Association of central blood pressure with markers for target organ damage in chronic kidney disease patients: Comparison between central and peripheral blood pressure

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Association of central blood pressure with markers for target organ damage in chronic kidney disease patients: Comparison between central and peripheral blood pressure

Directed by Professor Tae-Hyun Yoo

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This certifies that the Master's Thesis
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Youn Kyung Kee

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ABSTRACT

Association of central blood pressure with markers for target organ damage in chronic kidney disease patients
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(Directed by Professor Tae-Hyun Yoo)

Background Hypertension (HTN) is an established cardiovascular risk factor and is closely related with mortality in chronic kidney disease (CKD) patients. Recent studies demonstrated central blood pressure (CBP) was a significant predictor of cardiovascular disease (CVD) and had stronger relationship with vascular damage such as vascular calcification and stiffness than peripheral blood pressure (PBP). Therefore, we investigated the association of CBP or PBP with markers for target organ damage measured by pulse wave velocity (PWV) and coronary calcium score (CCS) in CKD patients including end-stage renal disease (ESRD) patients.

Method Patients enrolled by Cardiovascular and Metabolic Disease Etiology Research center (CMERC) of Yonsei University College of Medicine between November 2013 and May 2015 were eligible in this study. We analyzed the associations between central or peripheral blood pressure values (systolic blood pressure and pulse pressure) and parameters for target organ damage measured by PWV and CCS in CKD patients.

Result Among a total of 424 CKD patients, 248 (58.4%) were male and mean age was 59±12.4 years. Mean central systolic blood pressure (SBP) and pulse pressure

(PP) were 132.7 and 54.8 mmHg and mean peripheral SBP and PP were 135.7 and 58.2 mmHg in study patients. The central SBP and PP were significantly higher in patients with advanced CKD stage compared to those in less advanced CKD patients. There were significant correlations between central or peripheral SBP and markers for target organ damage (PWV; r = 0.424 vs 0.361 and CCS; 0.262 vs 0.196, all $p < 0.001$). The associations of central SBP with presented markers for target organ damage were significantly stronger than peripheral SBP in total CKD patients (PWV; Z = 2.050, P = 0.040 and CCS; Z = 2.010, P = 0.044). When we evaluated the associations between blood pressure values and markers according to CKD stage, central SBP was more closely correlated with markers for target organ damage compared to peripheral SBP in early CKD population. However, present study did not show better association of CBP with markers for target organ damage compared to PBP in ESRD patients.

Conclusion Central SBP and PP are significantly associated with markers for target organ damage in CKD patients. In addition, central SBP has stronger associations with CCS and PWV compared to peripheral SBP in non-dialysis CKD patients. However, CBP is not superior to PBP for predicting target organ damage in ESRD patients.

Key words: chronic kidney disease, central blood pressure, pulse wave velocity, coronary calcium score

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I.INTRODUCTION

Cardiovascular disease (CVD) is highly prevalent and a major cause of death in patients with chronic kidney disease (CKD).[1,2] Hypertension (HTN) is known as a major risk factor for CKD progression[3] and CVD.[4,5] Since it is simple and non-invasive for measurement of arterial blood pressure (BP), cuff sphygmomanometer has been widely used for checking BP and monitoring the efficacy of anti-hypertensive medications. Not only accurate and reproducible measurement of BP, but also predictive power for clinical outcomes including CVD is important. Recently, numerous studies demonstrated that peripheral blood pressure (PBP) measured at brachial artery poorly reflects central blood pressure (CBP) measured at large arteries located near the heart such as aorta or carotid artery.[6] SBP amplification from aorta to radial artery is caused by accentuated arterial stiffness during traveling away from the heart. Stiffer peripheral artery than central artery makes the prominent and narrow systolic peak in radial artery. The extent of SBP amplification might be changed by several variables including age, gender and height[7]. Recent reports showed that CBP is much strongly associated with prevalence of CVD than PBP.[8-10] In addition, CBP is much useful to monitor the

efficacy of different hypertensive drugs.[11,12] Based on these concepts, it is suggested that CBP is a better predictor of cardiovascular risk compared to PBP. In the past, clinical relevance was limited due to invasiveness of CBP measurement, but several non-invasive methods for measurement of CBP has been introduced during a last decade. Along with wide applications of CBP, several studies had confirmed the clinical significance of CBP in various populations, however, there are still controversies about the superiority of CBP in predicting CVD risk.[13] To date, only a few studies have been conducted in CKD population and the results were conflicting. Moreover, that the associations between CBP, PBP and several markers for target organ damage in this population according to CKD stage has never been explored. Since pulse wave velocity (PWV) and coronary calcification score (CCS) are well known predictors for cardiovascular morbidity and mortality in CKD patients, we investigated the associations between PWV, CCS and BP values in CKD patients. In addition, we compared the associations of CBP and PBP with markers for target organ damage in CKD patients.

