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9. HMG-COA REDUCTASE INHIBITOR IMPROVES ENDOTHELIAL DYSFUNCTION IN SPONTANEOUS HYPERTENSIVE RATS VIA DOWN-REGULATION OF CAVEOLIN-1 AND ACTIVATION OF ENOS

Dong-Ju Choi, Eun-Ji Kim, Min-Jung Park, Jung-Won Suh, Hyuk-Jae Chang, Young-Seok Cho, Tae-Jin Yeon, In-Ho Chae, Kwang-Il Kim, Cheol-Ho Kim, Hyo-soo Kim, Buyng-Hee Oh, Young-Bae Park

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(hcPWV), heart-femoral PWV (hfPWV), femoral-ankle PWV (faPWV) using carotid and femoral sensor of form PWV/ABI. Therefore we examined prognostic impact of each regional PWV on stroke and cardiovascular disease (CVD) compared with baPWV in the cohort study of hypertensive patients.

Methods: This study included 387 patients with essential hypertension (male/female = 218/169, mean age 61.1 ± 11.8 , mean follow period 43 months) whose ba- and regional PWV could be measured from October, 2000 to December, 2004. We set up stroke ($n = 20$) and CVD ($n = 21$) as a primary end point by the questionnaire. We classified the participants by the highest quartile of each PWV; high baPWV group, high hcPWV, high hfPWV and high faPWV; by the lowest quartile of ABI as low ABI group.

Results: There was a significant correlation between baPWV and regional PWV; faPWV ($r = 0.560$), hcPWV ($r = 0.253$) and hfPWV ($r = 0.506$). By Kaplan-Meier analysis, only high baPWV group showed the prognostic impact of stroke and CVD ($p = 0.0099$) but not high faPWV ($p = 0.6982$), high hcPWV ($p = 0.5740$), high hfPWV ($p = 0.0773$) and low ABI group ($p = 0.8008$). Only low ABI group showed the prognostic impact on mortality ($p = 0.0223$), high baPWV on stroke ($p = 0.0155$) and high hcPWV on CVD ($p = 0.0382$).

Conclusion: As a further, larger, multicenter cohort study is needed, our study indicated that higher level of baPWV might be a risk factor of stroke and CVD, but prognostic impact of regional PWV is not still unclear in hypertension.

6.

BRACHIAL-ANKLE PULSE WAVE VELOCITY AND CHRONIC KIDNEY DISEASE AS A PROGNOSTIC IMPACT IN HYPERTENSION

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Background: Many reports have shown that brachial-ankle pulse wave velocity (baPWV) has an effect on evaluation of atherosclerotic change and would be one of the prognostic factors for hypertension (HT). It has been reported that chronic kidney disease (CKD) would influence the prognosis of HT or diabetes mellitus. Therefore we examined how baPWV and CKD effects the incidence of cardiovascular disease (CVD) by the cohort study in hypertensive patients using the AT-form which we can measure PWV easily.

Methods: This study included 380 patients with essential HT (male/female 206/174, mean age 60.9 ± 12.1 , mean follow period 41 months) whose baPWV could be measured from October, 2000 to December, 2004. We set up stroke ($n = 19$) and CVD ($n = 18$) as a primary end point by the questionnaire. We estimated CKD as lower glomerular filtration rate (GFR) with MDRD formula and proteinuria. We produced quartile groups according to the baseline measurements of baPWV or the presence of CKD and assessed the prognostic impact on stroke and CVD.

Results: There was a significant negative correlation between baPWV and GFR ($P < 0.0001$, $r = 0.256$). The baPWV with CKD ($n = 287$; 1654 ± 331 cm/sec) was significantly higher than that without CKD ($n = 93$; 1771 ± 333 cm/sec). By Kaplan-Meier analysis, highest quartile of baPWV was the prognostic impact of stroke ($p = 0.0062$) but not CKD ($p = 0.3947$). The incidence of stroke and CVD did not correlated with baPWV ($p = 0.0912$) or CKD ($p = 0.1381$). When we classified into 4 groups; high PWV + CKD, high PWV + non CKD, low PWV + CKD and low PWV + non CKD, high PWV + CKD showed significantly higher prognostic impact of stroke and CVD.

Conclusion: Our study indicated that higher level of baPWV and the existence of CKD might be a risk factor of stroke and CVD in hypertension.

7.

