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ARTICLE

# Relationship between arterial stiffness and chronic kidney disease in patients with primary hypertension

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## Abstract

To investigate the association of noninvasive indices of arterial stiffness with chronic kidney disease (CKD) in patients with primary hypertension, 547 (mean age 60 years, 63% males) hypertensive hospital inpatients were recruited, comprising 337 hypertensives without CKD and 210 hypertensives with CKD. Noninvasive arterial stiffness indices were obtained, including central arterial haemodynamics derived from the radial artery waveform using SphygmoCor V8.0 system, carotid-femoral pulse wave velocity (cfPWV), large and small artery elasticity indices (C1, C2 respectively). Intima-media thickness (IMT) was evaluated by ultrasonography. The diagnosis of CKD was assessed by the estimated glomerular filtration rate (eGFR) or urinary albumin creatinine ratio (ACR). Compared with hypertension without CKD, hypertensive patients with CKD were older, had higher central systolic blood pressure, cfPWV, and IMT (all $P < 0.01$). With decreasing eGFR, cfPWV and augmentation index adjusted to heart rate of 75 bpm increased progressively whereas C2 decreased ($P < 0.05$) in subjects with CKD. In the overall population, cfPWV showed a significant trend of a negative association with eGFR ($P = 0.04$) after adjusting for age, gender, and brachial systolic blood pressure. Multiple logistic analysis showed that 1 SD (3 m/s) increase in cfPWV entailed a 1.35 (95% Cl: 1.018–1.790) times higher likelihood of the presence of CKD even after adjustment for confounding factors. The association of arterial stiffness and CKD suggests that cfPWV may be a potential hemodynamic index to evaluate cardiovascular risk in CKD patients with primary hypertension.

## Introduction

The risk of fatal or nonfatal cardiovascular events in patients with chronic kidney disease (CKD) is much higher than for progression to end-stage renal disease [1, 2]. A significant contribution to this may be the role of non-traditional risk factors including arterial stiffening [3, 4]. The damage to function and structure of large arteries is an early vascular change caused by many cardiovascular risk factors such as hypertension and CKD [5].

It has been shown that there is a complex relationship between CKD and arterial stiffness [6]. High-volume pulsatile flow constantly keeps the kidneys passively infused. Therefore, the renal parenchyma is particularly susceptible to changes in diastolic blood pressure and systolic blood pressure caused by an increase in arterial stiffness. Aortic stiffness may result in excessive flow pulsatility to the renal microcirculation, and transmission of excessive flow pulsatility into the susceptible renal microvasculature may contribute to lower GFR [7]. In addition, changes in blood pressure variability caused by increased arterial stiffness may also lead to the development of renal injury [8].

Numerous noninvasive measurements to assess arterial stiffness have been developed over the past decades. In particular, carotid-femoral pulse wave velocity (cfPWV) is considered as a gold-standard measure of aortic stiffness and is suggested to represent a cumulative measure of the damaging effects of cardiovascular risk factors on the arterial wall with aging, especially in persons over 40 years

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**Table 1** Indices of arterial stiffness

| Index | Description | Measurement/device | Characteristics |
|---|---|---|---|
| cfPWV | Carotid–femoral PWV | Complior SPIV | Arterial function, aortic stiffness |
| CAP | Central arterial pressure | SPhygmoCor-Px V8.0 | Central haemodynamics, left ventricular load |
| AIx | Aortic pressure augmentation index | computed from the augmentation of AP | Wave reflection, arterial stiffness |
| C1 | Large artery elasticity index | CVProfilor DO-2020, HDI | Large artery compliance |
| C2 | Small artery elasticity index | CVProfilor DO-2020, HDI | Small artery compliance |

of age [9]. The purpose of this study was to evaluate the difference in indices of vascular stiffness in hypertensive patients with and without CKD.

## Materials and methods

A total of 547 hypertensive inpatients (mean age 60 ± 10 years) were recruited between 2007 and 2008 from the Hypertension Department, Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine. Patients in this study are those without acute heart failure or myocardial infarction admitted to hospital for diagnosis and treatment of primary, secondary, and resistant hypertension. Inclusion criteria included three consecutive measurements of office systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg after resting in a supine position for 5 min, or the use of antihypertensive drugs in the absence of secondary forms of hypertension. Exclusion criteria were clinical or laboratory evidence of acute cardio-cerebrovascular disease within the previous 3 months, any life-threatening disease, any condition preventing the technical quality of arterial stiffness monitoring, such as atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia. All patients underwent a standardized questionnaire for collection of information on medical history, smoking habits, and the use of medications. Serum total cholesterol, high-density lipoprotein cholesterol, triglycerides, blood glucose, serum creatinine, and urinary albumin creatinine ratio (ACR (single measurements) were extracted from patient records (~9% of blood glucose data were missing). All noninvasive measurements, including blood pressure, pulse wave analysis, and arterial stiffness measures were made by trained investigators while patients were in the hospital. The study protocol was reviewed and approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine. All patients provided written informed consent.