II.MATERIALS AND METHODS

Study population

The current study used the Cardiovascular and Metabolic disease Etiology Research Center-High risk cohort (CMERC-HI) data, which is a prospective cohort study aimed at developing individual prevention strategies for patients with high risks of CVD (clinicaltrial.gov NCT02003781). A total of 1,345 patients were enrolled between November 2013 and May 2015. Among them, 424 patients with impaired renal function (estimated GFR less than 60mL/min/1.73m^2 or on renal replacement therapy) finally included in this analysis. The value of estimated GFR (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration

(CKD-EPI) equation from serum creatinine.[14] The patients were divided into three groups according to CKD stage specified in Kidney Disease Improving Global Outcomes (KDIGO) guideline – group 1 (CKD stage 3), group 2 (CKD stage 4 or pre-dialysis CKD stage 5) and group 3 (CKD stage 5 maintained with dialysis). The patients who had missing data about eGFR, CCS or PWV were excluded. The present study was approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Center and written informed consent was obtained from all participants

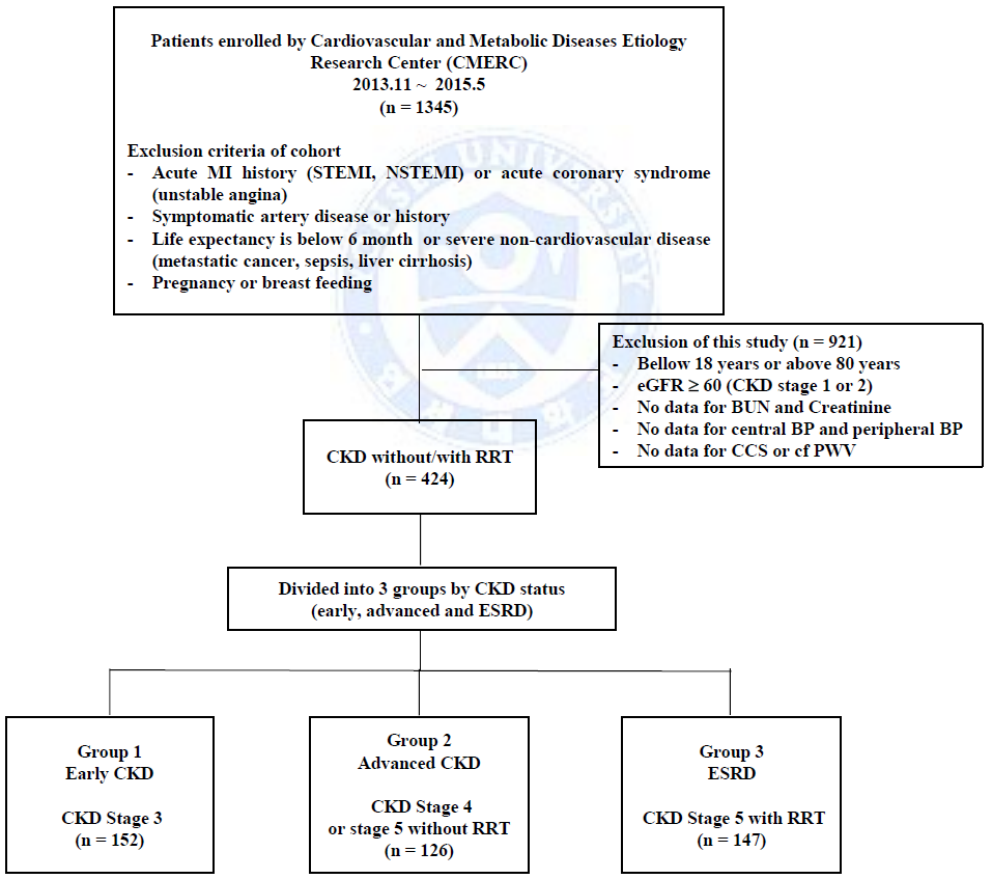


Figure 1. Flow chart of the study population

Data collection

Demographic and clinical data were collected at the time of cohort enrollment. These included age, sex, underlying diseases, and laboratory parameters including blood urea nitrogen (BUN), creatinine, albumin, calcium, phosphate, total cholesterol, HDL cholesterol and LDL cholesterol.

Blood pressure measurement

CBP was measured noninvasively by mathematically transforming the radial artery pulse waveform to the aortic pulse wave form with radial applanation tonometry using a Millar transducer and customized software (SphygmoCor, AtCor Medical, Sydney, Australia). Radial artery waveforms were obtained from the arm without the arteriovenous fistula. The SphygmoCor system obtains the ascending aortic pressure waveform from the radial artery waveform using its validated mathematical transfer function. Central systolic BP, diastolic BP, and pulse pressure (PP), were acquired from the aortic pressure waveform analyses. The measurements of CBP were performed by trained observer in supine position after at least 5 min of rest. PBP was measured three times with conventional mercury cuff sphygmomanometer (Omaron HEM-708IC) at 5 min interval after 10 min of resting in a sitting position and the measured values were averaged. PP was determined as difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP) and was calculated after measurement of CBP and PBP.

Assessment for target organ damage

We used PWV and CCS as target organ damage markers in this study. The Carotid femoral pulse wave velocity (cfPWV) was measured as previously described.

Briefly, electrocardiogram and carotid/femoral pulse waves were obtained simultaneously to calculate the transit time using the foot-to-foot method. The distance traveled by the pulse wave was calculated by subtracting the sternal notch-right carotid site from right femoral site-sternal notch distances. Arterial calcification was assessed by coronary calcium score (CCS). CCS was performed with multi-detector row computed tomography scanners of 64 rows or greater (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan). The total calcium score was calculated as the sum of the individual lesion score in all coronary arteries.

Statistical analysis

All variables are expressed as the mean ± standard deviation or percentage. One-way ANOVA was used to evaluate the differences of means among three groups with Bonferroni correlation. Categorical variables of the groups were compared by chi-squared test. Correlations between blood pressure values and markers for target organ damage were assessed by calculating Pearson's correlation coefficient. Comparisons between two correlation coefficients were carried out using the formula of Steiger's *Z*-test. Multivariable linear regression was performed to evaluate the association of CBP values with markers for target organ damage after adjustment of influencing factors. P-values less than 0.05 were considered to be statically significant. Data were analyzed using SPSS 23 (SPSS Inc., Chicago, IL, USA).

