Association of Pulse Wave Velocity and Pulse Pressure With Decline in Kidney Function

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The association between arterial stiffness and decline in kidney function in patients with mild to moderate chronic kidney disease (CKD) is not well established. This study investigated whether pulse wave velocity (PWV) and pulse pressure (PP) are independently associated with glomerular filtration rate (GFR) and rapid decline in kidney function in early CKD. Carotid femoral PWV (cfPWV), brachial-ankle PWV (baPWV), and PP were measured in a cohort of 913 patients (mean age, 63±10 years; baseline estimated GFR, 84±18 mL/min/1.73 m^2). Estimated GFR was measured at baseline and at follow-up. The renal outcome examined was rapid decline in kidney function (estimated GFR loss, >3 mL/min/1.73 m^2 per year). The median follow-up duration was 3.2 years. Multivariable adjusted linear regression model indicated that arterial PWV (both cfPWV and baPWV) and PP increased as estimated GFR declined, but neither was associated with kidney function after adjustment for various covariates. Multivariable logistic regression analysis found that cfPWV and baPWV were not associated with rapid decline in kidney function (odds ratio [OR], 1.39, 95% confidence interval [CI], 0.41–4.65; OR, 2.51, 95% CI, 0.66–9.46, respectively), but PP was (OR, 1.22, 95% CI, 1.01–1.48; *P*=.045). Arterial stiffness assessed using cfPWV and baPWV was not correlated with lower estimated GFR and rapid decline in kidney function after adjustment for various confounders. Thus, PP is an independent risk factor for rapid decline in kidney function in populations with relatively preserved kidney function (estimated GFR ≥30 mL/min/1.73 m^2). *J Clin Hypertens (Greenwich).* 2014;16:372–377.

In patients with chronic kidney disease (CKD), cardiovascular disease is twice as common as it is in the general population,[1] and the burden of cardiovascular disease risk factors is high among CKD patients. Thus, early detection of decreasing kidney function and appropriate interventions are important for improving cardiovascular outcomes. Hypertension and diabetes are well-established risk factors for end-stage renal disease in individuals with preserved kidney function.[2] Considerable data are available on the association between nontraditional risk factors and declining kidney function in CKD patients.[3–6] Arterial stiffness increases progressively with decline in renal function.[7] Further, arterial stiffness as measured by carotid-femoral pulse wave velocity (cfPWV), a measure of aortic stiffness, and brachial-ankle pulse wave velocity (baPWV), a measure of both central and peripheral arterial stiffness, are associated with increased cardiovascular mortality and has been identified as a potential nontraditional risk factor for CKD.[6–9] In addition, increased pulse pressure (PP), which is thought to reflect arterial stiffness, has emerged as an independent determinant of decline in renal function in hypertensive patients.[10,11]

Increased arterial stiffness may reduce the cushioning function of the arteries and may attenuate pulsations from the heart; this damages renal endothelial and smooth muscle cells and disrupts the function of vessels, leading to a decline in kidney function.[12] However, in mild and moderate CKD, the relationship between arterial stiffness and renal function decline remains controversial. Several studies have reported that in early CKD, increased arterial stiffness and decline in glomerular filtration rate (GFR) show a strong association.[6,7,13–15] On the other hand, other studies have reported that PWV is not associated with decline in GFR in early CKD.[5,16–21] Therefore, in a cohort of patients with relatively preserved kidney function, we investigated whether arterial stiffness is associated with GFR and attempted to identify which component of arterial stiffness affects decline in kidney function.

METHODS

Participants

This retrospective study recruited 934 participants who underwent PWV testing between December 2005 and August 2010 (age, 18–86 years; mean, 62.5 years) at Chonnam National University Hospital. The medical records and laboratory results of these patients were reviewed. Subsequently, 16 participants with estimated GFR values <30 mL/min/1.73 m^2 and end-stage renal disease (patients with a history of hemodialysis, peritoneal dialysis, or kidney transplantation), one participant who did not have sufficient laboratory data, and 4 participants with atrial fibrillation and uncontrolled ventricular response were excluded. Additionally, among the total of 934 participants, 12 (1.3%) died.