### Definition of chronic kidney disease

The definition and the diagnostic criteria for chronic kidney disease were proposed in the K/DOQI guidelines: estimated glomerular filtration rate (eGFR < 60 ml/min/1.73 $m^2$) calculated by the MDRD formula [10] or urinary albumin/creatinine ratio (ACR > 3.5 mg/mmol in females and >2.5 mg/mmol in males) were used to screen hypertensive patients with CKD. Individuals with acute kidney injury were excluded.

### Indices of arterial stiffness

#### Carotid-femoral pulse wave velocity (cfPWV)

Patients fasted overnight, and no caffeine beverage or smoking was allowed within 3 h of the measurement (Table 1). cfPWV was measured automatically using two mechanotransducers (Complior SPIV, France). cfPWV was calculated as the ratio of the direct distance between the carotid and femoral sites of measurements and pulse transit time calculated as a direct delay between the two waves [11]. Following the measurement of office blood pressure, the carotid and femoral arterial waveforms at the patient's right side were recorded by applanation tonometry sequentially a short time apart by trained investigators.

#### Measurement of arterial elasticity

The large arterial elasticity index (C1) and small artery elasticity index (C2) were measured by the HDI system DO-2020 (CVProfilor, HDI, USA) using pulse contour methodology and fitting a mathematical model to estimate central large artery (C1) and small artery peripheral (C2) compliances from the peripheral pulse at the wrist obtained by radial tonmetry [12–14]. In the supine position, the right arm was fixed, and the probe was fixed at the strongest point of radial artery pulsation. The pulse pattern and maximum signal intensity were obtained. The blood pressure of left upper arm was measured synchronously. After recording the pulse wave for 30 s, brachial systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, pulse pressure, pulse rate, C1 (mL/mmHg × 10) and C2 (mL/mmHg × 100) were provided automatically by the HDI system.

### Pulse wave analysis

Pulse wave analysis was performed using applanation tonometry of the radial artery (SPhygmoCor-Px V8.0, AtCor Medical, Sydney, Australia). Participants were placed in supine position with the right upper limb in external rotation and 45° to the trunk. The probe was placed at the strongest point of the right radial artery pulsation. Radial artery pulses were recorded for at least 12 s. The computer automatically converted the peripheral pulse wave to a central aortic pressure pulse using a validated transfer function [15] and then generated central systolic pressure (CSBP), central diastolic pressure (CDBP), central pulse pressure (CPP), central augmented pressure (CAP), central augmentation index (AIx), and AIx adjusted to heart rate of 75 bpm (AIx@HR75).

### Intima-media thickness (IMT)

The IMT of carotid arteries was examined bilaterally using high-resolution echocardiography Doppler ultrasound (HD11EX Ultrasound; Philips Medical Systems, Andover, MA, USA) with a broad-band linear array transducer (multiple frequency: 4–12 MHz). IMT was measured on both the left and right common carotid artery starting ~1.5 cm proximal to the carotid artery bulb. Three recordings were taken and the mean value was calculated for each side.

## Statistical analysis

All analyses were performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA). A two-sided $P < 0.05$ was considered statistically significant. Continuous variables are expressed as mean ± SD. Pearson's and partial correlation (adjusted for age, sex, brachial systolic blood pressure) were used to assess the relations between arterial stiffness and eGFR or ACR. Differences in indices of arterial stiffness between patients with or without CKD were estimated by means of independent samples *t* test. The association of arterial stiffness indices with eGFR stratified for different stages of CKD was assessed by means of one-way analysis of variance (ANOVA). Association between the arterial stiffness indices with the presence of CKD was assessed by means of logistic regression analysis (backward likelihood ratio (LR)) adjusted for age, sex, height, smoking, and body mass index, use of antihypertensive drugs, total cholesterol, triglycerides, fasting blood glucose, heart rate, and brachial pulse pressure (BPP).

# Results

## Population characteristics

A total of 547 hypertensive patients comprised of 337 patients without CKD and 210 patients with CKD (37% with eGFR < 60 ml/min/1.73 $m^2$ and 77% with ACR abnormality). ACR was skewed so Log ACR for the logistic regression. Other skewed parameters such as triglycerides and duration of HT (Table 2) and C1 and C2 (Table 3) provided medians and interquartile range (IQR). However, eGFR was normal distribution. Compared with hypertensive patients without CKD, hypertensive patients with CKD group were older ($P < 0.001$), had longer duration of hypertension ($P < 0.001$), higher urine protein/creatinine level ($P < 0.01$) and lower eGFR level ($P < 0.05$) (Table 2). Table 3 shows the difference in arterial stiffness indices between two groups. BPP, CPP, cfPWV and IMT were significantly higher in the hypertensive group with CKD than in the group without CKD ($P < 0.01$) and C2 was significantly lower ($P < 0.01$). Comparing arterial stiffness indices in patients with different stages of CKD, the patients were divided into four groups according to eGFR staging: eGFR-1 to eGFR-4 (with eGFR ≥ 90 mL/min 1.73 $m^2$, 60–90 mL/min 1.73 $m^2$, 30–60 mL/min 1.73 $m^2$, ≤30 mL/min 1.73 $m^2$, respectively). Among them, eGFR-4 ($n = 8$) were merged with stage 3 (eGFR-3) in subjects with CKD. ANOVA showed cfPWV and AIx@HR75 increased progressively while C2 decreased with decreasing eGFR in subjects with CKD, respectively ($P < 0.01$) (Supplementary Table 1). Table 4 shows the antihypertensive medication for both groups of hypertensive patients with and without CKD. The CKD group was prone to having more frequent use of calcium antagonists, diuretics and statin therapy ($P < 0.001$).