III.RESULTS

Baseline characteristics

Baseline characteristics of this study are shown in Table 1. A total of 424 patients

with CKD were participated in this cross-sectional study. The mean age was 59 years and mean eGFR was 24.5 mL/min/1.73m^2. Two-hundred and forty-eight patients (58.4%) were male and 356 patients (84.0%) have been treated for HTN and there were no significant differences in the proportion of gender or presence of hypertension or diabetes among three groups. Serum phosphate levels were significantly higher, and serum albumin, triglyceride and calcium levels were significantly lower in group 3 compared to those in group 1 and 2. The profiles of blood pressure values and markers for target organ damage are presented in Table 2. There were significant differences in mean values of SBP, DBP and PP among three groups, and the patients with advanced CKD showed higher blood pressure values compared to those of early CKD group. The dialysis group had significantly higher CCS than those in non-dialyzed CKD patients. cfPWV had increasing trends along with CKD stage, but didn't show significant differences among three groups.

Table 1. Baseline characteristics of study population according to CKD stage

	Total (n=424)	Group 1 (n=156)	Group 2 (n=121)	Group3 (n=147)	P-value
Age (year)	59 ± 12.4	62 ± 11.1	60 ± 11.7	54 ± 12.8	<0.001*
Gender, male (%)	248 (58.4%)	100 (64.1%)	61 (50.4%)	87 (59.2%)	0.071
BMI (kg/m^2)	24.8 ± 3.9	25.5 ± 3.7	24.7 ± 3.9	24.0 ± 3.8	0.003*
Hypertension, n (%)	356 (84.0%)	137 (87.8%)	104 (86%)	115 (77.7%)	0.059
Diabetes, n (%)	159 (37.4%)	56 (35.7%)	54 (44.6%)	50 (35.1%)	0.156
Hyperlipidemia, n (%)	178 (41.9%)	73 (46.8%)	58 (47.9%)	47 (33.8%)	0.010**
Current smoker, n (%)	216 (50.7%)	69 (44.2%)	74 (61.2%)	73 (49.3%)	0.019**
eGFR (mL/min/1.73m^2)	24.5 ± 18.9	46.1 ± 9.5	17.8 ± 6.5	5.7 ± 2.8	<0.001*
BUN (mg/dL)	43.2 ± 21.5	25.6 ± 7.3	49.0 ± 17.3	57.6 ± 21.8	<0.001*
Creatinine (mg/dL)	4.9 ± 4.2	1.5 ± 0.3	3.5 ± 1.3	9.9 ± 3.3	<0.001*
Total cholesterol (mg/L)	167.5 ± 39.6	168.6 ± 43.3	168.2 ± 37.1	165.6 ± 37.5	0.794
HDL cholesterol (mg/L)	46.3 ± 21.5	46.7 ± 14.2	45.0 ± 18.2	46.9 ± 30.2	0.750
LDL cholesterol (mg/L)	90.9 ± 30.4	92.8 ± 31.6	90.1 ± 29.9	89.4 ± 29.4	0.620
Triglycelride (mg/L)	140.8 ± 97.9	154.4 ± 115.7	145.9 ± 71.8	120.3 ± 93.9	0.013**
Calcium (mg/L)	8.9 ± 0.7	9.1 ± 0.4	8.8 ± 0.6	8.8 ± 0.9	<0.001*
Phosphate (mg/L)	4.1 ± 0.9	3.6 ± 0.5	4.04 ± 0.6	4.8 ± 1.1	<0.001*
Albumin (g/dL)	3.9 ± 0.5	4.2 ± 0.3	3.9 ± 0.4	3.7 ± 0.5	<0.001*
Glucose (mg/dL)	109.5 ± 36.9	110.8 ± 30.2	109.6 ± 43.5	108.2 ± 37.8	0.833
HbA1c (%)	6.1±1.0	6.2±0.9	6.2±1.0	5.8±1.1	<0.001*

*<0.01, among three groups; **<0.05, among three groups; Date are expressed as mean ± standard deviation, or number of patients (percent); hyperlipidemia, history of hyperlipidemia or on medication; Group 1, CKD stage 3; Group 2, CKD stage 4 or pre-dialysis CKD stage 5; Group 3, CKD stage 5 maintained with dialysis

Table 2. Central and peripheral blood pressure and markers for target organ damage according to CKD stage