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However, since data regarding rapid decline in kidney function had been assessed every year until their death, their data were included in the statistical analyses. Thus, 913 participants (521 men and 392 women) were finally included in the analysis. The study protocol was approved by the institutional review board of Chonnam National University Hospital, who also waived the need for informed patient consent. Further, the study was conducted according to the principles of the Declaration of Helsinki.

Assessment of Renal Function

Serum creatinine levels were analyzed using the Jaffe method calibrated for isotope dilution mass spectrometry. The estimated GFR was calculated at baseline and at follow-up using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows: GFR in mL/min/1.73 m^2=141 × minimum (creatinine/κ, 1) α × maximum (creatinine/κ, 1) − 1.209 × 0.993 age × 1.018 (if female) × 1.159 (if black), where κ is 0.7 for women and 0.9 for men and α is −0.329 for women and −0.411 for men.[22]

PWV and PP

The baPWV value was automatically determined using the oscillometric method with a volume plethysmography apparatus (VP-1000; Collin Co, Komaki, Japan).[23] In brief, participants attached cuffs around both arms and ankles after having rested for at least 5 minutes in the supine position. To calculate baPWV, pulse waves obtained simultaneously from the brachial and tibial arteries were recorded, and the transmission time was defined as the time interval between the initial increase in brachial and tibial waveforms. The transmission distance from the arm to each ankle was calculated according to body height. The baPWV value was automatically computed as the transmission distance divided by the transmission time. For the analysis, mean values for baPWV on both sides (ie, [value measured on the right side + value measured on the left side]/2) were used. Similarly, cfPWV was calculated using pulse waves and transmission distance recorded from the carotid and femoral arteries. The distance between the carotid and femoral sampling sites was also calculated according to body height.

Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured as the average of two measurements after a minimum of 5 minutes rest in the sitting position, using a calibrated oscillometric device (BP-203RV III; Omron Co, Kyoto, Japan). PP was defined as SBP minus DBP from the average of the two measurements.

Outcomes

Rapid decline in kidney function was defined as an estimated GFR decrease of >3 mL/min/1.73 m^2 per year, since prior studies have demonstrated that this rate is associated with increased cardiovascular morbidity and mortality, independent of the baseline estimated GFR.[24,25]

Statistical Analyses

We divided participants into 3 groups using the category of the baseline estimated GFR (≥90, 89–60, and 59–30 mL/min/1.73 m^2) and compared the demographic characteristics and covariates using the Pearson chi-square test for categorical variables and analysis of variance and the Kruskal-Wallis test for continuous variables as appropriate. Continuous variables are presented as mean±standard deviation or as medians with interquartile (25th and 75th percentiles) ranges for parametric and nonparametric variables, and categorical variables are presented as the number of patients and percentage. Pearson's test was used to evaluate the correlation between normally distributed univariate variables and estimated GFR. Spearman's test was used if the distribution was not normal. Partial correlations were used to correct for age. Multivariable linear regression was used to evaluate the association of baseline cfPWV, baPWV, and PP with baseline estimated GFR. Additionally, multivariable logistic regression was used to evaluate the association of baseline cfPWV, baPWV, and PP with rapid decline in kidney function. The variables for adjustment were selected on the basis of factors known to be associated with arterial stiffness and the results of the statistically significant univariate analysis ($P<.05$). Model 1 was adjusted for age and sex. Model 2 was adjusted for model 1 variables plus mean arterial pressure; diabetes mellitus; cerebrovascular disease; smoking; ejection fraction; levels of hemoglobin, uric acid, high-sensitivity C-reactive protein (hs-CRP), and low density lipoprotein (LDL) cholesterol; and use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or statins. Because the PWV variables showed nonparametric distribution, they were natural log-transformed for linear and logistic regression analyses. Linear regression results were reported as a decline in estimated GFR (mL/min/1.73 m^2) per doubling of PWV, which was used as an explanatory variable (transformation B × ln[2]). All statistical tests were two-tailed, and $P<.05$ was considered significant. The analyses were performed using SPSS, version 17.0 (SPSS, Chicago, IL).