## Correlation between the eGFR, LogACR, and arterial stiffness in patients with hypertension

In the overall study population, BPP, CPP, CAIX@HR75, CAP, and cfPWV were all positively correlated with LogACR ($P < 0.05$), whereas C1, C2 were negatively associated with LogAC ($P < 0.05$); BPP, CPP, CAP, cfPWV were all negatively correlated with eGFR ($P < 0.05$), whereas C1 and C2 were positively correlated with eGFR ($r = 0.10$, $P < 0.05$) (Table 5). After adjusting for age, gender, and brachial systolic blood pressure, only cfPWV was negatively but weakly associated with eGFR ($r = -0.092$ $P = 0.04$) but not with LogACR ($r = -0.082$ $P = 0.09$) (Fig. 1).

**Table 2** Characteristics of the study subjects

| Characteristics | Total 547 | Without CKD ($n = 337$) | With CKD ($n = 210$) | $P$ value |
|---|---|---|---|---|
| Age (years) | 59.6 ± 10.3 | 57.9 ± 9.3 | 62.3 ± 11.1 | <0.001 |
| Male gender $n$ (%) | 344 (62.9) | 202 (59.9) | 142 (67.6) | 0.084 |
| Height (cm) | 166.8 ± 7.9 | 166.8 ± 8.0 | 166.8 ± 7.7 | 0.969 |
| BMI (kg/m$^2$) | 25.0 ± 3.2 | 25.0 ± 3.1 | 25.2 ± 3.3 | 0.377 |
| Smokers $n$ (%) | 147 (26.9) | 91 (27.0) | 56 (26.7) | 1.000 |
| Duration of hypertension (years) | 16 (6 – 27) | 14.1 ± 11.9 | 19.9 ± 13.0 | <0.001 |
| Heart rate(bpm/min) | 70.6 ± 10.4 | 70.0 ± 10.4 | 71.6 ± 10.3 | 0.088 |
| Fasting Glucose (mmol/L) | 5.5 ± 1.2 | 5.2 ± 0.6 | 6.0 ± 1.5 | <0.001 |
| Triglycerides (mmol/L) | 2.3 (1.3 – 2.6) | 2.3 ± 5.1 | 2.2 ± 1.3 | 0.739 |
| Total cholesterol (mmol/L) | 4.9 ± 1.0 | 4.9 ± 1.0 | 5.0 ± 1.0 | 0.559 |
| LDL-c (mmol/L) | 2.9 ± 0.8 | 2.9 ± 0.8 | 3.0 ± 0.9 | 0.051 |
| HDL-c (mmol/L) | 1.3 ± 0.9 | 1.3 ± 0.4 | 1.4 ± 1.2 | 0.446 |
| Creatinine (μmol/L) | 86.8 ± 33.8 | 75.1 ± 16.0 | 103.0 ± 43.7 | <0.001 |
| eGFR [mL/(min 1.73 m$^2$)] | 83 (68–97) | 92.3 ± 18.5 | 70.6 ± 23.9 | <0.001 |
| Log ACR (mg/mmol) | 0.4 ± 0.6 | 0.1 ± 0.2 | 0.8 ± 0.6 | <0.001 |
| Diabetes | 82 | 9 (2.7) | 73 (34.6) | <0.001 |

Data from patients without acute heart failure or myocardial infarction admitted to hospital for diagnosis and treatment of primary, secondary and resistant hypertension. Data are mean ± SD or percentage as marked or Median (IQR). $P$ value, independent $t$ test analysis of variance for numeric variables and chi-square test for categorical variables

*BMI* body mass index, *CKD* chronic kidney disease, *LDL-c* low density lipoprotein cholesterol, *HDL-c* high density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *ACR* urinary albumin creatinine ratio