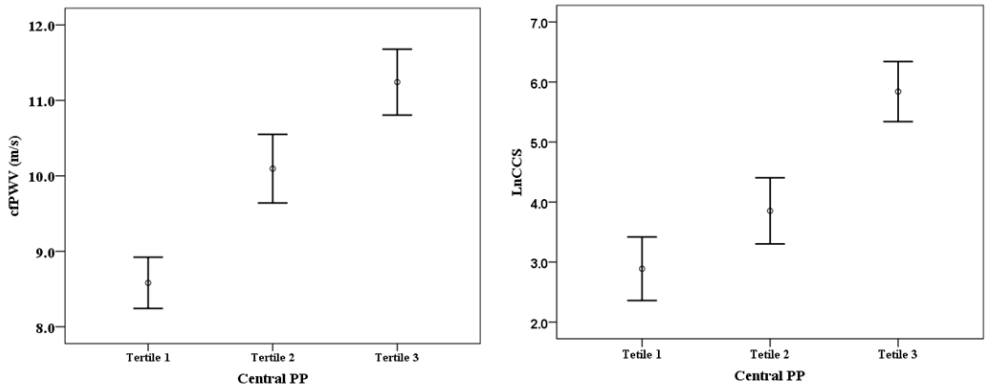
	Total (n=424)	Group 1 (n=156)	Group 2 (n=121)	Group3 (n=147)	P-value
Central SBP (mmHg)	132.7 ± 25.5	119.6 ± 16.9	130.5 ± 21.0	148.7 ± 27.8	<0.001*
Central DBP (mmHg)	77.9 ± 11.7	75.5 ± 9.6	77.1 ± 10.1	81.4 ± 13.9	<0.001*
Central PP (mmHg)	54.8 ± 20.6	44.1 ± 13.5	53.5 ± 19.3	66.9 ± 21.8	<0.001*
Peripheral SBP (mmHg)	135.7 ± 21.9	126.8 ± 15.4	137.4 ± 19.7	143.8 ± 25.8	<0.001*
Peripheral DBP (mmHg)	77.5 ± 11.7	75.5 ± 9.9	76.7 ± 11.1	80.2 ± 13.3	0.001*
Peripheral PP (mmHg)	58.2 ± 19.5	51.2 ± 13.2	60.7 ± 20.7	63.6 ± 21.8	<0.001*
cfPWV (m/sec)	9.9±2.7	9.8±2.7	10.0±2.8	10.2±2.7	0.505
Ln (CCS)	3.98 ± 3.01	3.52 ± 2.99	3.70 ± 3.1	5.96 ± 2.11	<0.001*

*<0.01, among three groups; **<0.05, among three groups; SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, cfPWV: carotid-femoral pulse wave velocity, CCS: coronary calcium score. Ln(CCS): log transformation of CCS

Association between markers for target organ damage and CBP values in CKD patients

We divided study subjects into three groups by tertiles of central SBP and PP. In CKD patients, the mean cfPWV and CCS were gradually increased according to incremental tertiles of central SBP and PP ($p < 0.001$ among the three groups, Figure 2).

1) Central SBP and target organ damage markers



2) Central PP and target organ damage markers

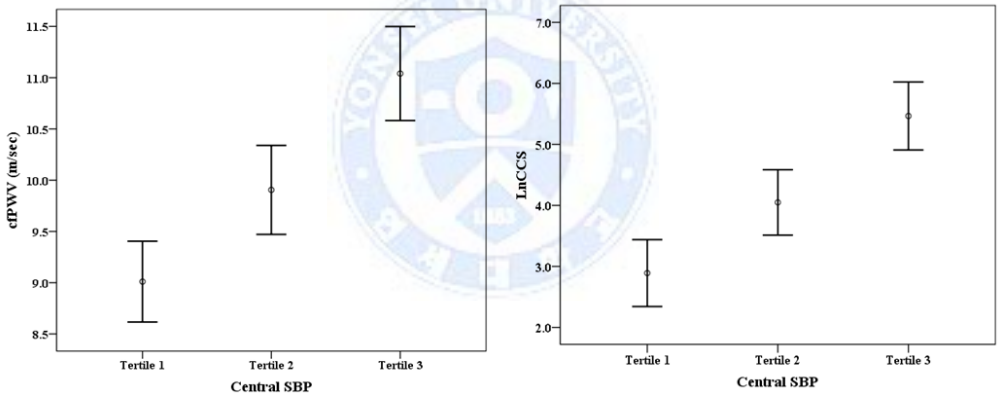
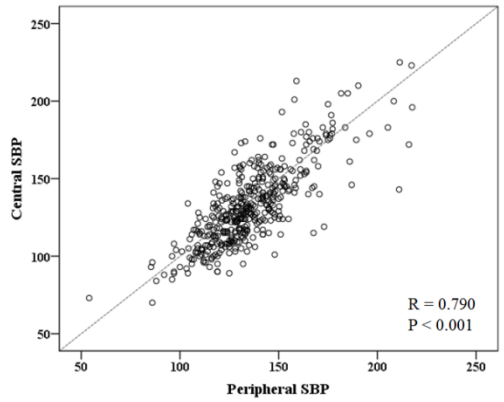


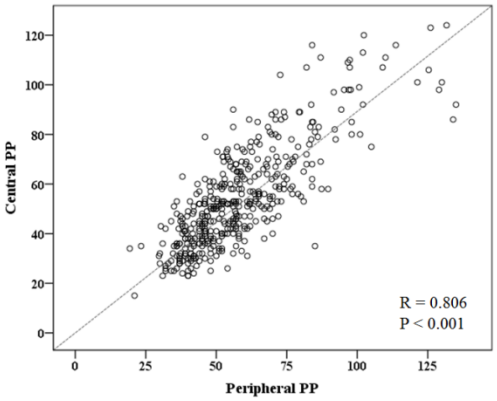
Figure 2. Association between markers for target organ damage and CBP values in CKD patients. The tertile for SBP and PP as follows; SBP tertile 1 (≤ 120, n = 142), tertile 2 (120 < and ≤ 140, n = 141), tertile 3 (140 <, n = 141) and PP tertile 1 (≤ 44, n = 151), tertile 2 (44 < and ≤ 59, n = 134), tertile 3 (59 <, n = 139)