RESULTS

The mean age of the 913 participants was 62.5±10 years; 521 (57.1%) were men, and the mean baseline estimated GFR was 83.7±18 mL/min/1.73 m^2. The median follow-up duration was 3.2 years. The clinical characteristics of the study participants are given in Table I according to the category of the baseline estimated GFR. Diabetes mellitus; high DBP; cerebrovascular disease; history of smoking; and use of ACE inhibitors, ARBs, statins, aspirin, and insulin tended to be more frequent in participants with low estimated GFR. As the estimated GFR decreased, the cfPWV, baPWV, and PP increased. However, the ejection fraction was significantly lower in participants with low estimated GFR.

TABLE I. Clinical Characteristics of the Study Participants Categorized According to the Baseline Estimated GFR

	Estimated GFR, mL/min/1.73 m^{2a}				
	≥90 (n=370)	89 to 60 (n=443)	59 to 30 (n=100)	*P* Value	Linea *P* Value
Age, y	57.3±9.5	65.0±8.9	70.6±7.4	<.001	
Male sex, %	50.3	59.4	72.0		<.001
Hypertension, %	95.1	94.3	100		.204
Diabetes mellitus, %	17.0	27.7	37.6		<.001
Dyslipidemia, %	10.8	13.6	9.9		.710
Body mass index, kg/m^2	24.2±2.9	24.5±2.8	24.3±2.8	.393	
Heart rate, beats per min	66.7±10.6	67.3±12.4	69.8±14.6	.061	
Systolic blood pressure, mm Hg	125±17	125±18	124±21	.921	
Diastolic blood pressure, mm Hg	76±11	75±11	72±11	.008	
Mean arterial pressure, mm Hg	92±12	91±12	89±14	.143	
Coronary artery disease, %	42.8	48.2	49.5		.112
Cerebrovascular disease, %	2.7	7.7	14.9		<.001
Smoking, %	27.9	31.8	40.6		.018
Heart failure, %	0.0	1.8	1.0		.062
Pulse pressure, mm Hg	49.3±10.1	50.1±12.1	52.7±15.3	.041	
cfPWV, cm/s	899 (814, 1029)	982 (858, 1130)	1047 (940, 1229)	<.001	
baPWV, cm/s	1429 (1277, 1600)	1495 (1325, 1700)	1585 (1363, 1820)	<.001	
Estimated GFR, mL/min/1.73 m^{2a}	100.0±7.4	78.0±8.5	48.8±8.0	<.001	
Ejection fraction, %	66.1±6.5	64.7±7.9	63.5±9.4	.002	
Hemoglobin, g/dL	13.7±1.5	13.5±1.6	12.7±1.9	<.001	
Uric acid, mg/dL	4.7±1.3	5.3±1.5	6.4±1.7	<.001	
hs-CRP, g/L	0.48 (0.23, 1.08)	0.66 (0.29, 1.76)	0.97 (0.40, 2.54)	<.001	
LDL cholesterol, mg/dL	107.2±35.6	104.1±33.0	96.0±31.4	.028	
Medications					
ACE inhibitor or ARB, %	53.4	59.5	63.8		.005
Calcium channel blocker, %	54.5	55.1	47.5		.403
β-Blocker, %	39.6	41.2	52.5		.051
Statins, %	66.4	71.1	76.2		.037
Aspirin, %	65.3	74.9	80.2		<.001
Insulin, %	12.1	10.1	45.0		.008
Biguanide, %	21.2	15.9	25.0		.873
Sulfonylurea, %	81.8	81.2	65.0		.202
TZD, %	3.0	2.9	0.0		.543

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; baPWV, brachial-ankle pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; TZD, thiazolidinedione. [a]Estimated glomerular filtration rate (GFR) calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation.

Correlation and Association Between Arterial Stiffness and Baseline Estimated GFR

Table II shows arterial stiffness components that were correlated with baseline estimated GFR. Age, uric acid level, PP, cfPWV, and baPWV were inversely correlated with baseline estimated GFR, while the ejection fraction was directly proportionate to the estimated GFR. After adjustment for age, which could strongly influence kidney function, the significant negative correlation between PP, cfPWV, and baPWV and estimated baseline GFR disappeared.