**Table 3** Comparison of arterial stiffness indices between two groups with hypertensions

| Variables | Total ($n = 547$) | Without CKD ($n = 337$) | With CKD ($n = 210$) | $P$ value |
|---|---|---|---|---|
| BSBP (mmHg) | 141.7 ± 20.9 | 137.7 ± 18.2 | 148.1 ± 23.3 | <0.001 |
| BDBP (mmHg) | 81.9 ± 11.7 | 80.7 ± 10.8 | 83.8 ± 12.7 | 0.003 |
| BPP (mmHg) | 59.8 ± 15.6 | 57.1 ± 13.7 | 64.2.1 ± 17.4 | <0.001 |
| CSBP (mmHg) | 129.6 ± 20.0 | 126.2 ± 17.5 | 135.1 ± 22.5 | <0.001 |
| CDBP (mmHg) | 83.2 ± 12.0 | 82.0 ± 11.0 | 85.2 ± 13.1 | 0.003 |
| CPP (mmHg) | 46.4 ± 14.1 | 44.2 ± 12.5 | 49.9 ± 15.7 | <0.001 |
| BPP/CPP | 1.3 ± 0.2 | 1.3 ± 0.2 | 1.3 ± 0.2 | 0.751 |
| CAP (mmHg) | 13.0 ± 7.7 | 12.5 ± 7.3 | 13.8 ± 8.3 | 0.05 |
| AIx@HR75/% | 24.1 ± 9.3 | 24.2 ± 9.2 | 24.0 ± 9.5 | 0.807 |
| C1 [mL/(mmHg × 10)] | 17.4 (10.8 – 21.4) | 17.6 ± 9.6 | 16.9 ± 9.5 | 0.411 |
| C2 [mL/(mmHg × 100)] | 4.3 (2.3 – 5.5) | 4.5 ± 2.9 | 3.9 ± 2.2 | 0.002 |
| cf-PWV (m/s) | 12.5 ± 3.0 | 11.7 ± 2.4 | 13.6 ± 3.4 | <0.001 |
| IMT (mm) | 0.81 ± 0.17 | 0.79 ± 0.16 | 0.84 ± 0.0.17 | 0.004 |

Data are mean ± SD or percentage as marked or Median (IQR). $P$ value: independent $t$ test analysis of variance for numeric variables and chi-square test for categoric variables

*BSBP* brachial systolic blood pressure, *BDBP* brachial diastolic blood pressure, *BPP* brachial pulse pressure, *CSBP* central SBP, *CDBP* central DBP, *CPP* central PP, *CAP* central augmented pressure, *AIx* augmentation index, *AIx@HR75* AIx adjusted to heart rate of 75 bpm, *C1* small artery elasticity index, *C2* large artery elasticity index, *cf PWV* carotid femoral pulse wave velocity, *IMT* intima-media thickness

## Multivariate regression analysis the relationship between the arterial stiffness indices with the presence of CKD

In additional analyses, hypertension with or without CKD was used as a binary variable for further multivariate logistic regression analysis. This analysis showed that 1 SD (3 m/s) increase in cfPWV entailed a 1.35 times higher likelihood of the presence of CKD even after adjustment for various confounding factors and other arterial stiffness indices related to blood pressure. The drug treatment remained significant in the multivariate model ($OR = 5.7$, $P = 0.013$) (Table 6).

**Table 4** Comparison of antihypertensive drugs in the study population with hypertension

| Variable | Total ($n = 547$) | Without CKD ($n = 337$) | With CKD ($n = 210$) | $P$ value |
|---|---|---|---|---|
| Calcium antagonists | 302 (55.2) | 167 (49.6) | 135 (64.3) | <0.001 |
| Angiotensin II receptor antagonists ($n$, %) | 156 (28.5) | 94 (27.8) | 62 (29.5) | 0.697 |
| ACE inhibitors ($n$, %) | 141 (25.6) | 77 (22.8) | 64 (30) | 0.071 |
| Diuretics ($n$, %) | 91 (16.6) | 47 (13.9) | 44 (21) | 0.034 |
| β-blockers ($n$, %) | 129 (23.6) | 72 (21.4) | 57 (27.1) | 0.147 |
| α-blockers ($n$, %) | 16 (3.6) | 9 (3.8) | 7 (3.3) | 1.000 |
| Statins ($n$, %) | 103 (19.1) | 44 (13.4) | 59 (28.1) | <0.001 |
| Antiplatelet drugs ($n$, %) | 93 (17.0) | 49 (14.5) | 44 (20.9) | 0.061 |

*CKD* chronic kidney disease

**Table 5** Relationship between indices of arterial stiffness with LogACR and eGFR in hypertensive patients with CKD

| Variable | Log ACR (mg/mmol) | | eGFR mL/(min 1.73 m$^2$) | |
|---|---|---|---|---|
| | $r$ value | $p$ value | $r$ value | $p$ value |
| BSBP (mmHg) | 0.303 | <0.001 | −0.144 | 0.001 |
| BDBP (mmHg) | 0.229 | <0.001 | −0.064 | 0.154 |
| BPP (mmHg) | 0.236 | <0.001 | −0.144 | 0.001 |
| CSBP (mmHg) | 0.302 | <0.001 | −0.144 | 0.001 |
| CDBP (mmHg) | 0.233 | <0.001 | −0.068 | 0.131 |
| CPP (mmHg) | 0.238 | <0.001 | −0.151 | 0.001 |
| CAP (mmHg) | 0.166 | 0.001 | −0.102 | 0.022 |
| AIx (%) | 0.086 | 0.080 | −0.047 | 0.294 |
| AIx@HR75 | 0.133 | 0.007 | −0.048 | 0.285 |
| BPP/CPP | −0.079 | 0.105 | 0.068 | 0.129 |
| C1/[mL/(mmHg × 10)] | −0.129 | 0.008 | 0.03 | 0.504 |
| C2/[mL/(mmHg × 100)] | −0.164 | 0.001 | 0.106 | 0.018 |
| cf-PWV (m/s) | 0.224 | <0.001 | −0.26 | <0.001 |
| IMT (mm) | 0.066 | 0.191 | −0.157 | 0.001 |