Correlation between CBP and PBP according to CKD stage

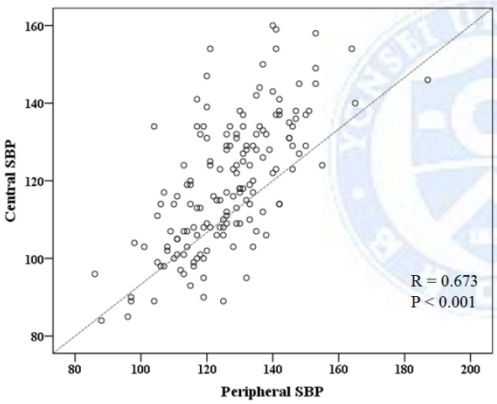
We analyzed the correlations between central and peripheral SBP/PP according to CKD stages. There were strong correlations between CBP and PBP in all study subjects (central SBP vs. peripheral SBP, $R = 0.790$; $P < 0.001$ and central PP vs. peripheral PP, $R = 0.806$; $P < 0.001$). Compared to those of each CKD groups, there were stronger correlations between CBP and PBP in patients with advanced CKD, especially in dialysis population. (Figure 3)

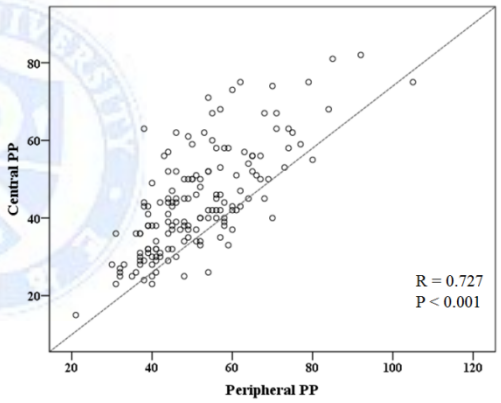
A) Total study subjects



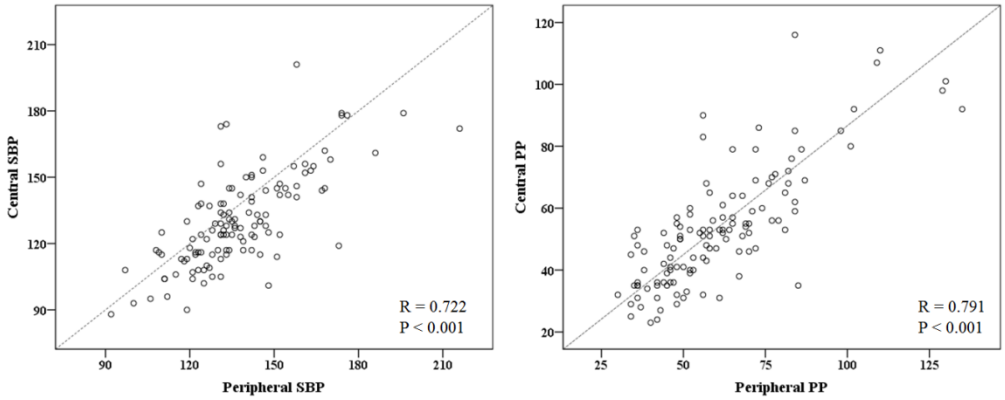


B) Group 1

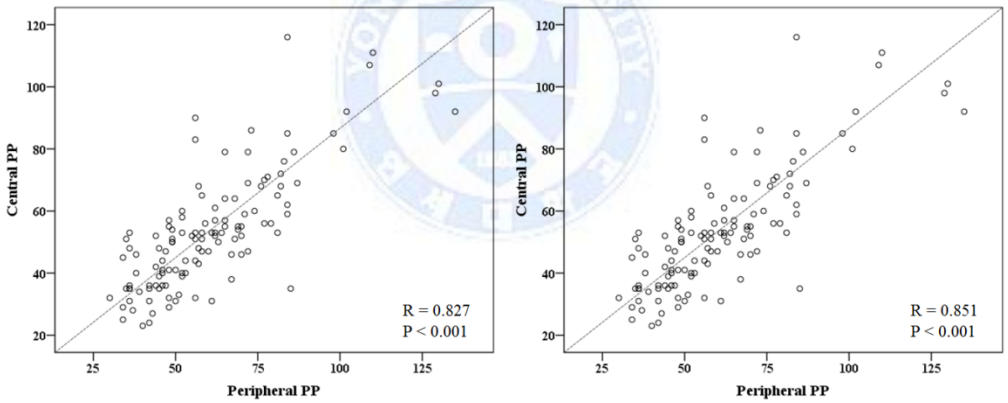




C) Group 2



D) Group 3



R: Pearson's correlation coefficients; All correlation were significant (P < 0.001)

Figure 3. *Correlation between CBP and PBP according to CKD stage*

Comparisons of CBP and PBP to detect the presence of target organ damage in CKD patients

Table 3 showed the associations of central and peripheral SBP with markers for target organ damage including PWV and CCS. In total subjects, there were significant associations of central and peripheral SBP with presented markers for target organ damages (PWV; r = 0.424 vs 0.361 and CCS; 0.262 vs 0.196, respectively, $p < 0.001$) and the associations of central SBP with markers for target organ damages were significantly stronger than those of peripheral SBP (PWV; Z = 2.050, P = 0.040 and CCS; Z = 2.010, P = 0.044). When we evaluated the associations of central and peripheral SBP with markers for target organ damage according to CKD stage, there were quite differences in the degree of correlation among three groups. In early CKD patients (group 1), the correlation between central SBP and cfPWV and CCS were stronger than those with peripheral SBP. In group 2, despite of close correlation with central SBP and each of markers, there was no significant difference in the associations between presented markers and central or peripheral SBP. In CKD stage 5 on dialysis, there were no differences in correlation with markers for target organ damage between central and peripheral SBP. We also investigated associations of central and peripheral PP with presented markers (Table 4). In total subjects, there were significant correlations between both PP and markers for target organ damage, and correlation between central PP and PWV was significantly stronger than peripheral PP. In subgroup by CKD stage, central PP didn't show significantly stronger correlation with markers for target organ damage than peripheral PP except correlation with CCS in early stage CKD group (Z = 2.050, P = 0.040). In subgroup analysis according to dialysis, CBP was significantly associated with markers for target organ damages in non-dialysis CKD group (table 5). However, in dialysis CKD group, CBP didn't provide superior correlations with markers for target organ damage to PBP. When adjusted for

relevant variables including PBP values, CBP was still significantly associated with PWV and CCS in multivariate regression analysis. (Table 6)