THE VALUE OF PULSE WAVE VELOCITY AS AN INDEX FOR THE PREDICTION OF CORONARY ATHEROSCLEROSIS

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Background: Arterial stiffness has been known as an independent contributory factor for coronary artery disease (CAD). Pulse wave velocity (PWV) is widely accepted as a simple non-invasive measure of arterial stiffness. The aim of our study was to test whether abnormal PWV could identify patients with significant CAD

Methods: We enrolled 174 consecutive patients who were referred for evaluation of suspected CAD and underwent PWV measurement and cardiac CT for calcium scoring. Age-matched normative data was used to define

subgroups with normal or abnormal PWV. The severity of CAD was categorized based on the coronary artery calcium score (CACS) and the number of obstructive CAD was also defined in patients who underwent subsequent invasive coronary angiogram.

Results: Brachial-ankle PWV (baPWV) was correlated with $\ln(\text{CACS} + 1)$ and the number of obstructive CAD ($p < 0.05$). However, after adjustment for age, baPWV did no longer correlate with them. Furthermore, abnormal baPWV were neither sensitive nor specific index for detection of moderate to severe coronary calcification (CACS ≥ 700 , or ≥ 75 th percentile), and the presence of obstructive CAD (sensitivity: 0.61, 0.62 and 0.55; specificity: 0.56, 0.63 and 0.70, respectively).

Conclusion: Our findings suggest that PWV was associated with the severity of CAD, however, which may primarily attributed to common risk factors such as age. Furthermore, abnormal PWV failed to predict significant CAD. Therefore, PWV may be of limited value in identifying patients at increased risk of cardiovascular events.

8.

USEFULNESS OF BRACHIAL-ANKLE AND CAROTID-FEMORAL PULSE WAVE VELOCITY AS PREDICTIVE VALUES OF CARDIOVASCULAR EVENTS

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Background: The measurement of carotid-femoral pulse wave velocity (cfPWV) is useful to predict stroke and cardiovascular events in hypertensive patients as our previous cohort study Non-invasive Atherosclerotic evaluation in Hypertension (NOAH) study. As the cfPWV is useful, but not easy to measure, it couldn't be suitable for a practical use. Therefore we evaluated the usefulness of brachial-ankle PWV (baPWV) as a predicting factor of cardiovascular events, which was measured by widely-used equipment formPWV/ABI (Colin Co. Ltd.), compared with cfPWV.

Methods: We designed this study as a part of NOAH study. We selected 414 outpatients (male/female = 242/172, mean age = 61.2 ± 12.0 y.o.) from participants of NOAH study ($n = 813$ with essential hypertension), who were simultaneously undergone baPWV and cfPWV measured by AT-form, and their prognoses were followed by questionnaire or medical records. Mean follow-up period was 43.0 ± 17.2 months. We set stroke and/or cardiovascular disease (CVD) as primary endpoint, and stroke, CVD, coronary artery disease (CAD) and mortality as secondary endpoint. During this follow-up period, 36 primary endpoints, 18 brain attacks, 19 heart diseases, 15 CADs and 10 deaths were recorded.

Results: The baPWV were strongly correlated with cfPWV (regression analysis; $r = 0.580$). Patients were equally divided into 4 groups by either baPWV or cfPWV and evaluated the prognostic impact by Kaplan-Meier analysis (Log-rank test). For primary endpoint, baPWV and cfPWV showed significant distributions ($p = 0.0268$ and 0.0002 , respectively). The baPWV did not show significant distribution for CVD, CAD, and mortality, but only for stroke ($p = 0.0015$). On the other hand, cfPWV showed significant distribution for CVD, stroke ($p = 0.0094$ and 0.0338 , respectively), but neither for CAD nor mortality. By Cox proportional hazard model adjusted with confounders; age, sex, blood pressure, serum creatinine, diabetes and dyslipidemia, only cfPWV was adopted as predictive factor, but not baPWV.

Conclusion: Although a further large scale multicenter trial is necessary, measurement of cfPWV may be better to predict cardiovascular event, but baPWV also can be a useful screening marker and predictor of future cardiovascular event.

9.

HMG-COA REDUCTASE INHIBITOR IMPROVES ENDOTHELIAL DYSFUNCTION IN SPONTANEOUS HYPERTENSIVE RATS VIA DOWN-REGULATION OF CAVEOLIN-1 AND ACTIVATION OF ENOS

Dong-Ju Choi, Eun-Ji Kim, Min-Jung Park, Jung-Won Suh, Hyuk-Jae Chang, Young-Seok Cho, Tae-Jin Yoon, In-Ho Chae, Kwang-Il Kim, Cheol-Ho Kim, Hyo-soo Kim, Bueng-Hee Oh, Young-Bae Park.