*BSBP*, brachial systolic blood pressure, *BDBP* brachial diastolic blood pressure, *BPP* brachial pulse pressure, *CSBP* central SBP, *CDBP* central DBP, *CPP* central PP, *CAP* central augmented pressure, *AIx* augmentation index, *AIx@HR75* AIx adjusted to heart rate of 75 bpm, *C1* small artery elasticity index, *C2* large artery elasticity index, *cf PWV* carotid femoral pulse wave velocity, *IMT* intima-media thickness, *eGFR* estimated glomerular filtration rate, *ACR* urinary albumin creatinine ratio

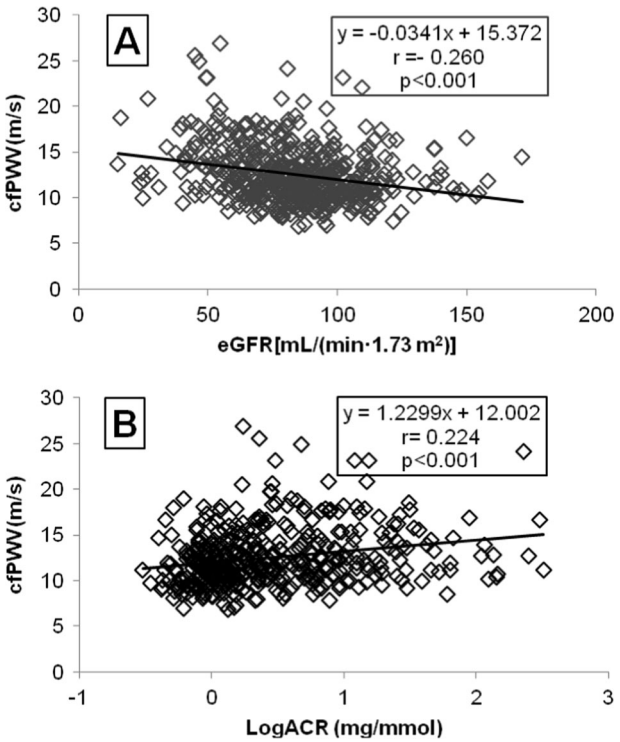


**Fig. 1** Relationship between carotid-femoral pulse wave velocity (cfPWV) and **a** estimated glomerular filtration rate (eGFR), **b** urinary albumin creatinine ratio (ACR). Linear regression lines for ($x$) and ($y$) variables are shown with correlation coefficients and $P$ values

## Discussion

Our study demonstrated that cf-PWV was significantly higher in the group of hypertensive patients with CKD than in those without CKD group after adjusting for cardiovascular confounding factors. This is consistent with previous findings showing that arterial stiffness is elevated in CKD patients even with masked hypertension [16]. Evidence has confirmed that cfPWV can predict the risk of cardiovascular events in patients with CKD [5, 17–19] or diabetes [20]. In the Chronic Renal Insufficiency Cohort (CRIC) study, cfPWV has been shown to be superior to blood pressure in discriminating presence of prior cardiovascular disease [21]. There is a negative correlation between eGFR and cfPWV in patients with CKD [22], but there is no significant correlation between cfPWV and ACR after adjusting for confounding factors [7]. Our study found the higher cfPWV observed in hypertensive patients with CKD in comparison with hypertensive patients without CKD reflects the severity

**Table 6** Associations of arterial stiffness indices with CKD as determined by separate multilogistic regression models

| Variable | $\beta$ | SE | Exp β | 95%CI | *P* value |
|---|---|---|---|---|---|
| cfPWV (per SD, 3 m/s) | 0.300 | 0.144 | 1.350 | 1.018–1.790 | 0.037 |
| Age (per SD, 10 years) | 0.170 | 0.128 | 1.186 | 0.923–1.523 | 0.183 |
| Sex (female vs. male) | −0.300 | 0.277 | 0.741 | 0.430–1.275 | 0.278 |
| Height (cm) | 0.001 | 0.014 | 1.001 | 0.974–1.029 | 0.928 |
| BMI (kg/m$^2$) | 0.062 | 0.034 | 1.064 | 0.996–1.138 | 0.066 |
| Antihypertensive drugs (yes vs. no) | 1.748 | 0.704 | 5.744 | 1.445–22.838 | 0.013 |
| Smoking (yes vs. no) | 0.103 | 0.282 | 1.109 | 0.638–1.928 | 0.714 |
| Triglycerides (mmol/L) | −0.010 | 0.030 | 0.990 | 0.933–1.050 | 0.729 |
| Total cholesterol (mmol/L) | 0.037 | 0.111 | 1.037 | 0.834–1.290 | 0.742 |
| BPP (mmHg) | −0.023 | 0.062 | 0.977 | 0.866–1.102 | 0.706 |
| CAP (mmHg) | −0.031 | 0.069 | 0.970 | 0.847–1.110 | 0.656 |
| CPP (mmHg) | 0.053 | 0.092 | 1.055 | 0.880–1.264 | 0.565 |
| AIx (%) | −0.015 | 0.042 | 0.985 | 0.908–1.069 | 0.716 |
| BPP/CPP | −0.670 | 3.214 | 0.512 | 0.001–278.3 | 0.835 |
| C1 (per SD, 9.6 mL/(mmHg × 10) | 0.037 | 0.122 | 1.038 | 0.817–1.318 | 0.761 |
| C2 (per SD, 2.6 mL/(mmHg × 100) | −0.065 | 0.142 | 0.937 | 0.710–1.237 | 0.647 |
| IMT (mm) | −0.229 | 0.716 | 0.796 | 0.195–3.239 | 0.749 |
| Fasting glucose (mmol/L) | 0.847 | 0.188 | 2.333 | 1.615–3.371 | <0.001 |
| Heart rate (beat/min) | 0.006 | 0.015 | 1.006 | 0.977–1.035 | 0.692 |