Table 3. Association of central and peripheral SBP with markers for target organ damage in CKD patients

	Central SBP		Peripheral SBP			
	r	***p***	**r**	***p***	**Steiger's Z**	**P**
			Total			
cfPWV	0.424	<0.001*	0.361	<0.001*	2.210	0.040**
LnCCS	0.262	<0.001*	0.196	<0.001*	2.410	0.044**
			Group 1			
cfPWV	0.361	<0.001*	0.201	<0.001*	2.130	0.033**
LnCCS	0.186	0.021**	0.037	0.660	2.830	0.004*
			Group 2			
cfPWV	0.442	<0.001*	0.415	<0.001*	0.450	0.654
LnCCS	0.419	<0.001*	0.405	<0.001*	0.230	0.822
			Group 3			
cfPWV	0.478	<0.001*	0.560	<0.001*	0.420	0.674
LnCCS	0.209	0.056	0.288	0.019**	-0.670	0.095

*P < 0.01; **P < 0.05; Pearson correlation coefficients are displayed in the table and CCS were calculated on log transformed variable. Steiger's Z and P value refer to the comparison of correlations with target organ damage markers between central and peripheral SBP.

Table 4. Association of central and peripheral PP with target organ damage markers in CKD patients

	Central PP		Peripheral PP			
	r	***p***	**r**	***p***	**Steiger's Z**	**P**
			Total			
cfPWV	0.479	<0.001*	0.367	<0.001*	3.970	<0.001*
LnCCS	0.406	<0.001*	0.370	<0.001*	1.300	0.194
			Group 1			
cfPWV	0.511	<0.001*	0.508	<0.001*	0.060	0.952
LnCCS	0.231	0.005*	0.157	0.060	1.270	0.205
			Group 2			
cfPWV	0.458	<0.001*	0.385	<0.001*	1.400	0.162
LnCCS	0.478	<0.001*	0.507	<0.001*	0.580	0.561
			Group 3			
cfPWV	0.549	<0.001	0.518	<0.001*	0.820	0.413
LnCCS	0.264	0.059	0.317	0.022**	1.220	0.222

*P < 0.01; **P < 0.05; Pearson correlation coefficients are displayed in the table and CCS were calculated on log transformed variable. Steiger's Z and P value refer to the comparison of correlations with target organ damage markers between central and peripheral PP.

Table 5. Association of CBP and PBP with target organ damage markers in non-dialysis CKD patients and ESRD patients

	Central SBP		Peripheral SBP			
	r	p	r	p	steiger's Z	P
non-dialysis CKD						
cfPWV	0.406	<0.001**	0.312	<0.001**	2.040	0.041**
LnCCS	0.301	<0.001**	0.183	<0.003**	2.450	0.014**
Dialysis CKD						
cfPWV	0.442	<0.001**	0.415	<0.001**	0.450	0.654
LnCCS	0.419	<0.001**	0.421	<0.001**	-0.030	0.974

	Central PP		Peripheral PP			
	r	p	r	p	steiger's Z	P
non-dialysis CKD						
cfPWV	0.462	<0.001**	0.451	<0.001**	0.300	0.767
LnCCS	0.359	<0.001**	0.320	<0.001**	0.990	0.324
ESRD						
cfPWV	0.591	<0.001**	0.618	<0.001**	-0.760	0.446
LnCCS	0.358	0.001**	0.433	<0.001**	-1.810	0.070

*P < 0.01; **P < 0.05; Pearson correlation coefficients are displayed in the table and CCS were calculated on log transformed variable. Correlations compared by Z statistics.

Table 6. Multivariate linear regression: determinant of target organ damage markers

1) Target organ damage markers with SBP

	cfPWV		LnCCS	
	ß	p-value	ß	p-value
Adjusted R^2	0.389		0.280	
Age (per 1 years)	0.083	<0.001**	0.083	<0.001**
Gender (male)	-0.552	0.028**	-1.273	<0.001**
DM	-1.003	<0.001**	-0.792	0.005*
HTN	0.375	0.207	0.446	0.231
BMI (per 1 kg/m^2)	0.075	0.009**	0.025	0.473
WBC (per 1000 cells/μL)	0.045	0.165	0.028	0.670
Hemoglobin (per 1 g/dL)	-0.024	0.747	-0.109	0.228
Total cholesterol (per 1 mg/L)	-0.002	0.527	-0.007	0.055
Serum albumin (per 1 g/dL)	-0.398	0.197	-0.149	0.694
BUN (per 1 mg/dL)	-0.006	0.470	0.002	0.887
Creatinine (per 1 mg/dL)	-0.015	0.735	-0.056	0.365
Calcium (corrected, per 1 mg/L)	0.197	0.896	0.416	0.097
Phosphorus (per 1 mg/L)	0.161	0.338	0.359	0.107
Peripheral SBP (per mmHg)	0.009	0.206	-0.003	0.695
Central SBP (per mmHg)	**0.035**	**<0.001***	**0.024**	**0.006****

