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### 5. BRACHIAL-ANKLE AND REGIONAL PULSE WAVE VELOCITY AS A PROGNOSTIC IMPACT IN HYPERTENSION

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## 2. INCREASED ARTERIAL STIFFNESS FOLLOWING ACUTE RESISTANCE EXERCISE IS ASSOCIATED WITH CHANGES IN AUTONOMIC TONE

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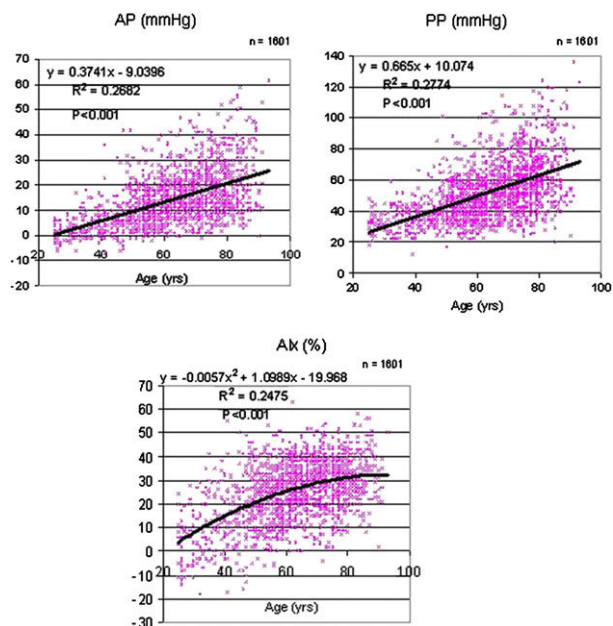
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**Background:** Although acute and chronic resistance exercise is associated with increases in arterial stiffness, the underlying mechanisms are not completely understood. Autonomic nervous system function is associated with arterial stiffness. Therefore, the purpose of this study was to test the hypothesis that acute resistance exercise would increase arterial stiffness and this increased arterial stiffness would be related to changes in autonomic nervous system function.

**Methods:** Using a randomized cross over design, 14 healthy young subjects (age  $20.8 \pm 2.2$  yrs, BMI  $23.4 \pm 1.9$ ) completed a resistance exercise session and a sham control session (seated rest in the exercise room) on two separate days. Carotid-femoral pulse wave velocity (PWV) and aortic augmentation index (Alx) were used as indices of arterial stiffness. Heart rate variability was used to assess autonomic function. Vascular and autonomic measures were made at baseline and 20 minutes after resistance exercise (8 exercises, 60% of 1 repetition maximal).

**Results:** There were significant increases in resting heart rate ( $59.2 \pm 2.6$  to  $80.4 \pm 3.1$  bpm), aortic systolic blood pressure ( $96.6 \pm 2.4$  to  $102.4 \pm 2.1$  mmHg), PWV ( $6.07 \pm 0.3$  to  $6.36 \pm 0.2\%$ ), and Alx@75 bpm ( $-15.3 \pm 3.4$  to  $-0.07 \pm 3.3\%$ ) (all  $p < 0.05$ ) after resistance exercise compared with sham control. The root-mean square of successive differences (RMSSD), number of RR intervals differing by greater than 50 ms (NN50), and percentage of NN50 (pNN50) as an indices of parasympathetic modulation were significantly decreased after resistance exercise ( $p < 0.05$ ). Also, changes in PWV after resistance exercise were associated with changes in RMSSD ( $r = -0.39$ ,  $p = 0.02$ ) after resistance exercise.

**Conclusion:** These data indicate that arterial stiffness is increased following acute resistance exercise and changes in arterial stiffness are associated with changes in heart rate variability. This would suggest that increases in arterial stiffness following resistance exercise are associated with changes in autonomic tone.