Table III shows the results of the multivariable linear regression analyses performed to evaluate the association of arterial stiffness with baseline kidney function, with and without adjustments. High cfPWV, baPWV, and PP values were significantly associated with a lower baseline estimated GFR before adjustments. However, no significant correlation was found between cfPWV, baPWV, or PP and the baseline estimated GFR after adjustment for only age or various covariates (including age; sex; mean arterial pressure; diabetes mellitus; cerebrovascular disease; smoking history; ejection fraction; levels of hemoglobin, uric acid, hs-CRP, LDL cholesterol; and use of ACE inhibitors, ARBs, or statins). In this context, age may have been the most significant factor, as it eliminated the significance of the association between arterial stiffness and baseline kidney function.

Association of Arterial Stiffness With Rapid Decline of Kidney Function

A total of 210 (23%) participants in this study showed rapid decline in kidney function. Multivariable logistic regression models were used to evaluate the association

TABLE II. Correlation of Various Covariates With Baseline Estimated GFR

	Total Cohort (Unadjusted)		Total Cohort (Adjusted for Age)	
	r	*P* Value	*r*	*P* Value
Age, y	−0.546	<.001	–	–
MAP, mm Hg	0.045	.176	0.006	.859
BMI, kg/m^2	−0.576	.085	−0.105	.004
Ejection fraction, %	0.073	.029	0.110	.003
Uric acid, mg/dL	−0.317	<.001	−0.385	<.001
Pulse pressure, mm Hg	−0.076	.021	−0.010	.793
cfPWV, cm/s	−0.317	<.001	−0.065	.058
baPWV, cm/s	−0.223	<.001	−0.011	.744

Abbreviations: BMI, body mass index; baPWV, brachial-ankle pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; GFR, glomerular filtration rate; MAP, mean arterial pressure. *r*=correlation coefficient. For adjusted values, partial correlations were used.

TABLE III. Association of PWV and PP With Baseline Kidney Function Indicated by Estimated GFR

	B Value (95% Confidence Interval)	R^2	*P* Value
Unadjusted			
Pulse pressure, 10 mm Hg	−1.090 (−2.557 to −0.589)	0.011	.002
cfPWV, cm/s[a]	−18.43 (−22.30 to −13.93)	0.094	<.001
baPWV, cm/s[a]	−15.07 (−19.33 to −10.81)	0.050	<.001
Age-adjusted			
Pulse pressure, 10 mm Hg	−0.049 (−0.917 to 0.777)	0.292	.871
cfPWV, cm/s[a]	−3.406 (−7.347 to 0.534)	0.290	.090
baPWV, cm/s[a]	0.177 (−3.875 to 4.230)	0.292	.932
Fully adjusted[b]			
Pulse pressure, 10 mm Hg	−0.222 (−1.402 to 0.763)	0.423	.562
cfPWV, cm/s[a]	−3.234 (−7.950 to 1.483)	0.407	.179
baPWV, cm/s[a]	−1.273 (−6.433 to 3.887)	0.424	.628

Abbreviations: baPWV, brachial-ankle pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; PP, pulse pressure; PWV, pulse wave velocity. [a]Continuous log-transformed. B values represent a decline in estimated glomerular filtration rate (GFR) (mL/min/1.73 m^2) per doubling of pulse wave pressure. [b]Adjusted for age; sex; mean arterial pressure; diabetes mellitus; cerebrovascular disease; smoking history; ejection fraction; levels of hemoglobin, uric acid, high-sensitivity C-reactive protein, and low-density lipoprotein cholesterol; and medication with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins. B=unstandardized coefficient.

between arterial stiffness and this rapid decline in kidney function (Table IV). In the age- and sex-adjusted model 1, high cfPWV and baPWV were significantly associated with the rapid decline in estimated GFR, but the association disappeared in model 2, in which further adjustments were made for comorbidities and medications. However, a significant association was found between PP and rapid decline in kidney function despite all these adjustments (odds ratio, 1.22; 95% confidence interval, 1.01–1.48; *P*=.045). LDL cholesterol was the most significant confounding factor that influenced the significance of the association between PWV or PP and rapid decline in kidney function in model 2.