*P < 0.01; **P < 0.05, Adjusted R^2; Adjusted coefficients of variation

2) Target organ damage markers with PP

	cfPWV		LnCCS	
	ß	p-value	ß	p-value
Abjuseted R^2	0.396		0.283	
Age (per 1 years)	0.060	<0.001**	0.071	<0.001**
Gender (male)	-0.428	0.089	-1.223	<0.001**
DM	-0.826	<0.001**	-0.701	0.014**
HTN	0.458	0.121	0.459	0.217
BMI (per 1 kg/m^2)	0.072	0.011**	0.023	0.506
WBC (per 1000 cells/μL)	0.049	0.127	0.024	0.716
Hemoglobin (per 1 g/dL)	0.047	0.536	-0.069	0.448
Total cholesterol (per 1 mg/L)	-0.002	0.485	-0.007	0.043
Serum albumin (per 1 g/dL)	-0.324	0.292	-0.111	0.771
BUN (per 1 mg/dL)	-0.010	0.229	-0.001	0.925
Creatinine (per 1 mg/dL)	-0.002	0.966	-0.054	0.385
Calcium (corrected, per 1 mg/L)	-0.076	0.703	0.372	0.140
Phosphorus (per 1 mg/L)	0.181	0.259	0.399	0.073
Peripheral PP (per mmHg)	0.031	0.001**	0.006	0.617
Central PP (per mmHg)	**0.030**	**0.002****	**0.026**	**0.025****

IV.DISCUSSION

This study was performed to investigate the clinical importance of CBP in CKD patients by evaluating associations of CBP with markers for target organ damage. Several studies showed that CBP was a much powerful prognostic factor for patient mortality, including cardiovascular outcomes compared to PBP. The Strong Heart study, a population-based longitudinal study of prevalent and incident CVD in American Indians, demonstrated stronger relations of central SBP than PBP and central PP with variable cardiovascular surrogate markers including left ventricular mass, carotid intima-media thickness, and cfPWV.[15] A prospective observational study of normotensive and untreated hypertensive participants from a Chinese community also showed that central SBP was more predictable for cardiovascular mortality than other BP variables.[16] The prospective study in a geriatric population with normotensive and hypertensive subjects demonstrated the superior prognostic significance of CBP over PBP, showing that central PP more strongly correlated with cardiovascular mortality and morbidity than peripheral PP.[10] In contrast, central PP had no additional value in predicting outcome beyond peripheral PP in specific population, such as older female hypertensive patients.[17] With regard to patients with decreased renal function, Safar et al.[9] found that central PP was more powerful predictor for overall mortality than peripheral PP in ESRD patients. Cohen et al.[18] conducted to pre-dialysis CKD population also revealed the associations of CBP values with CKD progression. It is well known that CKD patients have higher prevalence of CVD compared to the general population, and incidence of CVD is notably increased with CKD progression.[19] Furthermore, HTN is highly prevalent and is related to CKD progression and developing CVD in CKD patients. [20,21] Despite of close relationship between HTN and CVD in CKD patients, it has been still elusive on the clinical significance of CBP in predicting CVD, and the superiority of CBP to PBP should be elucidated in CKD population.

Numerous studies demonstrated that arterial stiffness was independently associated with target organ damage such as coronary, cerebral, and peripheral arteries and was forceful predictor of CVD events.[22] Arterial stiffness can be practically assessed by measurement of aortic PWV and PWV is also strongly associated with the presence or extent of atherosclerosis and subsequent CVD outcomes.[23] Vascular calcification assessed by CCS could also reflect atherosclerosis and is significantly associated with CVD events.[24] A previous study showed that cfPWV and CCS were significantly associated with the progression of CVD and helped to assess response to therapeutic intervention.[25] Therefore, assessment of cfPWV and CCS contributes to cardiovascular risk stratification.[26,27] In CKD patients, arterial stiffness and vascular calcification appear even in early stage of CKD and tend to be worsen as the progression of CKD stage.[28,29] Increased arterial stiffness and vascular calcification have been widely used to predict CVD outcomes and mortality in CKD patients.[30] We investigated the associations of CBP or PBP with target organ damage, by measuring cfPWV as a marker for arterial stiffness and CCS as a marker for vascular calcification. In present study, cfPWV and CCS were closely associated with traditional risk factors for CVD such as age, gender, and diabetes. Present study also showed the strong correlation between PWV and CCS in CKD patients ($r = 0.437$, $p < 0.001$) similarly with previous observation.[31] We also found that central SBP and PP were closely related with markers for target organ damage assessed by cfPWV and CCS in CKD patients. Furthermore, this study showed that central SBP was more strongly associated with PWV and CCS than peripheral SBP in this population.

When we conducted subgroup analysis according to CKD stages, there were considerably different associations of CBP or PBP with markers for target organ damage depending on CKD stage. Central SBP showed stronger association with markers for cardiovascular damages than peripheral SBP in early stage of CKD.

However, the predictive ability of CBP for target organ damage was not superior to PBP in patients with advanced CKD including ESRD. With CKD progression, not only conventional risk factors such as HTN, DM and hyperlipidemia, but also non-conventional (uremic toxin, oxidative stress, anemia, mineral bone disease) risk factors affected cardiovascular damages and gradually induced arterial calcification and stiffening. Therefore BP role for predicting target organ damage would tend to be weakened with CKD progression, especially in ESRD patients. In addition, with aging, peripheral and central arteries become much stiffer and decrease in vascular elasticity. And SBP amplification (i.e., difference between peripheral and central SBP) resulting from increase in arterial stiffness moving to peripheral artery, would be attenuated with progression of vascular aging.[32] In ESRD patients, like aging vessel, arterial stiffness and calcification could be severe and extend whole arteries leading to disappearance of the arterial stiffness gradient.[29] Consequently, CBP directly transfers to PBP and the correlations between CBP and PBP are more likely to close with CKD progression. Present study also showed that CBP was much closely associated with PBP at advanced CKD stage and was the strongest correlation with PBP in ESRD patients. And attenuated SBP amplification can be expected with reduced predictive power of CBP over PBP for cardiovascular damages and CBP did not provide additional information beyond PBP especially in ESRD group.

