Differential effects of selective cyclooxygenase-2 inhibitors on endothelial function in salt-induced hypertension

Hermann, M

Abstract: In view of the ongoing controversy of potential differences in cardiovascular safety of selective COX-2 inhibitors (coxibs), we compared the effects of two different coxibs and a traditional NSAID on endothelial dysfunction, a well established surrogate of cardiovascular disease, in salt-induced hypertension. Salt-sensitive (DS) and salt-resistant (DR) Dahl rats were treated with a high-sodium diet (4% NaCl) for 56 days. From days 35 to 56, diclofenac (6 mg/kg/d; DS-diclofenac), rofecoxib (2 mg/kg/d; DS-rofecoxib), celecoxib (25 mg/kg/d; DS-celecoxib) or placebo (DS-placebo) were added to the chow. Vascular reactivity of isolated aortic rings was assessed by isometric tension recording. Blood pressure increased with high sodium diet in the DS-groups which was more pronounced after diclofenac and rofecoxib treatment ($p<0.005$ vs DS-placebo), but slightly blunted by celecoxib ($p<0.001$ vs DS-placebo). Sodium diet markedly reduced NO-mediated endothelium-dependent relaxations to acetylcholine (ACh, 10−10−10−5 mol/L) in untreated hypertensive rats ($p<0.0001$ vs DR-placebo). Relaxation to ACh improved after celecoxib ($p<0.005$ vs DS-placebo and DS-rofecoxib), but remained unchanged after rofecoxib and diclofenac treatment. Vasoconstriction after NOS inhibition with N -Nitro-L-Arginine Methyl Ester (10-4 mol/L) was blunted in DS rats ($p<0.05$ vs DR-placebo), normalized by celecoxib, but not affected by rofecoxib or diclofenac. Protein expression of eNOS was decreased in DS rats with a trend for increased eNOS levels in the DS-celecoxib group (97.8±25.6 vs 54.8±2.8 %, $p=0.088$ vs DS-placebo). Indicators of oxidative stress, 8-isoprostane levels, were elevated in untreated DS rats on 4% NaCl (6.55±0.58 vs 3.65±1.05 ng/ml, $p<0.05$) and normalized by celecoxib only (4.29±0.58 ng/ml), while SOD protein expression was decreased in DS rats and not affected by any treatment. Plasma levels of prostaglandines did not change during high sodium diet or any treatment. These data show that celecoxib, but not rofecoxib or diclofenac, improves endothelial dysfunction and reduces oxidative stress, thus pointing to differential effects of coxibs in salt-sensitive hypertension. Am J Hypertens (2004) 17, 243A-243A; doi: 10.1016/j.amjhyper.2004.03.650

DOI: https://doi.org/10.1016/j.amjhyper.2004.03.650

Conclusions: These results suggest that superoxides generated by angiotensin II-stimulated granulocyte mediate the adhesion of granulocytes to endothelial cells.

Key Words: Phagocytes, Superoxide, Adhesion

P-576

DIFFERENTIAL EFFECTS OF SELECTIVE CYCLOOXYGENASE-2 INHIBITORS ON ENDOTHELIAL FUNCTION IN SALT-INDUCED HYPERTENSION

Matthias Hermann, Giovanni Camici, Felix C Tanner, Joachim Thiery, Steffen Gay, Thomas F Luscher, Frank Ruschitzka. Cardiovascular Center, Cardiology, University Hospital, Zurich, Switzerland; Institute of Clinical Chemistry, Universitiy of Leipzig, Leipzig, Germany; Center for Experimental Rheumatology, University Hospital, Zurich, Switzerland.

Background: In view of the ongoing controversy of potential differences in cardiovascular safety of selective COX-2 inhibitors (coxibs), we compared the effects of two different coxibs and a traditional NSAID on endothelial dysfunction, a well established surrogate of cardiovascular disease, in salt-induced hypertension.

Methods and Results: Salt-sensitive (DS) and salt-resistant (DR) Dahl rats were treated with a high-sodium diet (4% NaCl) for 56 days. From days 35 to 56, diclofenac (6 mg/kg/d; DS-diclofenac), rofecoxib (2 mg/kg/d; DS-rofecoxib), celecoxib (25 mg/kg/d; DS-celecoxib) or placebo (DS-placebo) were added to the chow. Vascular reactivity of isolated aortic rings was assessed by isometric tension recording. Blood pressure increased with high sodium diet in the DS-groups which was more pronounced after diclofenac and rofecoxib treatment ($p<0.005$ vs DS-placebo), but slightly blunted by celecoxib ($p<0.001$ vs DS-placebo). Sodium diet markedly reduced NO-mediated endothelium-dependent relaxations to acetylcholine (ACh, $10^{-10}-10^{-5}$ mol/L) in untreated hypertensive rats ($p<0.0001$ vs DR-placebo). Relaxation to ACh improved after celecoxib ($p<0.005$ vs DS-placebo and DS-rofecoxib), but remained unchanged after rofecoxib and diclofenac treatment. Vasoconstriction after NOS inhibition with N^{ω}-Nitro-L-Arginine Methyl Ester (10^{-4} mol/L) was blunted in DS rats ($p<0.05$ vs DR-placebo), normalized by celecoxib, but not affected by rofecoxib or diclofenac. Protein expression of eNOS was decreased in DS rats with a trend for increased eNOS levels in the DS-celecoxib group (97.8 ± 25.6 vs 54.8 ± 2.8 %, $p=0.088$ vs DS-placebo). Indicators of oxidative stress, 8-isoprostane levels, were elevated in untreated DS rats on 4% NaCl (6.55 ± 0.58 vs 3.65 ± 1.05 ng/ml, $p<0.05$) and normalized by celecoxib only (4.29 ± 0.58 ng/ml), while SOD protein expression was decreased in DS rats and not affected by any treatment. Plasma levels of prostaglandines did not change during high sodium diet or any treatment.