## 3. MECHANISMS FOR AGE-CHANGE IN AORTIC AUGMENTATION PRESSURE

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Augmentation index (Alx) is a widely used measure of wave reflection and aortic stiffness. It rises with age in a curvilinear manner whereas central augmentation pressure (AP) and pulse pressure (PP) from which it is determined (as  $Alx = AP \div PP$ ) rise linearly with age. Apparent flattening of Alx over age 60 has been attributed to decreased peripheral wave reflection in older subjects. We sought a purely mathematical explanation of this phenomenon – that two positively sloped linear equations with different intercepts on the y-axis yield a curvilinear change when one is divided by the other. Data were from 1601 patients previously described attending an outpatients clinic and aged from 25 to 93 years. The rise in AP and PP could be described by straight lines (top figure), whereas their ratio as Alx was curvilinear (bottom figure) and approximated the change with age as described in other studies. Change in Alx with age cannot simply be attributed to decrease in peripheral wave reflection. The phenomenon described here must be considered together with change in shape of the left ventricular ejection pattern with age, since wave reflection may cause a decrease in late systolic flow.

## 4. CORONARY CALCIUM SCORE, RATHER THAN CAROTID INTIMA-MEDIA THICKNESS, IS MORE PREDICTIVE OF CORONARY RESTENOSIS AFTER DES IMPLANTATION

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**Background:** Calcium scoring on MDCT and carotid intima-media thickness (IMT) have been widely used as indices of atherosclerosis. However, the clinical correlation between carotid IMT and the severity of coronary artery disease (CAD) is relatively poorly established. The aim of this study was to determine the relation between coronary restenosis after DES implantation and carotid IMT.

**Methods:** Among a total of 3041 patients who underwent carotid ultrasonography, 956 patients (male:female = 583:373, mean age =  $61 \pm 11$  years) with DES implantation who had undergone follow-up coronary angiography were divided into two groups. Group 1 ( $n = 861$ , male = 61%, mean age  $60 \pm 11$  years) was the no ISR group. Group 2 ( $n = 95$ , male = 67.4%, mean age =  $65 \pm 9$  years) was the ISR group. ISR was defined as a more than 50% reduction in luminal stent diameter on follow-up coronary angiography. Carotid IMT was measured using a 15 MHz high frequency transducer on the far walls of both carotid arteries. Intimal thickness, defined as high echogenic thickening in the intimal area on carotid ultrasound, was also measured. The calcium score on MDCT was also compared between the two groups.

**Results:** On comparison between the two groups (group 1 vs group 2), 1. The right mean IMT and media thickness were larger in Group 1 ( $p = 0.023$ ,  $p = 0.048$ ). 2. There was no significant difference in the right and left maximal IMT or left medial thickness (Table). 3. Calcium scores were significantly higher on MDCT in the ISR group ( $427 \pm 86$  vs  $1599 \pm 482$ ,  $p < 0.05$ ). On multivariate analysis after adjustment for age, the calcium score on MDCT was the strongest predictor of coronary artery restenosis (odds ratio 1.3,  $p = 0.027$ , 95% CI: 1.02-1.89).

**Conclusion:** The coronary calcium score is a better predictive marker for stent restenosis after DES implantation when compared to the carotid IMT. Noninvasive measurement of the calcium score and carotid IMT might be useful for evaluation of coronary restenosis.

## 5. BRACHIAL-ANKLE AND REGIONAL PULSE WAVE VELOCITY AS A PROGNOSTIC IMPACT IN HYPERTENSION

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**Background:** Many reports have shown that brachial-ankle pulse wave velocity (baPWV) as well as carotid-femoral PWV would be one of the prognostic factors for hypertension. We can evaluate heart-carotid PWV

(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  $61.1 \pm 11.8$ , 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  $60.9 \pm 12.1$ , 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 ( $n = 287$ ;  $1654 \pm 331$  cm/sec) was significantly higher than that without CKD ( $n = 93$ ;  $1771 \pm 333$  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  $\geq 700$ , or  $\geq 75$ 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 =  $61.2 \pm 12.0$  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  $43.0 \pm 17.2$  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

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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