Hypertension is associated with endothelial dysfunction and increased cardiovascular risk. Caveolin-1 regulates nitric oxide (NO) signaling by modulating endothelial nitric oxide synthase (eNOS). The purpose of this study was to examine whether HMG-CoA reductase inhibitor improves impaired endothelial function of the aorta in spontaneous hypertensive rat (SHR) and to determine the underlying mechanisms involved.

Eight-week-old male SHR were assigned to either a control group (CON, $n = 11$) or a rosuvastatin group (ROS, $n = 12$), rosuvastatin (10 mg/kg/day) administered for eight weeks. Abdominal aortic rings were prepared and responses to acetylcholine (10^{-9} – 10^{-4} M) were determined in vitro. To evaluate

the potential role of NO and caveolin-1, we examined the plasma activity of NOx, eNOS, phosphorylated-eNOS and expression of caveolin-1. The relaxation in response to acetylcholine was significantly enhanced in ROS compared to CON. Expression of eNOS RNA was unchanged, whereas NOx level and phosphorylated-eNOS at serine-1177 was increased accompanied with depressed level of caveolin-1 in ROS.

We conclude that HMG-CoA reductase inhibitor can improve impaired endothelial dysfunction in SHR, and its underlying mechanisms are associated with increased NO production. Furthermore, HMG-CoA reductase inhibitor can activate the eNOS by phosphorylation related to decreased caveolin-1 abundance. These results imply the therapeutic strategies for the high blood pressure-associated endothelial dysfunction through modifying caveolin status.

10.

THE USEFULNESS OF ESTIMATED CAROTID SYSTOLIC BLOOD PRESSURE USING FORM PWV/ABI IN BLOOD PRESSURE LOWERING THERAPY

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Background: Central systolic blood pressure (central-SBP) can be estimated noninvasively and antihypertensive drugs may exert different effects on central-SBP. We investigated the usefulness of carotid systolic blood pressure (carotid-SBP) estimated by form PWV/ABI in blood pressure lowering therapy.

Methods: We evaluated pulse wave velocity, carotid augmentation index (AI), carotid-SBP in 329 patients (301 hypertensives, 172 men, 65 ± 12 years old) using form PWV/ABI. Antihypertensive drugs were evaluated in those patients.

Results: Mean brachial blood pressure (b-SBP) was 136 ± 21 mmHg and carotid-SBP was 147 ± 25 mmHg. We determined delta-SBP as carotid-SBP - b-SBP, and we divided the subjects into group A (delta-SBP < 0 mmHg) and group B (delta-SBP > 0 mmHg). The number of group A was 22 patients and that of group B was 307 patients. There were no differences of mean age between these two groups. Although b-SBP of group A (137 ± 21 mmHg) was similar to that of group B (136 ± 21 mmHg), b-diastolic BP of group A (83 ± 12 mmHg) was different from that of group B (77 ± 13 mmHg, $p = 0.0456$). Carotid AI of group A ($13 \pm 14\%$) is lower than that of group B ($23 \pm 18\%$, $p = 0.0160$). The evaluation of the effect of antihypertensive agents showed that Ca antagonists, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and diuretics did not affect delta-SBP significantly. However, those who had β blockers or blockers showed higher delta-SBP compared to those who without these drugs.

Conclusion: Estimation of carotid-SBP using form PWV/ABI is useful for the evaluation of the effects of antihypertensive drugs on brachial and central BPs.

11.

THE EFFECT OF LONG-TERM ADMINISTRATION OF HYDROCHLOROTHIAZIDE ON CENTRAL BLOOD PRESSURE

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Background: It's unknown wheather there is much benefit on central aortic pressure than brachial pressure while long-term administration of hydrochlorothiazide in patients with essential hypertension.

Methods: The retrograde analysis was conducted at three of the participating centers in the Felodipine Event Reduction (FEVER) study. 76 of 129 patients in placebo group, who kept hydrochlorothiazide monotherapy over 36 months period, and took pulse wave recording at randomization, 12 month, 24 month and 36 month, were included into the final analysis. Radial artery pressure waveforms were measured with applanation tonometry, and convolved into the ascending aortic pressure waveforms, using the FDA-approved SphygmoCor system. The analysed parameters in aortic pressure waveform included first peak pressure, secondary peak pressure, diastolic pressure, pulse pressure, augmentation and augmentation index.

