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Dominance of traditional cardiovascular risk factors over renal function in predicting arterial stiffness in subjects with chronic kidney disease

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Abstract

Background. The predictors of arterial stiffness across the spectrum of renal function are unclear. These predictors were investigated across a wide range of estimated glomerular filtration rates (eGFR).

Methods. Carotid-femoral pulse wave velocity (PWV; an index of arterial stiffness) was measured in 264 subjects with chronic kidney disease (CKD) stages 3–5 from three nephrology clinics (‘lower GFR group’). PWV was also measured in 149 subjects without previously recognized CKD (‘higher GFR group’) including n = 26 with eGFR between 30 and 60 ml/min/1.73 m2 and n = 123 with eGFR between 60 and 100 ml/min/1.73 m2. The association between PWV and eGFR was investigated using linear regression.

Results. The 413 subjects had a mean age of 61.9 years, were 51% male, 28% diabetic and 79% hypertensive. In age-adjusted analyses within the ‘lower GFR group’, ‘higher GFR group’ and combined group, PWV correlated with higher systolic blood pressure (SBP), pulse pressure (PP), diabetes mellitus, body mass index (BMI) and resting heart rate (all P < 0.0008). In addition, PWV correlated inversely with eGFR in the ‘higher GFR group’ (P < 0.03) and combined group (P < 0.0001). In multivariable regression analyses of the combined group (n = 413), PWV was independently predicted by eGFR (P < 0.05). However, eGFR explained at most 4% of the variability in PWV in age-adjusted analyses (compared with 13–15% explained by SBP, PP or diabetes) and <1% of PWV variability in models adjusting for age, SBP, diabetes, heart rate and BMI (P < 0.0001).

Conclusion. Although eGFR may independently predict PWV, the contribution of GFR per se does not appear to be clinically meaningful when compared with traditional cardiovascular risk factors.

Keywords: arterial stiffness; arteriosclerosis; cardio-renal; kidney disease; pulse wave velocity

Introduction

Large ‘central’ artery stiffness, determined by the velocity of propagation of the percussion wave (pulse wave velocity, or PWV), predicts cardiovascular events in the general population and in end-stage renal disease [1–4]. Theoretical reasons support the hypothesis that chronic kidney disease (CKD) may modulate arterial stiffness. Progressive decrease in kidney function is associated with the same factors that predict increased arterial stiffness including aging, diabetes and hypertension [5,6]. Furthermore, other variables unique to CKD including vascular calcification...
and inflammation could contribute to arterial stiffness [7,8]. Currently prevailing opinion supports kidney function as a predictor of arterial stiffness, independent of traditional vascular risk factors [9,10].

However, the kidney function–arterial stiffness relationship has not been consistently reported. Wang et al. suggested a strong relationship [19], reporting that a 10ml/min reduction in estimated glomerular filtration rates (eGFR) independently predicted a 2.4m/s greater PWV. Although this study included subjects from all five CKD stages, it was limited by a relatively small size (n = 102). Two larger studies suggested that the relationship may be more modest. Both of these reported that a 10ml/min lower GFR predicted <0.1m/s higher PWV [9,10]. These studies were limited by either a lack of statistical adjustment for diabetes or inclusion of few individuals with stages 4–5 CKD.

A recent relatively large study (n = 767) contrasts these by reporting no significant relationship between eGFR and central arterial stiffness [23]. Unlike the previous studies, this study included a proportion of diabetics typically seen in a nephrology practice. However, the study population was limited almost exclusively to stages 2–3 CKD. The apparent lack of a relationship may have been due to this narrow range.

The purpose of our study was to examine the relationship between GFR and central arterial stiffness over a broad range of kidney function in patients with comorbidities including hypertension and diabetes.

Methods

The present study derived subjects (n = 267) principally from the Renal Research Institute (RRI)–CKD Study, which included individuals with stages 3–5 CKD (‘lower GFR group’; described below) (Figure 1). The ‘higher GFR group’ (described below) was obtained by selecting subjects (n = 149) with an eGFR >100ml/min/1.73m² from four studies that measured PWV at the University of Michigan. In this latter group, formal staging could not be confirmed due to absence of testing for proteinuria. To ensure that the ‘higher GFR group’ contained a similar range of comorbidities as the ‘lower GFR group’, studies of hypertensive, diabetic and normotensive individuals were selected. Combining these studies provided a unique opportunity to analyze observations from a large group of subjects with a wide distribution of eGFR.