All variables adjusted for age, sex, height, smoking, and body mass index, total cholesterol, triglycerides, fasting blood glucose, heart rate, BPP, and all arterial stiffness indices

*BMI* body mass index, *CKD* chronic kidney disease, *BPP* brachial pulse pressure, *CPP* central PP, *CAP* central augmented pressure, *AIx* augmentation index, *C1* small artery elasticity index, *C2* large artery elasticity index, *cf-PWV* carotid femoral pulse wave velocity, *IMT* intima-media thickness

of vascular disease imparted by CKD, which was consistent with the findings of other study [23]. The findings of the present study also showed that 1 SD (3 m/s) increase in cfPWV entailed a 1.35 times higher prevalence of CKD in primary hypertensive patients. Various mechanisms could explain how arterial stiffness influences kidney function. Since the kidney is a high-flow organ, the renal vasculature may be more readily affected by haemodynamic stress, which could result in microvascular ischemia, endothelial dysfunction, and ultimately kidney dysfunction [24]. Higher IMT was associated progressively with decreasing eGFR. This indicates potential damage of both structure and function of large vessels in patients with CKD. Although several aspects in the complex pathophysiology of arterial remodeling in CKD remain unclear, a number of factors related to deterioration of renal function, such as elevated collagen along with reduced elastic fiber content, persistent vascular inflammation, vascular calcification with increasing nonenzymatic glycation end products, phenotype transformation of vascular smooth muscle cells. All of these factors contribute to increased arterial stiffness, resulting in higher PWV that can lead to early wave reflection, elevated systolic blood pressure and left ventricular hypertrophy [25], all factors which will increase cardiovascular morbidity and mortality. In comparison to non-CKD patients, those with hypertension and CKD have higher stiffness level after adjustment for covariates. In addition, the risk of having CKD for an increased stiffness level has been demonstrated in this study, suggesting that higher cfPWV is associated with increased likelihood of CKD in hypertensive patients.

The association of arterial function and hemodynamics with CKD has been investigated in other studies, notably the extensive longitudinal CRIC study, which has delivered invaluable information on the progression of factors of cardiovascular risk associated with CKD [4, 21, 26, 27]. Findings for our study complement findings of the CRIC and other studies but extends the investigation to a Chinese cohort only with primary hypertension and excluding cardiac and cerebrovascular complications. In addition, the study evaluates other indices of arterial function and central aortic pressure (Table 1).

Central aortic pressure and CAIX have been shown to be independent predictors of cardiovascular mortality in end-stage renal disease patients [28]. A recent study [29] showed that CAIx increased significantly in hyperuricemic patients with CKD, and CAIx increased with the increase of microalbuminuria [30]. Central aortic pressure can accurately reflect the hemodynamic load on central organs; it is more closely related to cardiovascular risk and has been

shown to predict cardiovascular events independently of brachial arterial blood pressure [31].

In our study, no significant correlation was found between CAIx and CKD after adjusting for cardiovascular confounding factors, including brachial arterial blood pressure, suggesting that whether central aortic blood pressure is superior to peripheral blood pressure in predicting cardiovascular events needs to be further validated by prospective cohort studies. As there is no normal reference value for central aortic blood pressure at present, it remains limited in clinical application. Therefore, CAIx was not regarded as a target for organ damage in hypertensive patients in hypertension guidelines [32]. Recently, 130/90 mmHg has been suggested as a reference value for the diagnosis of arterial hypertension in relation to the risk of cardiovascular events [33]. The 2013 European Hypertension Guidelines [32] recommend that no clinical study confirms the effectiveness of antihypertensive therapy in young patients with isolated systolic hypertension whose central aortic systolic blood pressure (CSABP) may be normal. Therefore, CSABP has once again become a focus of international research. It can be seen that since different arterial function indices adopt different theoretical principles and measurement methods, the clinical significance is not consistent [34], so different arterial stiffness indices cannot be replaced or substituted in clinical application. This also applies to studies in specific populations such as those with CKD.