This study has several potential limitations that should be mentioned. First, because of cross-sectional design, we could not determine the causative relationship between CBP and target organ damage markers. And our study only showed the correlation of CBP and target organ damage markers measured at the point of enrollment, so these significant associations did not directly reflect future cardiovascular disease and mortality. Therefore follow-up period is required to reveal the prognostic meanings for cardiovascular outcomes about central

hemodynamics. Second, the present study included a relatively small numbers of subjects limited one center. A large number of patients enrolled by multicenter should be analyzed for confirmation of our result about CKD population. Third, information of CBP is that derived from automated radial artery tonometry indirectly, that is not accepted as standardized method for measurement of CBP. However, many studies revealed that CBP from radial automated tonometry showed excellent correlation with direct measured CBP.[33] Nevertheless, our study was meaningful in that is the first study for evaluation of relationships between CBP and target organ damage markers compared with PBP depending on degree of renal impairment, and was the review of the clinical significance of CBP in patients with renal impairments.

V.CONCLUSION

Central SBP and PP were significantly associated with markers for target organ damage in CKD patients. In this study, central SBP has stronger associations with PWV and CCS compared with peripheral SBP in CKD patients. However, CBP is not superior to PBP for predicting CVD risk in ESRD patients. Therefore, degree of renal impairment and dialysis therapy should be considered in application of CBP and PBP.

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ABSTRACT (IN KOREAN)

만성 신부전 환자에서 중심 혈압과 표적기관 손상 예측인자와의 연관성 : 중심 혈압과 말초 혈압의 비교

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기 연 경

배경 고혈압은 만성 신부전 환자에서 잘 알려진 심혈관 질환 위험 인자이며, 만성 신부전 환자의 사망률과 밀접하게 관련되어 있다. 최근 여러 연구들에서 중심혈압이 심혈관 질환의 중요한 예측인자이며 혈관 강성 및 석회화와 같은 혈관손상과 밀접하게 관련이 있음을 보여 주었다. 따라서 본 연구에서는 말기 신부전 환자를 포함한 만성 신부전 환자에서 신기능에 따른 맥파 속도와 관상 동맥 칼슘 지수로 측정된 표적기관 손상 예측인자들과 중심 혈압 또는 말초 혈압과의 연관성에 대해 분석하였다.

방법 연세 대학교 의과대학의 심뇌혈관 및 대사질환 원인 연구 센터에 2013년 11월부터 2015년 5월까지 등록된 환자들을 대상으로 연구를 진행하였다. 이들 환자에서 만성 신부전의 단계에 따른 중심 또는 말초 혈압 측정값 (수축기 혈압과 맥압)과 맥파 속도 및 관상동맥 칼슘 지수로 측정된 표적기관 손상 예측 인자들과의 연관성에 대해 분석하였다.

결과 총 424명의 만성 신부전 환자 중 248 (58.4%)이 남성이었으며 평균 나이는 59세였다. 전체 환자에서 평균 중심 수축기 혈압 및 맥압은 각각 132.7과 54.8 mmHg 이었으며, 평균 말초 수축기 혈압 및 맥압은 135.7과 58.2 mmHg 이었다. 중심 수축기 혈압 및 맥압은 진행된 만성 신부전에서 유의하게 더 높은 값을 보여 주었다. 전체 만성 신부전 환자

에서 중심 및 말초 수축기 혈압과 표적기관 손상 예측인자들간에는 유의한 연관성을 보여 주었으며 (맥압 r = 0.424 vs 0.361; 관상동맥 칼슘 지수 0.262 vs 0.196, all p < 0.001), 특히 중심 수축기 혈압의 경우 말초 수축기 혈압과 비교하여 표적기관 손상 예측인자들과 유의하게 더 강한 상관관계를 보여 주었다. (맥압 Z = 2.050, P = 0.040; 관상동맥 칼슘 지수 Z = 2.210, P = 0.044) 만성 신부전 단계에 따라 중심 혈압과 표적기관 손상 예측인자와의 연관성에 대해 살펴 보면, 중심 수축기 혈압과 제시된 표적기관 손상 예측인자들은 조기 만성 신부전에서 말초 혈압과 비교하여 더 강한 연관성을 보여 주었다. 그러나 말기 신부전 환자에서는 말초 혈압과 비교하여 중심 혈압은 표적기관 손상 예측인자들과 더 나은 연관성을 보여주지 못하였다.

결론 만성 신부전 환자에서 중심 수축기 혈압과 맥압은 표적기관 손상 예측인자와 유의하게 연관성이 있다. 그리고 중심 수축기 혈압은 말초 수축기 혈압과 비교하여 맥파 속도 및 관상 동맥 칼슘 지수와 더 강한 연관성을 보여준다. 그러나 말기 신부전 환자에서 중심 혈압은 표적기관 손상 예측하는 데 있어 말초 혈압보다 더 우수한 결과를 보여주지는 못하였다. 따라서 중심 혈압과 말초 혈압의 임상적인 적용에 있어 신기능의 저하 정도 및 투석 여부에 대한 고려가 필요하다.

핵심 되는 말 : 만성 신부전, 중심 혈압, 맥파 속도, 관상 동맥 칼슘 지수