The ‘lower GFR group’ (the RRI–CKD study)

The RRI–CKD study is a prospective multi-centre observational study of CKD patients at four academic nephrology clinics [11]. Briefly, subjects were enrolled if they had an estimated eGFR <50ml/min/1.73m² as calculated by the four-variable Modification of Diet in Renal Disease (MDRD) equation. To exclude those with transient renal impairment, eGFR was assessed on two occasions separated by at least 1 month. Individuals with prior kidney transplantation or those likely to begin dialysis within 1 year were excluded. Medical history, medication use and blood/urine samples were collected.

At three of the four sites, individuals were invited to return for blood, urine and non-invasive cardiovascular studies including PWV at two time points 1 year apart. The present analysis included patients with at least one PWV measurement, serum creatinine measured within 90days of PWV testing and no prior aortic surgery. Although patients had an eGFR <50 ml/min/1.73m² at the time of enrollment, 10 patients had an eGFR between 50 and 60ml/min/1.73m² and three patients had an eGFR slightly above 60ml/min/1.73m² at the time of PWV testing. The latter three patients were analyzed with the ‘higher GFR group’. The study was approved by institutional review boards at each institution, and all participants gave written informed consent.

The ‘higher GFR group’ (studies A, B and C in Figure 2)

Subjects with an eGFR <100ml/min/1.73m² by the four-variable MDRD equation were selected from four other investigations measuring PWV among community-dwelling adults without recognized CKD. These studies included hypertensives (‘study A’), diabetics (‘study B’) and normotensives pooled data from two studies; ‘study C’.

The study of hypertensive adults aged 60–80years recruited individuals with treated high blood pressure (‘study A’). The eligibility criteria have been described previously [12]. Briefly, volunteers were excluded if they had fasting glucose ≥126mg/dl, serum creatinine ≥2.0mg/dl or history of cardiovascular disease (CVD). All were treated with diuretics.

The study of diabetic adults aged 60–80years recruited individuals with type 2 diabetes who were treated with insulin (‘study B’). The eligibility criteria have been described previously [13]. Briefly, volunteers were excluded if they had a haemoglobin A1C <7.0mg/dl or severe impairment of cardiac, hepatic or renal function. All were on stable antihypertensive medication.

Two studies of normotensives (the first in adults 60–80years; the second in adults 40–80years) recruited individuals without a history of hypertension, diabetes or CVD (jointly referred to as ‘study C’). The screening process to exclude these conditions has been described previously [14]. Briefly, volunteers were excluded if they had a fasting glucose ≥126mg/dl, serum creatinine >1.5mg/dl or history of CVD.

Arterial stiffness measurement

‘Central’ arterial stiffness was assessed using carotid-femoral PWV [15]. The reproducibility/reliability of technicians at University of Michigan has been reported previously [14]; these technicians trained the other two site technicians. Only the most experienced technician’s measurements were used in a given subject. Briefly, systolic and diastolic blood pressure (SBP, DBP) were measured after a 5-min supine rest. The descending aorta length was approximated by subtracting the manubrium–carotid artery distance from the manubrium–femoral artery distance. A hand-held tonometer was placed over the carotid and then femoral arteries to record pressure waves. Simultaneous electrocardiography tracings were recorded. PWV was calculated in an automated fashion (AtCor version 7.0). Four measurements were recorded for each subject. A measurement was excluded if the pressure contour was of poor quality or a >15% difference in heart rate (HR) was found between the carotid and femoral measurements. A subject’s PWV was the average of the acceptable measurements.
Tests of site and technician effects on PWV were adjusted for cardiovascular risk factors (age, diabetes, SBP, body mass index [BMI] and HR) using Tukey's multiple comparisons test. All technicians and all but one site had similar predicted means. Adjustment for this site was added; analyses excluding these patients \((n = 83)\) yielded similar results.

Linear regression was used to investigate cardiovascular risk factors and eGFR as predictors of PWV after adjusting for age and site. Significantly greater unexplained variability in PWV among diabetics versus non-diabetics was fit with heterogeneous variance models in the Mixed procedure of SAS version 9.1 (Cary, NC). Partial generalized \(R^2\) values were calculated by subtracting the generalized \(R^2\) of the model with age and site only from that of the model also including the predictor of interest.

Multivariable models were used to simultaneously test potential predictors of PWV. All subset regressions used Akaike's Information Criterion and generalized \(R^2\) to select the best models [17]; we further examined the eGFR–PWV relationship after adjustment. Greater variability was observed in the ‘lower GFR group’ versus the ‘higher GFR group’; this heterogeneity was incorporated in analyses of the combined studies. Two-sided testing was used throughout.