DISCUSSION

In the present study in a cohort of participants with relatively preserved kidney function, we found that although arterial PWV (both cfPWV and baPWV) and PP increased as the estimated GFR declined, these changes did not remain associated with kidney function after adjustments for various covariates. In addition, although no association was found between high arterial PWV and rapid decline in kidney function (estimated GFR <−3 mL/min/1.73 m^2 per year) after adjustments, a high PP remained associated with rapid kidney function decline.

With regard to the relationship between arterial stiffness and baseline kidney function, our results are in line with those of a previous study, which found no difference in the cfPWV among different stages of CKD and no correlation between cfPWV and the estimated GFR across CKD stages 2 through 5.[26] One finding that is different, however, is that some of the participants in the present study had relatively preserved kidney function (estimated GFR ≥30 mL/min/1.73 m^2). We evaluated the baPWV (indicating central and peripheral arterial stiffness) as well as cfPWV (indicating aortic stiffness), and neither showed any association with the baseline estimated GFR and rapid decline in kidney function in this population.

Our results are consistent with those of previous studies that have evaluated the association of arterial stiffness with decline in kidney function. In a study of 329 patients with stage 3 or 4 CKD (mean estimated GFR=39±18 mL/min/1.73 m^2) with an average age of 64±17 years, the baseline PP was found to be the only predictor of decline in kidney function.[27] In another recent study that included 2129 elderly patients (mean age, 74±4 years) who had a mean estimated GFR of 79±29 mL/min/1.73 m^2, kidney function was assessed using cystatin C, an accurate biomarker. In that study, PP was found to be a risk factor associated with rapid decline in kidney function, but cfPWV showed no association with rapid decline in kidney function.[20] Further, in a large multiethnic cohort, high PP and low arterial elasticity were found to be associated with rapid decline in kidney function with estimated GFR ≥60 mL/min/1.73 m^2, but this study did not evaluate arterial PWV.[28] McIntyre and colleagues[21] examined 1717 elderly patients with stage 3 CKD and found no independent negative association between estimated GFR and increased cfPWV. Similarly, in the longitudinal analysis in the Framingham Heart Study, arterial

TABLE IV. Association of PWV and PP With Rapid Decline in Kidney Function (Renal Outcome)

	Odds Ratio (95% Confidence Interval)		
	Unadjusted	Model 1	Model 2
Estimated GFR <−3 mL/min/1.73 m^2/y			
Pulse pressure, per 10 mm Hg	1.32 (1.15–1.50)[b]	1.31 (1.14–1.50)[b]	1.22 (1.01–1.48)[b]
cfPWV[a]	2.62 (1.18–5.82)[b]	2.36 (0.93–5.98)	1.39 (0.41–4.65)
baPWV[a]	4.27 (1.78–10.22)[b]	4.01 (1.52–10.56)[b]	2.51 (0.66–9.46)

Abbreviations: baPWV, brachial-ankle pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; GFR, glomerular filtration rate; PP, pulse pressure; PWV pulse wave velocity. [a]Continuous log-transformed. [b]$P<.05$. Model 1: adjusted for age and sex. Model 2: adjusted for age; sex; mean arterial pressure; diabetes mellitus; cerebrovascular disease; smoking; ejection fraction; levels of hemoglobin, uric acid, high-sensitivity C-reactive protein, and low-density lipoprotein cholesterol; and medication with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins.

stiffness, including cfPWV, was found to be correlated with albuminuria but not CKD progression.[19] Another study showed that only increased PP was associated with rapid decline in kidney function in 180 patients with CKD (mean estimated GFR, 32 mL/min/1.73 m^2).[4] Taken together with our study's findings, the results indicate that high PP is a possible cause of deteriorating kidney function across a large cohort showing wide age variation and relatively preserved kidney function.