Results: In comparison with baseline, there were substantial falls ($P < 0.001$) in brachial SP/DP and in central aortic SP/DP with no difference, slight falls ($P < 0.05$) in aortic augmentation, and no significant falls ($P > 0.05$) in augmentation index and heart rate.

Conclusion: Long-term administration of hydrochlorothiazide resulted in the similar reduction of both brachial pressure and central aortic pressure without the change of augmentation index, which could exclude definite benefit on central aortic pressure than brachial pressure.

12.

THE EFFECT OF ORALLY SINGLE DOSE OF SLOW-RELEASE ISOSORBIDE-5-MONONITRATE ON CENTRAL BLOOD PRESSURE IN HEALTHY VOLUNTEERS

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Background: The cuff sphygmomanometer failed to show consistent alteration in brachial blood pressure with slow-release isosorbide-5-mononitrate (IS-5-MN), even though the drug proved very effective in relieving angina pectoris. So far, the effect of orally single dose of slow-release isosorbide-5-mononitrate on central blood pressure is not known.

Methods: Using self-control study before and after treatment in a total of 22 healthy volunteers, the effects of slow-release IS-5-MN 60 mg in single dose form were assessed over a twenty four hour period through analysis of the radial pulse waveform, calibrated against conventional cuff sphygmomanometry. Ascending aortic pressure waveforms were generated from the radial waves, using a validated generalised transfer function. The concentration of 5-ISMN were measured by HPLC-MS.

Results: After taken the drug, the concentration of 5-ISMN was rapidly increased to peak at 4 h, then linearly decreased to 187.6 ng/ml at 24 h. There was no consistent change in heart rate or brachial pressures except for a decrease in systolic pressures and a increase in heart rate ($p < 0.01$) at 2-6 hour. In contrast, there were substantial and significant decreases in aortic systolic pressures, augmented pressures, augmentation index and ejection duration ($p < 0.001$) at 0.5 h-16 h.

Conclusion: Pulse waveform analysis exposes concentration dependent effects of 5-ISMN on the aortic waveform, suggesting muscular conduit arterial dilatation with reduced wave reflection and venous dilatation with reduced ejection duration at the low and intermediate concentration, arteriolar dilatation and decreased peripheral resistance at the high concentration.

13.

THE LONG-TERM EFFECT BETWEEN CO-ADMINISTRATION OF SIMVASTATIN AND EZETIMIBE AND ATORVASTATIN ON CENTRAL PULSE WAVE VELOCITY IN ADULTS WITH HYPERCHOLESTEROLEMIA

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Background: The various statin might contribute to a change in arterial stiffness independent of the cholesterol-lowering effects of statin therapy. The aim of this study was to compare the short-term effect between co-administration of simvastatin and ezetimibe (vytorin) and atorvastatin (lipitor) on pulse wave velocity (PWV).

Methods: We enrolled 27 patients with hypercholesterolemia (Total cholesterol > 200 mg/dL). The patients were randomly divided into two groups according to statin (vytorin: 13 patients, lipitor: 14 patients). They were treated vytorin 10/20 mg and Lipitor 20 mg for 1 month, then vytorin 10/10 mg and Lipitor 10 mg for 5 months. We measured the carotid-femoral PWV (cfPWV), and lipid profile at baseline, 1 month, and 6 months after treatment with the statin.

Results: The total cholesterol and LDL levels in both groups were significantly decreased 1 month later, and they were slightly increased 6 months later. In addition, the change of total cholesterol was not different in both groups. The central PWV (cfPWV) in lipitor group was significantly decreased compared with those in vytorin group after 6 months (-0.61 ± 1.23 , 0.24 ± 1.24 m/sec, respectively).

Conclusion: Although co-administration of simvastatin and ezetimibe for 6 months might show similar lipid lowering effect compared with atorvastatin, only atorvastatin might show pleiotrophic effect for long-term treatment in hypercholesterolemia.

14.

USING CENTRAL BLOOD PRESSURE TO GUIDE THERAPY IN HYPERTENSION: BP GUIDE STUDY DESIGN AND INITIAL FINDINGS

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Background: Estimated central blood pressure (BP) predicts cardiovascular mortality independent of brachial BP, but whether central BP may be useful in