Conclusion: These data show that celecoxib, but not rofecoxib or diclofenac, improves endothelial dysfunction and reduces oxidative stress, thus pointing to differential effects of coxibs in salt-sensitive hypertension.

Key Words: Inflammation, Nitric Oxide, Oxidative Stress

P-577

GENDER-RELATED DIFFERENCE IN THE ASSOCIATION BETWEEN C-REACTIVE PROTEIN AND AMBULATORY BLOOD PRESSURE IN JAPANESE HYPERTENSIVE PATIENTS

Joji Ishikawa, Kario Kazuomi, Masato Morinari, Satoshi Hoshide, Kazuo Eguchi, Shizukiyo Ishikawa, Kazuyuki Shimada. Cardiology, Jichi Medical School, Yakushiji 3311-1, Minamikawachimachi, Tochigi, Japan; Community and Family Medicine, Jichi Medical School, Yakushiji 3311-1, Minamikawachimachi, Tochigi, Japan.

Purpose: C-reactive protein (CRP), a marker of inflammation, is associated with cardiovascular events and may be related to the pathogenesis of hypertension. We evaluated the relationship between CRP and ambulatory blood pressure (BP) in Japanese.

Method: We studied 514 Japanese hypertensives (clinic BP≥140/90mmHg; 191 men and 323 women) aged≥50 years (mean age: 72 years) in Jichi Medical School and related facilities.

Results: CRP showed a skewed deviation and a median CRP level was 0.20 mg/dl (75 percentile: 0.40mg/dl, 90 percentile: 0.74mg/dl). In the total subjects, CRP level was positively correlated with age ($r=0.177$, $P<0.001$) and clinic heart rate ($r=0.093$, $P=0.034$). In men, CRP level was positively correlated with clinic heart rate ($r=0.251$, $P=0.003$), 24-hr systolic BP (24-hr SBP, $r=0.157$, $P=0.030$) bur not with 24-hr diastolic BP (24-hr DBP, $r=0.087$, $P=0.231$). In women, CRP level was correlated with neither 24-hr SBP ($r=0.007$, $p=0.901$) nor 24-hr DBP ($r=-0.027$, $p=0.625$). Sustained hypertensives men (24-hr SBP≥135mmHg) had higher CRP level than white-coat hypertensives (24-hr SBP<135mmHg) (0.455 vs. 0.286 mg/dl, $P=0.039$). In multiple regression analyses, 24-hr SBP in men was positively correlated with CRP ($r=0.165$, $P=0.024$) independently of confounding factors.

Conclusion: Gender-related difference was found in the association between CRP and ambulatory BP in hypertensive Japanese. Low-grade inflammation is involved in increased ambulatory BP in Japanese hypertensive men, but not in women.

Key Words: C-Reactive Protein, Ambulatory Blood Pressure Monitoring, Gender Difference

P-578

INTERLEUKIN 15 IS ASSOCIATED WITH CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH ESSENTIAL HYPERTENSION

Masaharu Kaibe, Mitsuru Ohishi, Norihisa Ito, Ming Yuan, Takeshi Takagi, Minako Terai, Hiromi Rakugi, Toshio Ogihara. Department of Geriatric Medicine, Osaka University Graduate School of Medicine, Suita City, Osaka, Japan.

A statement of the purpose of the study: IL-15 is a cytokine produced from inflammatory cells, of which expression is immunohistochemically found in inflammatory cells adjacent to vulnerable atherosclerotic plaques. Systemic inflammatory substances are related to cardiovascular events, however, influence of systemic IL-15 levels on cardiovascular diseases is still unclear. Therefore, we designed clinical investigations to clarify the relationship between serum IL-15 levels and hypertensive complications.

A statement of the methods used: Three hundreds and ninety-nine patients with essential hypertension (222 males and 177 females, mean age: 61 ± 0.7 y.o.) were enrolled. We excluded patients with inflammatory or infectious diseases, or patients who were administered steroids and aspirins. We divided objectives into the following 3 groups according to modified WHO classification in 1993; patients with no complication (NC, n=236), with mild organ damages (MOD, n=112), with severe organ damages (SOD, n=51). MOD was determined as left ventricular hypertrophy by electrocardiogram and echocardiography, narrowing of retinal artery, proteinuria (<20mg/dl), renal dysfunction (1.2mg/dL<serum creatinine<2.0mg/dL), and/or carotid plaque. SOD was determined as coronary artery diseases (CAD), congestive heart failure, stroke, and/or peripheral artery disease (PAD). Serum IL-15 levels were measured by ELISA kit (BioSource International, Inc).

A summary of the results presented in sufficient detail to support the conclusions: Serum IL-15 levels in patients with SOD (96.1 ± 20.7pg/ml) were significantly higher than that with MOD (46.5 ± 7.6pg/ml; $p<0.01$) and that with NC (56.3 ± 6.8pg/ml; $p<0.05$). Serum IL-15 levels in patients with CAD (n=17) were significantly higher than that without CAD ($p<0.0001$). Serum IL-15 levels with PAD (n=29) were significantly higher than that of patients without PAD ($p<0.05$). Moreover, serum IL-15 levels in patients with lacuna infarction (n=73) were significantly higher than that without lacuna infarction ($p<0.005$).