Several studies have shown that increased arterial stiffness (cfPWV and/or baPWV) is not only correlated with impaired kidney function but also with rapid decline in kidney function.[13,14] In a study of 120 patients with mean estimated GFR=32±11 mL/min/1.73 m^2 and an average age of 69±12 years, aortic stiffness (cfPWV) was found to be independently associated with change in kidney function (≥25% decline in kidney function or start of renal replacement therapy); however, the sample size in this observational study was small.[13] Another recent study of 2050 Japanese patients (mean age, 40±8 years) with estimated GFR ≥60 mL/min/1.73 m^2 showed that elevated baPWV was associated with lower estimated GFR and was an independent risk factor for decline in kidney function. However, the study enrolled younger participants than those in our study.[14] Indeed, after adjustment for age, the correlation between arterial stiffness and estimated GFR disappeared in the present study. Although several data show that arterial stiffness increases with decreasing estimated GFR, this relationship varies considerably in CKD patients with relatively preserved kidney function. This variation could be attributed to differences in the study populations, particularly with respect to age.

Even though arterial PWV and PP reflect arterial stiffness, the reason for their different effects on rapid decline in kidney function is unclear. Arterial PWV measured using the flow velocity of waves traveling to and from reflecting sites is used as a marker of arterial stiffness.[29] Thus, increased arterial PWV implies poor buffering of the pulsation pressure induced during ventricular pumping and results in an increase in the PP. Consequently, high PP is related to kidney function more strongly than just an increase in the arterial PWV, since it is the physiological outcome of increased arterial stiffness. In addition, PP is influenced not only by arterial stiffness but also non–stiffness-related factors (such as left ventricular contractility, pattern of left ventricle ejection, and competence of the aortic valve).[20]

Several mechanisms may underlie the effect of high PP on kidney function. The unique structure of renal microcirculation, in which glomerular capillaries are positioned between afferent and efferent arterioles, increases susceptibility to injury when PP is high. Because efferent arteriolar resistance is higher than afferent resistance, the mean and pulsation pressure in the glomerulus is relatively higher than those in other microvessels. Under normal conditions, a combination of myogenic reflexes in the afferent arteriole and tubuloglomerular feedback regulating afferent arteriole vasoconstriction and vasodilatation mediates GFR autoregulation across a wide range of pulsation pressures. However, the autoregulatory systems are altered by the chronically increased pulsation pressure, caused by high mean arterial pressure.[30,31] Taken together, the findings indicate that a long-term increase in PP may result in higher dissipation of pulsation energy in the microcirculation, which leads to kidney microcirculation remodeling and glomerular dysfunction.[12,29]

STUDY LIMITATIONS AND STRENGTHS

There are several limitations to our study. First, although we tried to include most confounders in the adjustments, some may have not been assessed. Nonetheless, antihypertensive medications, which affect mean arterial pressure, were included in the analysis. Second, our results may not be generalized to patients with severely decreased kidney function. Third, because we measured arterial stiffness only once, we could not completely evaluate the bidirectional relationship between changes in arterial stiffness and kidney function. Fourth, this study was performed retrospectively and we were unable to draw any definite conclusions regarding the association or causal relationship between arterial stiffness and renal outcomes. Finally, we could not collect detailed data on albuminuria in the participants, which may affect kidney function.

Our study has some strengths as well. First, we evaluated the association between arterial stiffness and kidney function using two measures, namely cfPWV and baPWV, which reflected aortic and peripheral stiffness. Second, our study population included participants of varying ages with relatively preserved basal kidney function (estimated GFR ≥30 mL/min/1.73 m^2), characteristics commonly seen in clinical practice. Finally, we used the recently validated CKD-EPI equation to calculate estimated GFR, while most previous studies use the Modification of Diet in Renal Disease equation.

CONCLUSIONS

Arterial stiffness assessed using cfPWV and baPWV was not correlated with estimated GFR and rapid decline in kidney function after adjustments for various confounders. However, PP was found to be an independent risk factor for rapid decline in kidney function in our study population with relatively preserved kidney function. These findings highlight the difficulty in interpreting the association between measures of arterial stiffness and changes in estimated GFR.

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