It is important to note that small arterial elasticity remains a significant predictor of cardiovascular events. Small arterial elasticity, which forms the main peripheral arterial reflection sites, has been shown to be associated with future CVD events in patients with hypertension [35]. C2 is an indicator of small artery elasticity (oscillatory compliance) and has been suggested to reflect high sensitivity to cholesterol levels predisposing to atherosclerosis [36]. Our study found that with the decrease of eGFR, C2 also decreased, but cfPWV and IMT gradually increased, suggesting that the structure and function in both large and small arterial systems are changed in CKD. However, the physiological meaning of C2 has been questioned [13, 14] and the meaning of C2 would need to be interpreted with caution. The main issue with both C1 and C2 is that stroke volume is required for their estimation and which is obtained using anthropometric data. While this poses a potential problem with interventions (e.g., exercise), the steady state values are reasonable, and so the estimates across populations are generally consistent. In addition, all blood pressure values were higher in the CKD group, which was prone to having more frequent use of calcium antagonist and diuretic therapy. High serum creatinine predisposes to resistant hypertension, which is less likely to be well controlled. However, these findings should be interpreted in the context of limitation of this study as it was a cross-sectional study, so the results should be confirmed in a prospective study. As expected, the associations between eGFR or ACR and the stiffness-related parameters are strongly attenuated after adjustments for age, sex, and SBP. There is a potential overestimation of cases of CKD if the classification was based on only a single creatinine measurement. In conclusion, due to the association between cfPWV and CKD, cfPWV may be a potential index for evaluating cardiovascular risk in CKD patients with primary hypertension. cfPWV is by far the best documented and physiologically most relevant stiffness parameter. The clinical significance and the validity of the claims for the other vascular stiffness indicators, such as CAP, CAIx@HR75, C1, C2, act as genuine arterial stiffness parameters in evaluating the vulnerability of different organs should be further evaluated.

## Summary

### What is known about topic

- Studies have shown that chronic kidney disease (CKD) is associated with increased arterial stiffness.
- Arterial stiffness is a potential predictor of cardiovascular risk in CKD.

### What this study adds

- This study provides information on arterial stiffness in CKD with primary hypertension in a large Chinese cohort.
- This study also evaluates other indices of arterial function and central aortic pressure as applied to this Asian cohort with CKD.
- There are few studies assessing C1 and C2 in CKD and this study largely confirms the expected associations with arterial elasticity, with the additional feature of distinguishing between central and peripheral vasculature.
- Studies of cf-PWV, AIx are also relatively scarce in Asian cohorts with CKD and this study provides data for further comparative studies.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests with regard to the data presented in this paper. There are no any competing financial interests in relation to the work described.

