitor (VPI), which displays equipotent, highly selective competitive activity against neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE). Previous studies demonstrated that ACE inhibitors or NEP inhibitors increased nitric oxide (NO) production in coronary microvessels. To date, there is no information regarding the effect of VPI on vasorelaxation and NO production. We hypothesized that long-term treatment with omapatrilat will increase generation of nitric oxide and enhance NO-mediated vasorelaxation in hypertensive rat. To test this hypothesis, we performed the current study in spontaneously hypertensive rats (SHR, n=5). Vehicle (NaHCO3, 0.5 ml/day) or omapatrilat (100 nM/kg/day) were administered to SHR once daily by gavage for six months. Mean blood pressure (MBP) was determined by tail cuff method. Omapatrilat significantly decreased MBP from day 1 through end of study. At 6 months, SHR was sacrificed and aortic ring was isolated. The effect of omapatrilat on vasorelaxation in aortic ring was determined by organ chamber study. Omapatrilat caused concentration-dependent vasorelaxation (10-10 to 10-6 M) in aortic rings isolated from SHR which received long-term treatment of omapatrilat. The maximal relaxation to omapatrilat (10-6 M) was 68±1.8%. In contrast, L-NAME (10-4 M) completely blocked omapatrilat-mediated vasorelaxation in aortic rings. This study first time demonstrated that omapatrilat has potent vasorelaxation effect through NO-dependent pathway in hypertensive rats. Therefore, nitric oxide may play an important role on omapatrilat-mediated antihypertensive actions.

Key Words: Vasorelaxation, Nitric oxide, Omapatrilat

---

**P-97**

CHRONIC TREATMENT WITH IRBESARTAN AMELIORATES ENDOTHELIUM-INDEPENDENT RELAXATIONS IN SPONTANEOUSLY HYPERTENSIVE RATS


In a previous work, we demonstrated that vascular smooth muscle modifies endothelium-independent relaxations in spontaneously hypertensive rats (SHR) by releasing cyclooxygenase-derived contracting factors. On the other hand, angiotensin II (ANG-II) is involved in the vascular function with antihypertensive treatment. Furthermore, the modification of the SNP-induced relaxations appears to be related to a lower production of cyclooxygenase-dependent contracting factors. Firstly, incubation of aortic rings from irbesartan-treated SHR with indomethacin did not significantly alter the relaxations in response to cumulative doses of SNP. Secondly, the dose-response curve to SNP for aortic rings from irbesartan-treated SHR was comparable to that obtained in aortic rings from non-treated SHR incubated in the presence of indomethacin. In conclusion, increased relaxation in response to the nitric oxide donor SNP in aortic rings from irbesartan-treated SHR could be related to a lower ANG-II-dependent production of cyclooxygenase-dependent contracting factors in smooth muscle cells. Further experiments are needed to validate these observations, but our findings open a new line of investigation into the mechanisms involved in improving vascular function with antihypertensive treatment.

Key Words: Irbesartan, Angiotensin II, Indomethacin

---

**P-98**

ENDOTHELIN AND NITRIC OXIDE BALANCE: COMPARISON BETWEEN ESSENTIAL HYPERTENSIVE AND CHRONIC RENAL FAILURE PATIENTS

Daniela Angelini, Manuela Parrini, Antonio Carlini, I talio Fiorini, Alessandro Antonelli, Nephrology, Hospital of Lucca, Lucca, Italy.

Endothelin 1, ABPM

We evaluated plasma levels of nitric oxide (NO), cyclic guanosin monophosphate (cGMP), endothelin-1 (ET-1) and cyclic adenosin monophosphate (cAMP) in 27 patients (17M and 10F) affected by essential hypertension (EH), aged between 25-65 years, with glomerular filtratio rate (GFR) 101.5 ml/min ± 22.8 and in 18 patients (10M and 8F) affected by chronic renal failure (CRF), aged between 29-56 years, with GFR 23.1 ml/min ± 8.3 and their relationship with the mean arterial pressure (MAP) obtained from ambulatory blood pressure monitoring (ABPM: automatic readings at 20 min. intervals). MAP was also evaluated during the day-time and the night-time (dMAP, nMAP). We excluded from the study patients with cardiovascular complications and patients in previous antihypertensive treatment. Thirty-three healthy subjects (21M and 12F) aged between 28-62 years with GFR 103.6 ml/min ± 21.2 were the control group. The results are expressed as mean ± S.D.: