ISO1-1 Role of Cry genes in Development and Progression of Atherosclerosis

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Cardiovascular disease is a major and increasing cause of death worldwide. Epidemiologic studies suggest an important role of circadian rhythms in the cyclic variation of cardiac vulnerability and susceptibility to adverse cardiovascular events. Cry genes are indispensable genes for circadian clock in mammals. Genetic disruption of Cry genes resulted in loss of behavioral and physiological rhythmicity. However, there are no experimental data linking circadian rhythm with cardiovascular remodeling post injury. In this study we investigate the role of Cry genes in the development and progression of atherosclerosis using Cry deficient mice (KO) subjected to carotid ligation. KO and WT mice were kept in light-dark cycle and constant darkness during experiment. At basal condition KO mice (n=8) had significantly higher blood pressure as compared to WT mice (n=6) (135.87±0.227 vs 110.833±0.401, p< 0.0001). Four weeks after ligation, higher systolic blood pressure was observed in KO mice kept in both light-dark cycle as well as constant darkness than that of WT mice. KO and WT mice showed neointimal formation in the ligated arteries. However the extent of neointimal formation showed by Intimal Medial Thickness Ratio was significantly higher in the KO mice kept in constant darkness as compared to the WT mice (3.897±0.781 vs 1.678±0.345, p=0.015). Total vessel area was similar in all groups suggesting no positive remodeling in this model.Our study demonstrates that disruption of Cry genes are associated with progression of neointimal formation in mouse flow cessation model. This further suggest the protective role of Cry genes in atherosclerosis.

ISO1-2 Manipulation of Intracellular Redox State using siRNA-mediated Knockdown of Thiol-metabolizing Pathways leads to Differential Modulation of Endothelial Nitric Oxide Pathways

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Cellular redox state is stringently maintained by thiol-based antioxidants to prevent the adverse consequences of generating excessive quantities of reactive oxygen species (ROS). The relative contributions of the thioredoxin (Trx) and glutathione/glutaredoxin systems to intracellular redox balance are incompletely understood, as are the consequences of altered thiol metabolism on eNOS and NO-dependent pathways in the endothelium. We designed duplex siRNA constructs to specifically "knock down" the expression of key thiol metabolizing enzymes in cultured aortic endothelial cells. siRNA-mediated knockdown of glutathione reductase (GR), cytosolic Trx reductase (TrxR1), or mitochondrial Trx reductase (TrxR2) markedly suppressed VEGF-induced eNOS enzyme activity by 97 ± 2%, 85 ± 2%, or 101 ± 1% (n = 4, p < 0.01), and also decreased NO production by 83 ± 2%, 92 ± 2%, or 96 ± 2% (n = 4, p < 0.01), respectively. TrxR2 knockdown led to a marked increase in ROS production (89 ± 5% increase; n = 4, p < 0.01); this effect was entirely unaffected by siRNA-mediated knockdown of eNOS. In contrast, knockdown of GR or TrxR1 slightly but significantly increased ROS production by 38 ± 4% or 32 ± 5% (n = 4, p < 0.01); these effects were abrogated by simultaneous eNOS knockdown. TrxR1, but not GR or TrxR2, knockdown inhibited VEGF-induced phosphorylation of eNOS at the activating site serine 1179 and Akt. These studies show that the differential regulation of thiol-metabolizing proteins has pleiotropic effects on endothelial function, leading to critical changes in oxidative and nitrosative stress pathways.

ISO1-3 Imidapril Prevents Contrast Media-Induced Nephropathy via Bradykinin Pathway

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Background: Iodinated contrast media (CM) is used for diagnostic procedures; CM-induced nephropathy (CIN) affects the morbidity and mortality of patients. Although the renin angiotensin system (RAS) mediates the development of CIN, little is known about the evidence obtained from experimental models. Methods: We performed 5/6 subtotal nephrectomy (NTX) and administered CM (iopamidol) intravenously into the mice 4 weeks after NTX. We administered imidapril, an angiotensin converting enzyme inhibitor (ACEI), into the first group, TA606 which is an angiotensin II receptor blocker (ARB) into the second group, or imidapril plus a bradykinin B2 receptor antagonist (Hoe-140) into the third group daily. Results: Serum creatinine levels on day 28 were significantly elevated in the NTX group (n=8, 0.26±0.01mg/dl, p<0.05) compared to those in the non-NTX group (n=8, 0.13±0.01mg/dl). A day after CM injection, creatinine levels were additionally elevated in the non-treated NTX group (n=8, 0.48±0.07mg/dl, p<0.05) compared to that of no CM injected NTX group. While imidapril treatment significantly suppressed creatinine levels (n=6, 0.34±0.04mg/dl, p<0.05) in the CM injected NTX mice, imidapril plus Hoe-140 treatment negated the suppression of creatinine levels (n=5, 0.43±0.07mg/dl, p=NS). TA606 treatment did not decrease creatinine levels (n=4, 0.47±0.06mg/dl, p=NS) in the CM injected NTX mice. These results indicate that ACEI treatment improves the renal function via bradykinin activation. Conclusion: ACEI treatment is useful for the prevention of CM-induced nephropathy because bradykinin pathway is critical to regulate CIN development.

ISO1-4 The Dual Regulatory Effects of Losartan in Angiotensin II-receptor Mediated Signal Transduction in Vascular Smooth Muscle Cells

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Objectives: Rgs2 (regulator of G-protein signaling-2)-deficient mice exhibit persistent vascular constriction and severe hypertension, and genetic variations of RGS2 occur in hypertensive patients. Moreover we have known that RGS2 mRNA expression was up regulated by angiotensin II (Ang II) stimulation in vascular smooth muscle cells (VSMC). This study was to disclose the role of losartan in Ang II receptor mediated signal transduction through RGS2. Methods: VSMC were isolated from thoracic aortas of male Wistar rats and cells between passages 4 to 6 were used at semi-confluence growth state. VSMC were incubated in losartan (-500nM) or olmesartan (-200nM) for different periods of time and cells were collected. RGS2 mRNA expression was performed by real-time quantitative reverse transcription-polymerase chain reaction (QRT-PCR).Results: RGS2 mRNA levels peaked at 2 hours of Ang II (100nM) stimulation compared with control in VSMC. Olmesartan, type-1 receptor specific antagonist, completely inhibited this increase of RGS2. On the other hand, losartan (-500nM) partially blocked the elevation of RGS2 and in the absence of Ang II, losartan dose-dependently increased the RGS2mRNA expression. This effect of losartan was not influenced by the type-2 receptor antagonist (PD 123,319), and the agonist (CGP-42112A). Moreover, pretreatment of olmesartan abolished the increase in RGS2mRNA by losartan treatment. Conclusion: These results suggest that losartan uniquely blocks Ang II receptor mediated signal transduction through Ang II receptor antagonistic action and a decrease of post-receptor signal transduction through the up-regulation of RGS2mRNA expression.

ISO1-5 β1(Arg389Gly, Ser49Gly)- and β2(Arg16Gly)-adrenoceptor Polymorphisms are Related to Left Ventricular Hypertrophy Using ECG in Middle-aged, Normotensive subjects

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Objective: Left ventricular hypertrophy (LVH) is more common in hypertensive and obese people. β2-adrenoceptor (ADRB2) polymorphisms are closely linked to hypertension and obesity. We examined the relationships between ADRB1 and ADRB2 polymorphisms and LVH. Methods: In 215 normotensive, Japanese men, ADRB1 polymorphisms (Arg389Gly, Ser49Gly), ADRB2 polymorphisms (Arg16Gly, Gln27Glu), BMI, BP, heart rates (HR), total body fat-mass, waist-to-hip ratio (W/H), plasma norepinephrine (NE) and ECG were measured. LVH was determined by ECG. Results: Twenty-four subjects (11.2%) showed LVH on ECG. Subjects with LVH had higher NE and HR compared to those without LVH (both P<.05). Distributions of Gly389 and Gly49 alleles of ADRB1 polymorphisms were 39.5% and 27.9%. >50% of subjects with LVH carried Gly389 and Gly49, especially homozygous. Subjects with Gly389 or Gly49 had higher frequencies of LVH, higher NE and HR (all P<.05), whereas BMI, fat-mass, W/H and BP were similar. Distributions of Gly16 and Glu27 alleles of ADRB2 polymorphisms were 74.4% and 11.2%. Twenty-two subjects (91.7%) with LVH carried Gly16, especially Gly16 homozygous, and 58.3% of subjects with LVH carried Glu27. Subjects with Gly16 had higher frequencies of LVH, and greater BMI, fat mass, W/H, BP, HR and NE compared to those without Gly16 allele (all P<.05). Conclusions: Subjects carrying Gly389 and Gly49 alleles of ADRB1 polymorphisms and Gly16 allele of ADRB2 polymorphisms had higher frequency of LVH accompanying high plasma NE. ADRB1 polymorphisms might relate to LVH through heightened sympathetic nerve activity, but ADRB2 polymorphisms might relate to LVH through obesity, hypertension and heightened sympathetic nerve activity.

ISO2-6 An Endogenous Estrogen Metabolite, 2-Methoxyestradiol, and Membrane Microviscosity in Normotensive and Hypertensive Postmenopausal Women : An Electron Spin Resonance Investigation

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Recent evidence indicates that 2-methoxyestradiol (2ME2), a non-feminizing metabolite of estradiol, may have a protective effect against cardiovascular diseases. The present study was undertaken to investigate the effects of 2ME2 on membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes in normotensive and hypertensive postmenopausal women by using an electron spin resonance (ESR) method. It was shown that 2ME2 significantly decreased the order parameter (S) for 5-nitroxide stearate (5-NS) and the peak height ratio for 16-NS in the ESR spectra of erythrocyte membranes in postmenopausal women (S: control 0.724±0.003, n=10, 2ME2 $1X10^{-8}$mol/L 0.710±0.005, n=10, P<0.05, 2ME2 $1X10^{-7}$ mol/L 0.703±0.003, n=10, P<0.005, 2ME2 $1X10^{-6}$ mol/L 0.694±0.003, n=10, P<0.001). The finding indicated that 2ME2 increased membrane fluidity of erythrocytes. The membrane action of 2ME2 was potentiated by the nitric oxide (NO)-donors (L-arginine and S-nitroso-N-acetylpenicillamine) and 8-bromo-cGMP, and, in contrast, was counteracted by the NO-synthase inhibitors (N^G-nitro-L-arginine-methylester and asymmetric-dimethylarginine). In hypertensive postmenopausal women, the order parameter (S) and the peak height ratio in erythrocytes were significantly higher than in normotensive postmenopausal women (S: HT 0.727±0.002, n=22, NT 0.710±0.002, n=16, P<0.01). The finding indicated that membrane fluidity of erythrocytes was decreased in hypertensive postmenopausal women. Furthermore, 2ME2 ameliorated membrane fluidity of erythrocytes to a greater extent in hypertensive postmenopausal women than in normotensive postmenopausal women. These results showed that 2ME2 increased membrane fluidity and improved membrane microviscosity of erythrocytes by the NO-dependent mechanism, suggesting that 2ME2 might have beneficial effects on blood rheological behavior and improvement of microcirculation in hypertensive postmenopausal women.

ISO2-7 Reproducibility of ambulatory blood pressure in hypertensive patients with treated and untreated conditions

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Objective: We tested the reproducibility of ambulatory BP (ABP), BP variability, and the BP reduction in hypertensive patients. Methods: Forty-two hypertensives were enrolled, and ABP monitoring (ABPM) was performed 4 times in each patient: each twice in untreated and treated conditions. Morning BP was defined as the average of 2 hours after waking, and morning BP surge (MBPS) was defined as the difference of morning BP and: lowest nighttime BP including trough, 2-hour BP before waking up, and 2-hour BP after sleep. The BP variability was evaluated by standard deviation (SD) and coefficient of variation (CV). The reproducibility was compared using the intraclass correlation coefficient (ICC) for agreements. Results: The ICC-agreements of awake, sleep, and 24-hour systolic BP (SBP) were 0.69, 0.75, and 0.77, and those of standard deviation (SD)/coefficient of variation (CV) were 0.36/0.38, 0.44/0.46, and 0.32/0.34. The ICC-agreement of morning SBP were 0.52, but that of MBPS were 0.18, -0.04, and 0.25, for sleep-trough, waking, and 2-h after sleep SBP surge, respectively. When the MBPS was redefined based on actigraphy-defined waking time, the ICC-agreements of MBPS improved to 0.21, 0.16, and 0.25. The 24-hour BP-lowering effect correlated well between the two sets of ABPM before and after treatments (ICC-agreement 0.56). Conclusions: The reproducibility of ABP levels and BP variability were fairly good, and that of MBPS was fair when defined by actigraphy. The good reproducibility of BP reductions means that each single ABPM, before and after treatment, is acceptable for the assessment of drug efficacy.

ISO2-8 Inappropriateness of Left Ventricular Hypertrophy influences BNP but not Influences Diastolic Filling in Untreated Hypertensive Patients

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[Background] Echocardiographically-determined inappropriateness of left ventricular mass is an independent risk factor of cardiovascular events. Although left ventricular hypertrophy is associated with an increase in plasma brain natriuretic peptide level and a deteriorated left ventricular diastolic filling, it is unknown whether the inappropriateness of left ventricular mass affects these or not. Any hypertensive medication should affect LV geometry and function; therefore, This was studied in untreated hypertensive patients. [Methods and Results] We studied 77 untreated hypertensive patients (49 males, 28 females, ages 59±12 years). Plasma brain natriuretic peptide level was measured in addition to routine echo Doppler indexes of left ventricular geometry and function. The appropriateness of LVM to cardiac workload was evaluated by the ratio of observed left ventricular mass to the value predicted for individual sex, stroke work, and height2.7 (oLVM/pLVM). Multivariate analysis showed plasma brain natriuretic peptide level increased with LVMI but decreased when oLVM/pLVM increased. E/E' correlated not only with oLVM/pLVM but also with left ventricular mass index (r=0.30, p<0.05, r=0.37, p<0.05). However, when multiple stepwise regression analysis was performed only left ventricular mass index was selected as a significant correlate of E/E' ratio, indicating that inappropriateness of left ventricular mass does not affect E/E' ratio in hypertensive patients. [Conclusions] Brain natriuretic peptide levels are influenced not only by the degree of left ventricular hypertrophy but also by the inappropriateness of hypertrophy in untreated hypertensive patients. Diastolic filling is mostly affected by the degree of left ventricular hypertrophy, and not by the appropriateness of hypertrophy.

ISO2-9 Benidipine has Similar Effects to Losartan at Modulating Arterial Stiffness and Central Blood Pressure in Mild to Moderate Essential Hypertension.

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Objectives: This study aimed to compare the effect of benidipine (Calcium Channel Blocker) and losartan (Angiotensin Receptor Blocker) on central blood pressure (BP) and arterial stiffness in mild to moderate essential hypertensives.Methods and Results: This 24 weeks, multi-center, open label, randomized, active drug comparative, parallel group study was designed as a noninferior study. Eligible patients (n=200) were randomly assigned to receive benidipine (n=101) or losartan (n=99). Radial artery applanation tonomery and noninvasive pulse wave analysis device were used to derive central BP, pulse wave velocity (PWV) and augmentation index (AIx). Additionally we measured the serum levels of hs-CRP, adiponectine, hs-RAGE, osteoprotegrein and procollagen type I C-peptide (PIP) and calculated HOMA index. No significant differences were found in the mean changes in central BP between two groups [-16.66 (systolic BP)/-10.70 (diastolic BP) mmHg in the benidipine group and -18.44/-11.79 mmHg in the losartan group; P=NS]. The mean changes in central aortic PWV and AIx were -(0.06&plusmn1.26) m/sec and -(5.46&plusmn14.42)% for the benidipine group and -(0.02&plusmn1.35) m/sec and -(4.22&plusmn14.62)% for losartan group (respectively; p=NS). There were no significant differences between two groups in the serum levels of metabolic and inflammatory biomarkers. Conclusion: These results suggested that benidipine was non-inferior to losartan to reduce central BP, brachial BP, and central aortic PWV, and also benidipine might have similar metabolic and inflammatory modulatory effects to losartan in mild to moderate essential hypertensives.

ISO2-10 Effects of valsartan and amlodipine on cardio-renal protection in Japanese hypertensive patients: The Valsartan Amlodipine Randomized Trial (VART)

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Purpose: We assessed whether treatment with an angiotensin II type 1 receptor blocker (valsartan) or a calcium channel blocker (amlodipine) lowers cardiovascular events in essential hypertensive patients in Japan.

Methods: The Valsartan Amlodipine Randomized Trial (VART) was a prospective, randomized, open-label, 2-arm parallel comparative study. The initial dose was 80 mg/day valsartan or 5 mg/day amlodipine. These doses were increased to 160mg and 10mg, respectively, and α-blockers or β-blockers or diuretics were added if blood pressure was over 135/85. After the registration, patients were followed-up for cardiovascular events for 3 years and 123I-metaidodobenzylguanidine imaging (heart/mediastinum ratio:H/M ratio) for 1 year.

Results: 1,020 patients were enrolled and assigned to the two groups. At 36 months, both agents evenly lowered blood pressure to the target level (valsartan: from158 ± 20/94 ±13 mmHg to134 ± 14/80 ± 13 mmHg; amlodipine: from158 ±19 mmHg /93 ± 13 mmHg to135 ±13/80 ±10 mmHg). At 24 months, we observed significant changes in the urinary albumin/ creatinine ratio (UACR) in the valsartan group but not in the amlodipine group. In the valsartan group, H/M ratio at 1year was significantly increased.

Conclusions: There were no significant differences in blood pressure level and the main outcome of cardiovascular events between the valsartan and amlodipine groups. However, we found significant improvements of UACR and cardiac sympathetic activity in the valsartan group. These results suggest that the effects of valsartan on heart and kidney were more beneficial than those of amlodipine in Japanese hypertensive patients.

ISO3-11 Effects of azelnidipine on systemic hemodynamics and diastolic function in patients with hypertension. The CALBLOC study.

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Diastolic heart failure forms an important subset with increasing incidence and prevalence in patients with hypertension, and risk of all cause mortality and cardiovascular events is significantly increased. Although the beneficial role of RAAS blockade has been well established, controversies continue to surround the efficacy of calcium antagonists for diastolic heart failure. Unlike other dihydropyridine calcium blockers, azelnidipine has the unique feature that has a gradual onset and has a long-lasting hypotensive effect, with little increase in heart rate. The aim of the CALBLOC study is to investigate the effecs of azelnidipine on blood pressure and diastolic failure in patients with hypertension. 243 hypertensive patients with diastolic heart failure were entried in this trial. Hemodynamic parameters, laboratory data (including BNP, hs-CRP), and echocardiographic parameters of diastolic function (E/A, DcT, e' and e/e')were assessed at baseline and 6 months after administration of azelnidipine. 78 patients were swiched from amlodipine to azelnidipine. Blood pressure (160±17mmHg to 138±11mmHg) and heart rate (87±14bpm to 78±9mmHg) were significantly decreased. Although BNP and other biomarkers were not significantly changed, diastolic function (e' (6.0±1.4 to 6.5±1.2) and e/e' (6.0±1.4 to 6.5±1.2)) were significantly improved. In the patients that were swiched from amlodipine, blood pressure and heart rate were siginificantly decreased, and there was tendency to improve diastolic function. These data suggested that azelnidipine might have cardioprotective effect on hypertensive patients with diastolic heart failure along blood pressure and heart rate lowering effect.

ISO3-12 Relationship between baseline renal dysfunction and atherosclerotic events in patients with type 2 diabetes: Sub-analyses from the JPAD trial

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Diabetes is a powerful risk factor for cardiovascular events. Accumulating evidence indicates that intensive control of glucose control and blood pressure decreases cardiovascular events. However, effect of anti-platelet therapy with aspirin for primary prevention of cardiovascular events had not been elucidated. Recently we have accomplished the Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) trial last year, which is multicenter, prospective, randomized, open-label blinded-endpoint trial, and enrolled 2539 type2 diabetic patients without a history of atherosclerotic disease. Low-dose aspirin did not reduce primary end points of atherosclerotic events which includes fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke including transient ischemic attack, and peripheral arterial disease. However, low-dose aspirin significantly ($p<0.0037$) reduced fatal stroke and acute myocardial infarction, and it also significantly ($p<0.047$) reduced the atherosclerotic events in subgroup of patients aged 65 or older. Now we are undertaking some sub-analyses from the JPAD study. In the JPAD study, overall mean age was 65 10 years, 55% of patients were men. The median duration of diabetes was 7.0 years. The prevalence of hypertensive and overt diabetic nephropathy was 58% and 18%, respectively. The mean serum creatinine level was 0.8±0.3mg/dl. Prevalence of patients with estimated glomerular filtration rate (eGFR)> 90ml/min/1.73m2, 60<eGFR<90, 30<eGFR<60, eGFR<30 was 21%, 54%, 24%, and 20%, respectively. Effects of blood pressure and renal function on incidence of primary atherosclerotic events will be disclosed. Preliminary analysis confirmed that overt proteinuria is a strong risk for atherosclerotic events in the JPAD population.

ISO3-13 Docosahexaenoic Acid or Olive Oil Supplementation on Blood Pressure and Serum Lipids in Scottish Men with Mild Hypertension and Hypercholesterolaemia

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The objective of this study was to investigate the effects of daily supplementation with docosahexaenoic acid (DHA) on blood pressure (BP), heart rate (HR) and serum lipids in fifty-six middle-aged Scottish men with mild hypertension (systolic BP (SBP) >=130mmHg) and mild hypercholesterolemia (total cholesterol (TC) >=220mg/dl). Methods : Subjects were assigned a five-week double blind placebo-controlled dietary supplementation with either 2g of DHA powder or active placebo (containing 2g olive oil powder) daily. Supplements were administered incorporated in bread rolls (2 bread rolls supplied one-day dose). Health survey was carried out twice before and after the intervention and 24-hour urine samples and fasting blood were analyzed according to WHO-CARDIAC study protocol. Result : The percent composition of DHA in plasma phospholipids among DHA supplemented group (DHA group) increased significantly from 1±0.4% at the beginning of the study to 3.5±0.9%($p<0.001$) at the end of five-week intervention. In the DHA group, significant changes were observed in SBP (5.8% decrease, $p<0.001$), diastolic BP (DBP) (3.7% decrease, $p<0.01$) and HR (7.5% decrease, $p<0.05$). The increment of DHA was related significantly with BP reduction. There was no significant decrease in SBP and DBP levels or changes in HR in the placebo group before and after intervention period. High density lipoprotein cholesterol (HDL-C) increased significantly and TC/HDL-C and non HDL-C/HDL-C ratios decreased significantly in both groups. Conclusion: DHA supplementation (2g/day) reduced BP and HR in mildly hypertensive, hyper-cholesterolemic Scottish men. (We acknowledge the great cooperates of Drs. NJELEKELA, M., ARMITAGE, L., BIRT N., and BIRT, C.)

ISO3-14 Undetected hypertension: Related factors and long term follow up in a representative Japanese cohort. NIPPON DATA80

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Background: It is important to audit the prevalence of undetected hypertension at the community level to identify related factors and long-term outcome to initiate avenues for improvement in population level hypertension control. Methods: We analyzed data from the NIPPON DATA80 consisting 8002 participants aged 30-65. As the baseline was conducted in the 1980, thus hypertension was defined as SBP≥160 and/or DBP≥95 and/or being on antihypertensive medication (JNC-2). We used multivariate logistic regression to identify independent predictors of undetected hypertension both in relation to normotensive and detected hypertensive. The multivariate-adjusted hazard ratio (HR) of cardiovascular disease (CVD) mortality was estimated for undetected hypertension in reference to both normotensive as well as detected hypertensive by Cox proportional hazard model.Result: We estimated that 23.9% of the population had hypertension and 29.9% of them were undetected of their hypertension problem. Increasing age, being male, having history of heart disease, being obese and having drinking habit were independently associated with undetected hypertension in relation to normotensive. The multivariate adjusted HR for CVD for undetected hypertension was 2.42 (95%CI:1.76-3.31) in reference to normotensive. In the comparison between detected and undetected hypertension; being younger, being male, not having history of stroke, heart disease or diabetes, and having lower BMI were independently associated with undetected hypertension. Though statistically insignificant, undetected hypertensive had 26% more chance of CVD death than participants with detected hypertension.Conclusion: These results points towards the importance of detecting hypertension vigorously in the community level which will have positive impact on long-term cardiovascular outcome.

IP01-001 Paradoxical activation of the aldosterone synthesis during a high salt intake in Dahl salt-sensitive rat

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[Introduction] A high salt fed-Dahl salt-sensitive rats develop hypertension associated with cardiovascular injury. We examined the different response of the adrenal aldosterone biosynthesis to salt in Dahl salt-sensitive rat as compared to salt-resistant rats.[Methods and Results] Dahl salt-sensitive (S), salt-resistant (R) rats were fed a high-salt (8 % NaCl) or a normal-salt (1 % NaCl) diet from 5th to 11th weeks of age. The expression level of CYP11B2 (aldosterone synthase) was determined by immunohistochemistory and Q-PCR. Steroid metabolites in adrenal glands, plasma, and left ventricle were measured by the liquid chromatography- tandem mass spectrometry analysis. Previous studies have shown that plasma renin activity is lower in normal salt-fed S than in normal salt-fed R. Consistently, the adrenal CYP11B2 expression was lower in S than R. Accordingly, adrenal aldosterone levels, as well as plasma and cardiac aldosterone levels, were significantly lower in normal salt-fed S than normal salt-fed R. At the end of high salt intake, the adrenal CYP11B2 expression was equally suppressed in both R and S. The adrenal, plasma and myocardial aldosterone levels were markedly suppressed in R. In contrast, they were paradoxically elevated in S. As a consequence, adrenal, plasma, cardiac aldosterone were 19-, 68-, 51-fold higher in S than in R. The plasma and cardiac aldosterone in high salt fed-S became undetectable after bilateral adrenalectomy. [Conclusions]These results suggested that CYP11B2-independent aldosterone synthesis emerged in S under a high salt intake. This abnormality may play a pathogenic role for the development of cardiovascular disease.

IP01-002 Existence of multiple binding sites in (pro)renin receptor for prorenin

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Objective: The binding properties of renin and prorenin to (P)RR were investigated by kinetic study in BIAcore assay system and thus, to elucidate the possibility of multiple binding sites in the receptor for renin/prorenin.
Methods: The (P)RR (35 kDa) was expressed in a cell free in vitro system and purified by affinity chromatography using His Trap column. A polyclonal antibody was prepared against a region close to the transmembrane part of the receptor (E^{221}IGKRYGEDSEQFRD^{235}), purified and immobilized on the CM5 sensor chip. The receptor bound to the immobilized antibody showed binding of human renin, prorenin (0.1-2.0 nM) and the peptides such as A^{248}KKRLFDYVV^{257}, the hinge S^{149}QGVLKEDVF^{158} from renin and L^{1P}PTD^{4P}, L^{1P}PTDTTTF^{8P}, L^{1P}PTDTTTFKRIFLKR^{15P} and the decoy R^{10P}IFLKRMPSI^{19P} from prorenin.
Results: The dissociation constants (K_D) for the human renin, prorenin, decoy and hinge peptides bound to the (P)RR were 4.4, 1.2, 3.5 and 17 nM, respectively, whereas these values for L^{1P}PTD^{4P}, L^{1P}PTDTTTF^{8P}, L^{1P}PTDTTTFKRIFLKR^{15P}and A^{248}KKRLFDYVV^{257} were 3.2 x 10^4, 52, 7.6 and 4.1 x 10^4 nM, respectively. Among these, peptides containing I^{11P}FLKR^{15P} sequence and hinge showed more stable complex as reflected from their K_Ds. Both decoy and hinge peptides reduced the resonance signal for the binding of human prorenin and renin to (P)RR.
Conclusion: The decoy had higher binding affinity ($1/K_D$) than the hinge and is only conserved in prorenin whereas the hinge is present in renin and prorenin molecules. These indicate (P)RR has at least two binding sites. Thus, this study is the first evidence of multiple binding sites in (P)RR.

IP01-003 *In vitro* inhibition of the activity of mature renin and (pro)renin receptor-bound activated prorenin by aliskiren

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Objective: Aliskiren, a nonpeptidic orally active direct inhibitor of renin, has been approved as an antihypertensive agent. In this study, the effects of aliskiren on the activities of human (pro)renin receptor [h(P)RR] bound active renin and prorenin were tested to evaluate its inhibitory ability on the circulating and tissue specific renin angiotensin system.
Methods: Plasmid pCDNA3 harboring h(P)RR lacking transmembrane sequence was ligated with a vector, pIVEX. Thus, the receptor was expressed in a cell free in vitro system based on wheat germ lysate. Chinese hamster ovary cell lines were maintained for the preparation of human mature renin and prorenin. Different concentrations of aliskiren (0.025, 0.05, 0.1, 0.2, 0.5 nM) were used to determine the IC50 of aliskiren for renin against the substrate sheep angiotensinogen. The K_i of aliskiren for human mature renin as well as receptor-bound renin and activated prorenin were measured.
Results: Aliskiren, a potent renin inhibitor, has an IC50 of 0.72 nM. The K_i of aliskiren for human mature renin was estimated 0.18 nM using sheep angiotensinogen as the substrate, while the values of K_i of aliskiren for receptor-bound renin and activated prorenin were measured at 0.1 and 0.042 nM, respectively.
Conclusion: This study showed that aliskiren inhibited renin activity competitively by repressing not only the activity of free form of mature renin but also the activities of receptor-bound renin and activated prorenin. Thus, aliskiren could be a potent agent in controlling the adverse effects of both the circulating and tissue-specific renin angiotensin system.

IP01-004 Tetrahydrobiopterin (BH4) Redox Recycling is a Key Determinant of eNOS-modulated Endothelial Responses

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BH4 is a key redox-active cofactor for eNOS. BH4 oxidation is observed in vascular cells in the setting of oxidative stress associated with diabetes and hypertension. However, the relative roles of de novo BH4 synthesis and BH4 redox recycling in regulation of eNOS bioactivity remain incompletely defined. We used siRNA-mediated "knock down" of GTP cyclohydrolase-1 (GTPCH1), the rate-limiting enzyme in BH4 biosynthesis, and dihydrofolate reductase (DHFR), an enzyme recycling oxidized BH4 (7,8-dihydrobiopterin: BH2), and studied the effects on eNOS regulation and biopterin metabolism in cultured aortic endothelial cells. Knockdown of DHFR or GTPCH1 attenuated VEGF-induced eNOS activity and NO production by 90 ± 9% ($n = 8$, $p < 0.01$); these effects were recovered by BH4 supplementation. In contrast, BH2 supplementation abolished VEGF-induced NO production. DHFR but not GTPCH1 knockdown increased ROS production by 77 ± 12% ($n = 8$, $p < 0.01$); this effect was abolished either by simultaneous siRNA-mediated knockdown of eNOS, or by BH4 supplementation. In contrast, BH2 supplementation increased ROS production by 119 ± 6% ($n = 10$, $p < 0.01$); this effect was blocked by BH4 supplementation. DHFR but not GTPCH1 knockdown inhibited VEGF-induced eNOS dephosphorylation at the inhibitory site serine 116; these effects were recovered by BH4 supplementation. Our findings suggest that the depletion of BH4 is not sufficient to perturb NO signaling, but rather that concentration of intracellular BH2, as well as the relative concentrations of BH4 and BH2, together play a determining role in the redox regulation of eNOS-modulated endothelial responses.

IP01-005 RhoA/rho-kinase pathway facilitates rat aortic contraction through increases in binding affinities of endotherin-1 and noradrenaline to their receptors

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Endothelin-1 (ET-1) and noradrenaline (NA) induce potent contraction of vascular smooth muscle which is closely related to hypertension. Smooth muscle contraction is regulated by $[Ca^{2+}]_i$ and Ca^{2+} sensitivity of contractile elements. It is known that activation of the rhoA (a small GTP-binding protein)/rho-kinase pathway inactivates MLC phosphatase by phosphorylation of its myosin-binding subunit, resulting in increasing MLC phosphorylation leading to enhancement of muscle contraction at a given intracellular Ca^{2+} concentration.This study found new functions of the rhoA/rho-kinase pathway. In rat isolated aorta without endothelium, the ET-1 (100nM)- or NA (1μM)-induced contraction was incompletely inhibited by the endothelin$_A$ receptor antagonist BQ-123 (1μM) or the α1-adrenergic receptor antagonist prazosin (0.001μM), respectively. The contractions induced by these agonists were also incompletely inhibited by the rho-kinase inhibitor Y-27632 (1μM). However, combination of Y-27632 (1μM) with BQ-123 (1μM) or prazosin (0.001μM) was rapidly and completely inhibited the ET-1 (100nM)- or NA (1μM)-induced contraction, respectively. Combination of the L-type Ca^{2+} channel blocker verapamil (10μM) with Y-27632 (1μM) completely and synergistically inhibited the ET-1-induced contraction. For inhibition of the ET-1-induced contraction, combination of the MLCK inhibitor wortmannin (10μM) with BQ-123 (1μM) did not show any synergistic effects. These results suggest that activation of the rhoA/rho-kinase pathway increases binding affinities of ET-1 and NA to their receptors, the pathway is also involved in the uptake of Ca^{2+}, and it does not affect the activation of MLCK.

IP01-006 Left Ventricle Compensates for Acute Mild and Moderate increase of Pulmonary artery pressure by Increased Torsion

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Background - The right ventricle (RV) and left ventricle (LV) share the interventricular septum (IVS), which mechanically transmits interventricular pressure gradients. With increased pulmonary artery pressure (PAP), 1) the IVS straightens with consequent LV end-diastolic volume decreases, and 2) RV stroke volume decreases. However, whether the acute mild to moderate increase of PAP affect LV function is controversial. The aim of this study was to investigate changes of LV torsion magnitude response to decrease of LV end-diastolic volume and RV stroke volume during graded acute elevation in PAP. Methods - In 14 open-chest pigs (43±4 kg) with preserved pericardium, acute mild (>35 and <50 mmHg) and moderate (>50 and <60 mmHg) increase of PAP were induced by constriction of the pulmonary artery. Hemodynamic parameters and LV torsion were evaluated at each condition. Results - At baseline and during mild and moderate increase of PAP, the mean RV systolic pressure was 31.0±4.3, 41.1±2.7, and 52.7±3.4 mmHg, respectively. LV torsion magnitudes increased from baseline to mild and moderate increase of PAP (2.7±0.9, 3.4±0.7, 3.7±1.0 degree/cm, respectively, P=0.029). LV systolic torsion magnitude correlated with RV systolic pressure (r=0.428, P=0.009). In multiple regression analysis, LV systolic eccentricity index was independently related to an increase in LV torsion magnitude (r=0.548, P=0.001). Conclusion - Consequent IVS displacement towards the LV free wall associated with acutely increasing pulmonary artery pressure associated with an increase in LV torsion magnitude. Increase of LV torsion magnitude reflects an LV functional compensatory mechanism during acutely increasing PAP.

IP02-007 Epigenetic transcriptional repression of the human CYP11B2 gene

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PURPOSE: The Ad1/cAMP response element (CRE) and Ad5 have been shown to play a crucial role in the transcriptional regulation of CYP11B2. These cis-acting elements contain CpG dinucleotides, which are target sites for DNA methylation. Our objective was to elucidate effect of CpG methylation on human CYP11B2 expression.METHODS: Human adrenocortical H295R cell lines were cultured to analyze endogenous CYP11B2 expression, transcription factor complex formation, and promoter activity.RESULTS: We found that CpG dinucleotides of the Ad1/CRE and Ad5 were largely unmethylated in tissues from aldosterone-producing adenoma and adjacent adrenal gland, compared to leukocytes. Analysis of the CYP11B2 promoter fused to a reporter gene showed that CpG dinucleotide methylation within its promoter completely abolished CYP11B2 promoter activities, which were stimulated by angiotensin II, KCL and cAMP. Promoter constructs with partial CpG methylation responded weakly to these stimuli, suggesting that the CYP11B2 promote activity was dependent upon CpG methylation. NoShift transcriptional factor assays demonstrated that CpG methylation significantly decreased CREB binding to the Ad1/CRE by 90% and NURR1 binding to the Ad5 by half in nuclear extracts from H295R cells. Likewise, CpG methylation significantly increased methyl CpG binding protein 2 (MeCP2) binding to the Ad1/CRE in vitro. Chromatin-immunoprecipitation-quantitative PCR showed that MeCP2 interacted strongly with methylated Ad1/CRE and weakly with methylated Ad5 in vivo. CONCLUSIONS: Taken together, CpG methylation repressed human CYP11B2 promoter activity by decreasing binding of activators as CREB and NURR1 and increasing binding of a repressor(s) as MeCP2. This is the first demonstration of methylation-dependent regulation of CYP11B2.

IP02-008 ChREBP promotes ERK phoshorylation through the crosstalk between cyclic mechanical strain and high glucose in rat mesangial cells

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MAP kinase activation caused by hypertension and hyperglycemia is known to play a pivotal role in the development of glomerular dysfunction by inducing mesangial proliferation. To elucidate the mechanism of strain and glucose stimulation leading to ERK phosphorylation, we focused on a recently-identified transcription factor, carbohydrate-responsive element-binding protein (ChREBP). This study was carried out to determine if ChREBP is involved in the signal transduction from glucose and mechanical stimulation leading to ERK phosphorylation in mesangial cells. When cyclic mechanical strain was applied to rat mesangial cells, ChREBP transcripts increased in a time- and elongation strength-dependent manner. From the results of chromatin immunoprecipitation-guided ligation and selection assay, a MAP kinase-related gene, MP1 emerged as a possible target gene. Electoro-Mobility Shift Assay using the MP1 promoter and crude nuclear extract from glucose-stimulated rat mesangial cells showed an increase in the signal shift. The mRNA expression of MP1 was increased in a high-glucose condition compared to low-glucose. When mesangial cells were subjected to mechanical stretch and then cultured in low or high glucose medium for 24 hours, the ratio of p-ERK to total ERK were elevated the most in the stretch plus high glucose group. In summary, stretch-induced ChREBP transcription and ChREBP nuclear translocation in response to glucose, leading to MP1 expression and ERK activation, may be one of the mechanisms linking mechanical stress and high glucose. ChREBP and MP1 may play a significant role in the pathophysiology of renal damage caused by hypertension and hyperglycemia.

IP02-009 Anti-Oxidant or potassium diet could reverse salt-sensitive hypertension via WNK4 regulation

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Recent reports showed that WNK kinases play important roles in the regulation of sodium transport in the distal nephron, therefore regulate the blood pressure. In this experiment we showed that WNK4 expression enhanced during anti-oxidant or potassium treatment, which could reverse the sodium-sensitive hypertension in Dalh S rats. We use 6 weeks old Dahl salt-resistance and salt-sensitive rats, treated with High salt diet, or high salt+potassium diet for 2 or 4 weeks. Then measured direct blood pressure and evaluate WNK4 expression by real time RT PCR. Sodium channel expression was checked by western blot. After that we use anti-oxidant medicine Tempol treated to DS rats with HS diet for 2 weeks, direct blood pressure was measured by catheter, WNK4 expression was evaluated by quantitative RT-PCR. After 2 weeks, young age rats showed no differences in blood pressure. However WNK4 expression in DR rats rose about 30 percent after HS diet which DS rats did not; During HS+potassium diet, WNK4 expression raised in both groups. After 4 weeks, DS rats with HS diet showed obvious high blood pressure, however all DR rats and DS with HS+potassium diet rats showed normal. Also, DS rats treated with HS diet and Tempol for 2 weeks increased WNK4 expression, then prevent the sodium-sensitive hypertension. In this study we found that WNK4 regulation might be one of the reasons why DS rats could easily cause salt-sensitive hypertension. Also, this sensitivity could be reduced by anti-oxidant or potassium treatment.

IP02-010 Oxidative stress in glucocorticoid-induced MR activation

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We have reported the role of ROS related mineralocorticoid receptor (MR) activation in Ang II induced cardiac dysfunction. In order to further investigate the underlining mechanism how MR was activated and caused cardiac dysfunction, we studied MR activation in cardiac muscle cells. Under high oxidative states (by high glucose, peroxide loading, or mechanical stretch), MR is translocated into nucleus by not only aldosterone but also by corticosterone. Also, when MR activity is monitored by MR-dependent gene expression, MR is activated by corticosterone only under high oxidative state. Combined with former reports, MR in the heart where 11b HSD2 is absent can be activated by corticosterone and that MR activation causes abnormal calcium handling in the heart results in diastolic dysfunction.

IP02-011 Urinary Neutrophil Gelatinase-Associated Lipocalin in Diabetic Nephropathy and Hypertension and Its Response to Angiotensin Receptor Blocker

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[Introduction] Neutrophil gelatinase-associated lipocalin (Ngal) is a secretory protein with various biological activities including protection of the kidney from injury and induction of kidney differentiation (K. Mori et al. Kidney Int 2007, J Clin Invest 2005, Semin Cell Dev Biol 2003). Urinary Ngal level is a promising biomarker for early prediction of acute kidney injury (Lancet 2005, Ann Intern Med 2008). In the present study, we investigated urinary excretion and metabolism of Ngal in diabetic nephropathy (DN) and hypertension, and the response to angiotensin receptor blocker (ARB). [Methods and Results] Urinary Ngal levels were highly elevated in two models of DN: A-ZIP/F-1 lipoatrophic diabetes (exhibiting insulin resistance and nephrotic range proteinuria) and STZ diabetic mice (with insulin deficiency and microalbuminuria). In STZ mice, reabsorption of labeled-Ngal was reduced by half and its urinary excretion was highly increased. Treatment of STZ mice with candesartan largely suppressed elevation of urinary Ngal concentrations. In hypertensive patients with diabetes or obesity, administration of ARB (candesartan, olmesartan or telmisartan) caused reduction of blood pressure, and urinary Ngal and albumin excretion after 3 months. In these patients, urinary Ngal and albumin levels were not significantly correlated, suggesting that these two are independent clinical parameters. [Conclusion] Urinary excretion of Ngal was increased mainly by tubular reabsorption impairment in DN. Furthermore, urinary Ngal level in DN and hypertension was significantly decreased by ARB treatment, suggesting that it may serve as a new biomarker for diabetes- or hypertension-related nephropathy.

IP03-012 Utility and feasibility of a new programmable home blood pressure monitoring device for the assessment of nighttime blood pressure.

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BACKGROUND:Recent evidence indicates that both ambulatory blood pressure monitoring and home blood pressure monitoring are more useful than the measurement of office blood pressure for evaluating cardiovascular risks in subjects with hypertension. The major advantage of ambulatory blood pressure monitoring over home blood pressure monitoring is the ability to measure nighttime blood pressure and ambulatory blood pressure during the day. A newly developed, programmable home blood pressure monitoring device (HEM-5041, OMRON, Kyoto, Japan) can record blood pressure upto 350 times and measure nighttime blood pressure automatically upto twenty times. METHODS:To validate the utility, feasibility and safety of this device, we measured blood pressure by home blood pressure monitoring using HEM-5041 and by ambulatory blood pressure monitoring and compared the values in healthy volunteers. RESULTS:As compared with ambulatory blood pressure monitoring, daytime blood pressures, coefficients of variation for systolic blood pressure, diastolic blood pressure, and pulse rate, and the % nighttime fall in these variables were significantly lower with home blood pressure monitoring. However, nighttime blood pressures did not significantly differ between home blood pressure monitoring and ambulatory blood pressure monitoring. The results of a questionnaire survey indicated that the subjects were more comfortable when blood pressure measured by home blood pressure monitoring than by ambulatory blood pressure monitoring, whereas the quality of sleep was similar. CONCLUSIONS:Our results suggest that HEM-5041 is useful for evaluating nighttime blood pressures as well as nighttime blood pressure falls, without causing clinically significant discomfort.

IP03-013 Hypertension Risk and Atherosclerosis parameter CAVI in Japan and Central EU

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Hypertension, obesity and metabolic syndrome as the cardiovascular risk is important problem not only in Japan, but also in European countries. In European Union (EU), the importance of obesity was increased more and more in every countries, when we consider the preventive medicine. Among E.U., worst group of obesity is Marta and Russia, and Czech, Lithuania, Belgium were in the second group. Thus, we evaluated the atherosclerosis in Czech, which exist in the center of E.U., as the typical example of the E.U. residence. For the evaluation of the atherosclerosis, the relationship between the Cardio Ankle Vascular Index (CAVI) and aging of the Japanese and Czech people was compared in this study. 157 Healthy Subjects 36 DM patients, and 58 hypertensive subjects were evaluated in the Brno, Czech, and compared with Japanese data. As the results, CAVI is increasing intentionally according to aging in also as for the Czech people, and Japanese people. Increase Rate of CAVI according to the Aging was larger, compared with Japanese data. Therefore, it was shown that the Czech people have a quick advance of the arteriosclerosis according to aging compared with Japanese people. In the analysis of an arteriosclerosis risk, it has become clear that existence of diabetes etc. has contributed to increase of CAVI greatly etc. Unfortunately, criteria of obesity and metabolic syndrome are different that comparison is a little bit difficult. Development of atherosclerosis research may be desired for the people's health in Japan and E.U. health.

IP03-014 The difference of therapeutic impact according to antihypertensive medicine to central aortic pressure.

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Objectives: After the publication of ASCOT-CAFE study, central aortic pressure(cAP) has been focused as a new risk factor or new therapeutic marker of cardiovascular disease. So we examined the effect of antihypertensive medicine to cAP in Japanese hypertensives. Methods: We enrolled hypertensive outpatients(n=135) who received Ca antagonist an /or rennin-angiotensin system(RAS) inhibitor. Objectives were divided into 3 groups according to medicine: Ca antagonist alone group(n=30), RAS inhibitor alone group(n=48) and Combination therapy group(n=57). Results: Systemic systolic and diastolic blood pressures were equal in all groups. And cAP of Ca alone and RAS inhibitor alone was not different. But cAP of combination group was about 5mmHg lower than other 2 groups and brain natriuretic peptide was about 35 pg/ml reduced only in combination group. Moreover, 42% patients in combination group cAP were lower than systemic BP. On the other hand about 80% patient cAP were not good control in rest 2 groups. In this study cardiac index and was reduced by using RAS inhibitor. Total peripheral resistance was reduced by Ca antagonist. And RAS inhibitor may be able to reduce oxidant stress and inflammation. These effects may act synergically and reduce cAP in combination group. Conclusion: This study suggest that combination therapy of Ca antagonist and RAS inhibitor can reduce central aortic pressure in Japanese hypertensives. The elucidation of mechanism and best combination need furthermore investigation.

IP03-015 Constructing Prediction Models for the Risk of New-onset Hypertension from a Prospective Cohort

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We aimed to propose prediction models for new-onset hypertension using a community-based cohort of middle and elderly ethnic Chinese in Taiwan. Among 2506 individuals (50.8% women) who were not hypertensive at the baseline (1990-91), 1029 cases of new-onset hypertension developed during a median of 6.15 (interquartile range, 4.04-9.02) years of follow-up. The multivariate Weibull model was applied to construct two prediction models. In the clinical model, gender (2 points), age (8 points), body mass index (10 points), systolic blood pressure (19 points), and diastolic blood pressure (7 points) were assigned. The biochemical measures, including white blood count (3 points), fasting glucose (1 point), uric acid (3 points), additional to clinical variables, were constructed. The areas under the receiver operative characteristic curves were 0.732 (95% confidence interval [CI], 0.712 - 0.752) for the points-based clinical model and 0.735 (95% CI, 0.715 - 0.755) for the points-based biochemical model. The points-based clinical model had a similar net reclassification improvement as the coefficient-based clinical model (P=0.30), and had a higher improvement than the points-based biochemical model (P=0.015). These prediction models outperformed available models, including John Hopkins and Framingham models, to predict hypertension risk. In conclusion, the points-based clinical model could be considered as the first step to identify high-risk populations for hypertension.

IP03-016 Ambulatory Blood Pressure monitoring by a dual home BP (HBP)/ABP Monitoring Device -Microlife WatchBP O3-

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Background: We evaluated whether ambulatory blood pressure (ABP) using a dual-mode oscillometric device that performs both home BP (HBPM) and ABP monitoring (ABPM) is related to ABP measured by a conventional ABPM device in addition to HBP.
Methods: Hypertensive patients performed HBPM (Microlife WatchBP Home), and 24-hr ABPM using a dual HBPM/ABPM device (Microlife WatchBP O3) and a conventional ABPM device (SpaceLabs 90207) within 4 weeks.
Results: There was no significant difference between awake systolic BP (SBP) by the conventional ABPM (138±16 mmHg) vs. awake SBP by the dual HBPM/ABPM device (139±16 mmHg, P=0.39) or vs. home BP (SBP 140±17 mmHg, P=0.23) (N=52). There was no significant difference between awake diastolic BP (DBP) by the conventional ABPM (81±13 mmHg) vs. home DBP (82±11 mmHg, P=0.29), but was vs. awake DBP by the dual HBPM/ABPM device(83±11 mmHg, P=0.019). In a multiple linear regression analysis, awake SBP by the dual HBPM/ABPM device (B=0.40, P=0.002) was a significant predictor of awake SBP by conventional ABPM, independently of home SBP (B=0.45, P=0.001) and office SBP (P=0.25). In the parallel analysis of DBP, awake DBP by the dual HBPM/ABPM device (B=0.55, P=0.001) was also a significant predictor of awake DBP by conventional ABPM, independently of home DBP (B=0.49, P=0.002) and office DBP (P=0.87).
Conclusion: These preliminary data indicate that home BP and ambulatory BP measured by the dual HBPM/ABPM device are each independently predictive, controlling for the other and office BP, of awake BP measured using a conventional ABPM device.

IP03-017 Automatic Office Blood Pressure Measurement without doctors or nurses present is Predictive of Ambulatory Blood Pressure-Microlife WatchBP Office-

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Backgrounds: We evaluated whether automatic office blood pressure (OBP), in which the readings were taken without doctors or nurses, is more strongly related to ambulatory blood pressure (ABP) than is OBP measured by mercury sphygmomanometer.
Methods: Hypertensive patients had their OBP measured using an automatic upper arm oscillometric monitor (Auto; Microlife WatchBP Office) and by mercury sphygmomanometer (Sphy), in 3 clinic visits. Between the visits, ABP monitoring (SpaceLabs 90207) and home BP monitoring (Microlife WatchBP Home) were also performed.
Results: Both Auto OSBP and Sphy OSBP were significantly correlated with 24-hr SBP (Auto OSBP, r=0.69; Sphy OSBP, r=0.68) and awake SBP (Auto OSBP, r=0.67; Sphy OSBP, r=0.64) (all P<0.001). The same was true for diastolic BP. In multiple linear regression analysis including Auto OSBP and Sphy OSBP together, Auto OSBP was more strongly related with awake SBP (B=0.54, P=0.021) and 24-hr SBP (B=0.51, P=0.024) than was Sphy OSBP (both P>0.05). Even when home SBP was included in the model, Auto OSBP was a significant predictor of awake SBP (B=0.36, P=0.046) and 24-hr SBP (B=0.33, P=0.0497). In parallel analyses for DBP, Auto ODBP was also more strongly related to awake DBP and 24-hr DBP than was Sphy ODBP.
Conclusion: These preliminary data indicate that office BP measured without doctors or nurses present is independently related to awake ambulatory BP, controlling for office BP measured by mercury sphygmomanometer; the opposite is not true.

IP04-018 Irbesartan, through VEGF, regulates cardiac and glomerular angiogenesis of obese and type 2 diabetic db/db mice

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Objective:We investigated the molecular mechanism of protective effects of irbesartan, an AT1 receptor blocker, against renal and cardiac complications in obese and type 2 diabetic db/db mice. Methods and Results:db/db mice were orally given irbesartan (20 mg/kg/day) or vehicle for 4 weeks. Compared with vehicle group, irbesartan significantly ameliorated the excretion of urinary albumin, glomerular inflammation (macrophage infiltration) and sclerosis, and also significantly attenuated cardiac inflammation and fibrosis. These beneficial effects of irbesartan on cardiorenal complications in type 2 diabetes were associated with the amelioration of cardiorenal superoxide, and this attenuation of oxidative stress was attributed to the restoration of Cu/Zn SOD by irbesartan. In db/db mice, CD31(+) capillary density and vascular endothelial growth factor (VEGF) were increased in glomeruli, while decreased in the heart. Irbesartan significantly reduced CD31(+) capillary density in glomeruli in db/db mice and suppressed renal mRNA and protein expression of VEGF. On the other hand, irbesartan significantly increased cardiac CD31(+) capillary density, being associated with the enhanced cardiac mRNA and protein expression of VEGF.Conclusions: Our work demonstrates that irbesartan, probably through VEGF, enhances angiogenesis in the heart and inversely reduces angiogenesis in glomeruli of obese and type 2 diabetic mice, which may contribute to the protective effects of irbesartan against diabetic cardiorenal complications.

IP04-019 Effects of Methylene chloride and Ethyl acetate Fractions Isolated from Rubus coreanum on Catecholamine Secretion in the Adrenal Medulla

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The purpose of the present study was to examine the effects of (ethyl acetate [EtOAc] and methylene chloride [CH2Cl2]) fractions isolated from Rubus coreanum on release of catecholamines (CA) in the rat adrenal medulla and to compare those effects between them. EtOAc (20~180 microG/mL) or CH2Cl2 (20~180 microG/mL) fraction, perfused into an adrenal vein for 90 min, dose- and time-dependently inhibited the CA secretory responses evoked by ACh, high K+, DMPP and McN-A-343. Also, in the presence of EtOAc or CH2Cl2 fractions, the secretory responses of CA evoked by veratridine, Bay-K-8644, and cyclopiazonic acid were reduced, respectively. In the simultaneous presence of EtOAc or CH2Cl2 fraction plus L-NAME, the CA secretion evoked by the above secretagogues were considerably recovered to the extent of the corresponding control compared with the inhibitory effect of EtOAc or CH2Cl2 fraction alone. In the presence of EtOAc or CH2Cl2 fraction, level of NO released from rat adrenal medulla was greatly increased. Collectively, these results demonstrate that EtOAc or CH2Cl2 fraction dose-dependently inhibits the CA secretory responses evoked by stimulation of cholinergic receptors as well as by direct membrane-depolarization. It seems that EtOAc or CH2Cl2 fraction-induced inhibition is exerted by inhibiting both Na+- and Ca2+-channels on the adrenomedullary cell membrane as well as by suppression of Ca2+ release from cytoplasmic calcium store at least through increased NO production due to activation of NOsynthase. Based on these results, it is thought that EtOAc or CH2Cl2 fraction possesses the active components helpful to alleviate hypertension and angina pectoris.

IP04-020 Losartan Causes Dual Effects on Catecholamine Release in the Perfused Adrenal Medulla

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The aim of this study therefore was to determine whether losartan could influence the CA release from the isolated perfused model of the rat adrenal medulla. Losartan (5~50 microM) perfused into an adrenal vein for 90 min produced dose- and time-dependently inhibited the CA secretory responses evoked by ACh (5.32 mM), high K+ (56 mM), DMPP (100 microM) and McN-A-343 (100 microM). Losartan failed to affect basal CA output. Furthermore, in adrenal glands loaded with losartan (15 microM), the CA secretory responses evoked by Bay-K-8644 (10 microM), cyclopiazonic acid (10 microM), and veratridine (100 microM), were markedly inhibited. However, at a high concentration (150~300 microM), losartan as well as olmesartan (150~300 microM) rather enhanced the CA secretion evoked by Ach. Collectively, these experimental results suggest that losartan at low concentrations inhibits the CA secretion evoked by cholinergic stimulation as well as by membrane depolarization from the rat adrenal medulla, but at high concentration it rather inhibits Ach-evoked CA secretion. It seems that losartan has dual action acting as both agonist and antagonist at nicotinic receptors of the isolated perfused rat adrenal medulla, which might be dependent on the concentration. It is also thought that this inhibitory effect of losartan may be mediated by blocking the influx of both Na+ and Ca2+ into the rat adrenomedullary chromaffin cells as well as by inhibiting the Ca2+ release from the cytoplasmic calcium store, which is thought to be relevant to AT1 receptor blockade, in addition to its enhancement effect on the CA release.

IP04-021 Correlations between different measures of clinic, home and ambulatory BP in hypertensive patients

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Objectives: We performed this study to clarify the agreements among different measures of clinic, home and ambulatory BP. Methods: We enrolled 56 hypertensive patients (mean age: 60±14 years; 54%: female). The study consisted of three clinic visits, self-monitoring of home BP between visits, and ambulatory BP (ABP) monitoring at the second visit. Patients were given a home BP monitor (HEM-5001, Omron, Japan) programmed to automatically take 3 consecutive readings at fixed intervals. They were asked to measure BP in the morning and evening for an 8-week period. The associations between clinic BP (mercury sphygmomanometer, HEM-5001, and HEM-907), home BP (the average of morning and evening, 2nd and 3rd BP readings), and average awake ABP were compared using the absolute values and intraclass correlation coefficients (ICC) for agreement. Results: The averages of office sphygmomanometer, office HEM5001, office HEM907, awake ABP, and home BP were 129/77 mmHg, 131/76 mmHg, 127/71 mmHg, 131/79 mmHg, and 133/77 mmHg, respectively. The office BP by two automated monitors was strongly correlated with that of mercury sphygmomanometer (ICC-agreements, both>0.95), especially HEM5001 SBP/DBP readings. Home SBP was fairly correlated with awake ABP (ICC-agreement, 0.73), but mercury DBP was more closely correlated with awake DBP than was home DBP. Conclusions: Clinic BP measured with automated monitors could be used as an alternative for the evaluation of BP in the office. With somewhat less precision, home BP could be used as an alternative to awake ABP.

IP04-022 Hypertension is a risk factor for depression in young-old female residents in Japan

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AIM: Depression is a common status in the elderly. However, the association of hypertension is not clarified, since both relatively lower and higher blood pressures were reported in subjects with dementia. The aim of present study is to elucidate association of hypertension to depression in the elderly. SUVJECTS AND METHODS: Subjects studied were 840 young-old (65-74 years old, 361 males and 479 females), and 550 old-old (≥75 years old, 197 males and 353 females) residents of Uchinada Town. Depression was evaluated by the short version of the Geriatric Depression Scale (≥2 in GDS-5). All the cross-sectional data of health examination in 2006 with possible association to depression by chi-square analysis or Mann-Whitney U test ($p<0.20$) were enrolled as confounding factors for multiple logistic regression analysis. RESULTS: Morbidity rates of depression in males and females were 12% and 16% in the young-olds, and 21% and 31% in the old-olds, respectively. Present hypertension (>140/90 mmHg, including both untreated treated subjects) was a significantly ($p=0.004$) and independently associating factor for depression in the young-old female group, but not in other three groups. CONCLUSION: Enough treatment of hypertension may be a key factor for prevention of depression in young-old females.

IP04-023 SNPs in 9p21 locus associated with CAD confirmed by angiography in Japanese

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Background: Genome wide association studies have consistently identified several SNPs on chromosome 9p21 as genetic risk factors of heart disease. Considering that the significant correlation between 9p21 loci and coronary artery diseases (CAD) does not point to any obvious physiological pathway yet, it is important to establish the association with precise clinical phenotypes.
Methods: Here, we analyzed the association of two SNPs, rs1333049 and 2891168 with angiographically diagnosed coronary artery stenosis. We genotyped 668 individuals (231 subjects with angiographic CAD and 437 controls with no history of CAD).
Results: The association with CAD was significant for both SNPs, the strongest association was detected with rs1333049 after adjustment by age (P value=0.006) showing an odds ratio per C allele of 1.398 (95% CI from 1.114 to 1.753). Recent evidence suggests that the locus is mainly associated with early onset of CAD rather than progression of disease. To assess this association in our sample, we evaluated the relationship between the severity of diseases (number of stenotic lesion: 1, 2, 3) and these SNPs. There was no significant association with these SNPs in the present study.
Conclusion: Here, we confirmed the association in the locus 9p21, identifying rs1333049 as strongest associated SNP with CAD confirmed by angiography in Japanese. Further investigations aimed to clarify its mechanism are necessary.

KJS-1 Hypertension and Cerebral Small-Vessel Disease: A New Radiologic Marker?

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Stroke is generally classified into ischemic and hemorrhagic stroke, and because of similarity of pathogenesis to coronary artery disease, large-vessel atherosclerosis appears to be considered as main cause of stroke. However, small-vessel disease arouses lacunar infarctions and intracerebral hemorrhage, which are amounted to over 40% of stroke incidence. Underlying vascular pathologic findings of small-vessel disease are lipohyalinosis, microatheroma, fibrinoid necrosis, microaneurysm, etc., which are mainly caused by chronic hypertension. These vascular lesions are responsible for ischemic (lacunar infarction and leukoaraiosis), or hemorrhagic damage (microbleeds and macrobleeds). The lesions were hardly identified in living human, but recent great advance of brain imaging including MRI enables us to identify the patients having small-vessel disease or the risk. Representatively, leukoaraiosis are easily seen on fluid-attenuated inversion recovery image (FLAIR) MRI as high intensity lesions in the periventricular area or the centrum semiovale. Microbleeds are visualized as minute signal loss lesions on T2*-weighted gradient-echo (GRE) MRI, which incorporates the dephasing of spins due to local magnetic filed inhomogeneities. Leukoaraiosis are associated with incident ischemic stroke, depression, behavioral dysfunction and dementia. Recently, we firstly found that leukoaraiosis are associated with increased risk of mortality after intracerebral hemorrhage in a nation-wide cohort study. Microbleeds are closely associated with past , and future occurrence of symptomatic intracerebral hemorrhage. In addition, we found that microbleeds increase the risk of symptomatic intracerebral hemorrhage in warfarin-users. These radiological findings should be used as new radiological findings to indicate patients with high risk of small-vessel disease.

KJS-2 Hypertension and Stroke: Clinical Aspects in Japan

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There is marked difference in the demographics of cardiovascular disease between Asian countries and Western countries. In Asian countries, stroke occurs more frequently than coronary artery disease. Blood pressure (BP) is linearly associated with stroke risk, and hypertension is the most powerful risk factor of stroke. Stroke risk is increased even in those with prehypertension (BP = 130-139/85-89 mmHg), which is determined by the modest increase in body mass index, and in normotensive subjects with left ventricular hypertrophy in a Japanese community-dwelling population. There is the growing evidence that out of clinic BP such as self-measured BP at home and ambulatory BP are more closely associated with stroke risk than clinic BP. In addition to the higher 24-hr BP level, the disrupted diurnal BP variation such as the riser pattern with higher nocturnal BP than awake BP is associated with cardiovascular risk, particularly in short sleepers. Exaggerated morning surge in BP is also associated with stroke risk in the hypertensive patients. The antihypertensive treatment targeting morning BP should be stressed to achieve the perfect 24-hr BP control including sleep and morning periods and more effective prevention for cardiovascular disease in the stroke-prone Asian countries.

KJS-3 Oxidative stress and its marker, as new and possible biomarkers in various cardiovascular diseases.

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Background and Objectives: Oxidative stress is closely related with the development or progression of aging process, malignancy, inflammatory disease, atherosclerosis and hypertension. Recently, investigations for the relation between oxidative stress and cardiovascular disease area are in the way. But, the precise examinations of oxidative stress effects in hypertensive, ischemic heart disease and heart failure model are very limited.
Methods: We examined dynamic and timely fashioned changes of the Thioredoxin (TRx) and Peroxiredoxin (PRx) system in rat cardiomyocyte (rCMC), rat vascular smooth muscle cell (rVSMC), HUVEC in 0.1 mM hydrogen peroxide stimulation for 2 hours, in heart and aortic tissue after the transaortic constriction (TAC) hypertensive/ventricular hypertrophy model and in doxorubicin (DOX) stimulated rCMC for 24 hours and human. And we checked serum TRx level changes in human ischemic heart disease and maintenance renal replacement therapy.
Results: Under the hydrogen peroxide stimulation, apoptotic portion was increased in 3 cell lines significantly, PRx-6, PRx-2, PRx-1,5 isoforms were increased in rCMC, rVSMC, HUVEC, respectively. In the TAC model, TRx/TRxnip ratio and m-RNA level of PRx-1,2,3,4,5 was increased to day 3 (acute hypertensive stress period) and the decreased thereafter (relative adapted period) the TAC. After the untying of TAC, TRx, TRxnip was reversed rapidly and mRNA-level of PRx-1,2,3,4,5 was increased immediately. In the DOX stimulated rCMC, increased non-specific oxidation (with OxiBlot), decreased PRx-2, SOD and unchanged TRx/TRxnip ratio was observed. In the early stage of human AMI, serum TRx level was significantly related with initial WBC count, peak CPK/CK-MB level and its increment, therefore serum TRx reflects myocardial damaged area in AMI.
Conclusion: The dynamic changes of Trx, PRx in cellular level and various cardiovascular disease models were observed. Initial serum TRx level in the early stage of human AMI showed close relationship with extent of damaged myocardium and its severity. Oxidative stress markers may have a value as the new functional biomarker of cardiovascular disease and its prognosis. The meticulous studies to enlighten the relationship between the changes or level of these markers and cardiovascular disease state should be investigated firstly.

KJS-4 Brain and Renin-Angiotensin System: Insight from Experimental Study

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The renin-angiotensin system (RAS) is involved in the pathological mechanisms of target organ damage as well as induction of hypertension. Recent large trials provided clinical evidences that blockade of RAS prevents cardio- and cerebrovascular diseases beyond antihypertensive effects. In Japan, angiotensin (Ang) II receptor blockers (ARBs) are widely used as one of the first choice drugs for treatment of hypertension recommended by Japanese guideline for management of hypertension (JSH 2009). In the brain, treatment with ARBs is effective to prevent a first or recurrent stroke beyond its blood pressure-lowering effects through clinical studies such as LIFE, MOSES and Jikei Heart Study and so on. Moreover, recent cohort studies indicate that onset of Alzheimer disease is less in the elderly individuals administrated with ARBs. However, detailed mechanism of protective effect of ARBs in the brain is clinically still enigma. Here we will overview brain RAS and demonstrate our animal studies in which we assessed an inhibitory effect of RAS by ARBs using ischemic brain injury and dementia models. Our previous studies indicates that ARBs prevent brain damage after stroke via reduction of oxidative stress, increase in cerebral blood flow and enhancement of neural differentiation via Ang II type-2 receptor. Moreover, treatment with ARBs in mice prevents cognitive impairment associated with diabetes mellitus, metabolic-prone diet and acute injection of amyloid β. Furthermore, our clinical investigation with cerebrospinal fluid suggests that brain RAS affects in some neurodegenerative diseases such as multiple sclerosis and amyotrophic lateral sclerosis. Therefore, regulation of RAS in the brain may protect brain and has been expected to become a new therapeutical approach for cranial nerve disorders. We will also discuss the future therapeutic approach for the elderly people suffering from the disabilities in this session.