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## References


1. Bansal N. Evolution of cardiovascular disease during the transition to end-stage renal disease. Semin Nephrol. 2017;37:120–31.
2. Cakiroglu U, Akdam H, Eryilmaz U, Akgullu C, Ozbek O, Buyukozturk AK, et al. The effect of hemodialysis on the body composition and cardiovascular disease markers in recently diagnosed end stage renal disease patients. Rev Assoc Med Bras (1992). 2018;64:354–60.
3. Briet M, Boutouyrie P, Laurent S, London GM. Arterial stiffness and pulse pressure in CKD and ESRD. Kidney Int. 2012;82:388–400.
4. Townsend RR, Anderson AH, Chirinos JA, Feldman HI, Grunwald JE, Nessel L, et al. Association of pulse wave velocity with chronic kidney disease progression and mortality: findings from the CRIC study (Chronic Renal Insufficiency Cohort). Hypertension. 2018;71:1101–7.
5. Tripepi G, Agharazii M, Pannier B, D'Arrigo G, Mallamaci F, Zoccali C, et al. Pulse wave velocity and prognosis in end-stage kidney disease. Hypertension. 2018;71:1126–32.
6. Salvi P, Parati G. Chronic kidney disease: arterial stiffness and renal function—a complex relationship. Nat Rev Nephrol. 2015;11:11–3.
7. Woodard T, Sigurdsson S, Gotal JD, Torjesen AA, Inker LA, Aspelund T, et al. Mediation analysis of aortic stiffness and renal microvascular function. J Am Soc Nephrol. 2015;26:1181–7.
8. Parati G, Ochoa JE, Bilo G. Blood pressure variability, cardiovascular risk, and risk for renal disease progression. Curr Hypertens Rep. 2012;14:421–31.
9. Nilsson PM, Boutouyrie P, Laurent S. Vascular aging: A tale of EVA and ADAM in cardiovascular risk assessment and prevention. Hypertension. 2009;54:3–10.
10. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006;17:2937–44.
11. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension. 1995;26:485–90.
12. McVeigh GE, Bratteli CW, Morgan DJ, Alinder CM, Glasser SP, Finkelstein SM, et al. Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: aging and arterial compliance. Hypertension. 1999;33:1392–8.
13. Rietzschel ER, Boeykens E, De Buyzere ML, Duprez DA, Clement DL. A comparison between systolic and diastolic pulse contour analysis in the evaluation of arterial stiffness. Hypertension. 2001;37:E15–22.
14. Segers P, Qasem A, De Backer T, Carlier S, Verdonck P, Avolio A. Peripheral "oscillatory" compliance is associated with aortic augmentation index. Hypertension. 2001;37:1434–9.
15. Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation. 1997;95:1827–36.
16. Drawz PE, Alper AB, Anderson AH, Brecklin CS, Charleston J, Chen J, et al. Masked hypertension and elevated nighttime blood pressure in CKD: prevalence and association with target organ damage. Clin J Am Soc Nephrol. 2016;11:642–52.
17. Baumann M, Wassertheurer S, Suttmann Y, Burkhardt K, Heemann U. Aortic pulse wave velocity predicts mortality in chronic kidney disease stages 2-4. J Hypertens. 2014;32:899–903.
18. Elias MF, Davey A, Dore GA, Gillespie A, Abhayaratna WP, Robbins MA. Deterioration in renal function is associated with increased arterial stiffness. Am J Hypertens. 2014;27:207–14.
19. McIntyre NJ, Fluck RJ, McIntyre CW, Fakis A, Taal MW. Determinants of arterial stiffness in chronic kidney disease stage 3. PLoS One. 2013;8:e55444.
20. Suto M, Tanaka H, Mochizuki Y, Mukai J, Takada H, Soga F, et al. Impact of overweight on left ventricular function in type 2 diabetes mellitus. Cardiovasc Diabetol. 2017;16:145.
21. Townsend RR. Arterial stiffness in CKD: a review. Am J Kidney Dis. 2019;73:240–7.
22. Sedaghat S, Mattace-Raso FU, Hoorn EJ, Uitterlinden AG, Hofman A, Ikram MA, et al. Arterial stiffness and decline in kidney function. Clin J Am Soc Nephrol. 2015;10:2190–7.
23. Geraci G, Mule G, Costanza G, Mogavero M, Geraci C, Cottone S. Relationship between carotid atherosclerosis and pulse pressure with renal hemodynamics in hypertensive patients. Am J Hypertens. 2016;29:519–27.
24. Brunner EJ, Shipley MJ, Ahmadi-Abhari S, Tabak AG, McEniery CM, Wilkinson IB, et al. Adiposity, obesity, and arterial aging: longitudinal study of aortic stiffness in the Whitehall II cohort. Hypertension. 2015;66:294–300.
25. Georgianos PI, Sarafidis PA, Liakopoulos V. Arterial stiffness: a novel risk factor for kidney injury progression? Am J Hypertens. 2015;28:958–65.
26. Townsend RR, Wimmer NJ, Chirinos JA, Parsa A, Weir M, Perumal K, et al. Aortic PWV in chronic kidney disease: a CRIC ancillary study. Am J Hypertens. 2010;23:282–9.
27. Chirinos JA, Khan A, Bansal N, Dries DL, Feldman HI, Ford V, et al. Arterial stiffness, central pressures, and incident hospitalized heart failure in the chronic renal insufficiency cohort study. Circ Heart Fail. 2014;7:709–16.
28. Ohno Y, Kanno Y, Takenaka T. Central blood pressure and chronic kidney disease. World J Nephrol. 2016;5:90–100.
29. Huang N, Foster MC, Mitchell GF, Andresdottir MB, Eiriksdottir G, Gudmundsdottir H, et al. Aortic stiffness and change in glomerular filtration rate and albuminuria in older people. Nephrol Dial Transpl. 2017;32:677–84.
30. Kalaitzidis RG, Karasavvidou DP, Tatsioni A, Pappas K, Katatsis G, Liontos A, et al. Albuminuria as a marker of arterial stiffness in chronic kidney disease patients. World J Nephrol. 2015;4:406–14.
31. Kollias A, Lagou S, Zeniodi ME, Boubouchairopoulou N, Stergiou GS. Association of central versus brachial blood pressure with target-organ damage: systematic review and meta-analysis. Hypertension. 2016;67:183–90.
32. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESc practice guidelines for the management of arterial hypertension. Blood Press. 2014;23:3–16.
33. Cheng HM, Chuang SY, Sung SH, Yu WC, Pearson A, Lakatta EG, et al. Derivation and validation of diagnostic thresholds for central blood pressure measurements based on long-term cardiovascular risks. J Am Coll Cardiol. 2013;62:1780–7.
34. Eeftinck Schattenkerk DW, van Gorp J, Vogt L, Peters RJ, van den Born BH. Isolated systolic hypertension of the young and its

association with central blood pressure in a large multi-ethnic population. The HELIUS study. Eur J Prev Cardiol. 2018;25: 1351–9.
35. Wan Z, Liu X, Wang X, Liu F, Liu W, Wu Y, et al. Small artery elasticity predicts future cardiovascular events in chinese patients with angiographic coronary artery disease. Angiology. 2014;65:298–302.
36. Podolecka E, Grzeszczak W, Zukowska-Szczechowska E. Correlation between serum low-density lipoprotein cholesterol concentration and arterial wall stiffness. Kardiol Pol. 2018;76:1712–6.