Results

Baseline characteristics are displayed in Table 1. Distributions of PWV and eGFR are shown in Figure 2 for the ‘lower GFR group’ and the studies making up the ‘higher GFR group’. Table 2 compares the relationships between PWV and CVD risk factors (including eGFR); the partial \(R^2\) indicates the predictive value of each factor. Relationships were age-adjusted due to age’s strong predictive power and the difference in age distributions across studies. Table 3 displays the eGFR–PWV relationship with sequentially increasing adjustment for CVD risk factors. Results are presented for the ‘lower GFR group’ \((n = 264)\), ‘higher GFR group’ \((n = 149)\) and combined group \((n = 413)\).

‘Lower GFR group’

Of these 264 patients, 89% had hypertension, 30% had diabetes and 51% were over age 60. Forty-five percent were stage 3, 44% stage 4 and 12% stage 5 CKD (Table 1). PWV strongly correlated with traditional predictors including SBP, pulse pressure (PP), diabetes status, body mass index (BMI) and resting HR \((P < 0.001)\;\text{Table 2}\). On average, diabetics had a 1.9 m/s greater PWV \((P < 0.0001)\). However, PWV was not significantly associated with eGFR in unadjusted \((P = 0.93)\) or age-adjusted analyses \((P = 0.28)\;\text{Table 2}\). Furthermore, no significant PWV–eGFR association was identified after sequential adjustment for age, SBP, diabetes, BMI and HR (Table 3).
Table 1. Characteristics of all CKD patients (n = 413) presented by study group and CKD stage

<table>
<thead>
<tr>
<th></th>
<th>Higher GFR group (UM-Other Studiesa, n = 149)</th>
<th>Lower GFR group (RRI–CKD study, n = 264)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) or mean (SD)</td>
<td>N (%) or or mean (SD)</td>
</tr>
<tr>
<td>Number of subjects (n)</td>
<td>15 108 26</td>
<td>118 115 31</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>9 (60.0) 48 (44.4) 15 (57.7)</td>
<td>56 (47.5) 66 (57.4) 17 (54.8)</td>
</tr>
<tr>
<td>Diabetes (DM)</td>
<td>3 (20.0) 22 (20.4) 12 (46.2)</td>
<td>32 (27.1) 32 (27.8) 13 (41.9)</td>
</tr>
<tr>
<td>Hypertension (HTN)</td>
<td>7 (46.7) 61 (56.5) 22 (84.6)</td>
<td>101 (85.6) 103 (89.6) 31 (100)</td>
</tr>
<tr>
<td>Assigned cause of CKDc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (20.0) 28 (25.9) 9 (34.6)</td>
<td>60 (50.8) 56 (48.7) 14 (45.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (20.0) 22 (20.4) 12 (46.2)</td>
<td>27 (22.9) 26 (22.6) 12 (38.7)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>1 (0.9)</td>
<td>6 (5.1) 21 (18.3) 3 (9.7)</td>
</tr>
<tr>
<td>Interstitial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic</td>
<td>5 (4.2)</td>
<td>7 (6.1) 5 (16.1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.9)</td>
<td>16 (13.6) 16 (13.9) 5 (16.1)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.6 (7.5) 66.1 (9.4) 68.4 (8.0)</td>
<td>64.9 (9.0) 64.6 (10.2) 64.6 (10.8)</td>
</tr>
<tr>
<td>Body mass indexd (kg/m2)</td>
<td>27.1 (4.4) 27.0 (5.3) 28.6 (4.4)</td>
<td>28.4 (5.7) 29.1 (5.6) 30.7 (8.0)</td>
</tr>
<tr>
<td>Resting heart rate (b.p.m.)</td>
<td>61.9 (8.3) 61.4 (8.5) 62.2 (11.3)</td>
<td>64.0 (9.9) 64.6 (10.2) 64.6 (10.8)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>125.7 (21.7) 130 (20.7) 141 (18.3)</td>
<td>139.7 (21.9) 136.1 (23.5) 139.4 (31.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>66.7 (7.0) 69.3 (10.5) 69.4 (7.6)</td>
<td>75.9 (11.4) 74.6 (13.7) 72.7 (14.6)</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>59.1 (21.7) 60.6 (15.5) 71.5 (16.7)</td>
<td>63.8 (20.9) 61.5 (18.6) 66.7 (28.7)</td>
</tr>
<tr>
<td>Pulse wave velocity (m/s)</td>
<td>8.0 (2.7) 8.5 (2.4) 10.5 (2.3)</td>
<td>8.4 (2.9) 8.7 (3.0) 8.1 (2.9)</td>
</tr>
<tr>
<td>eGFRd (ml/min/1.73m²)</td>
<td>92.7 (2.5) 74.7 (8.6) 50.1 (7.9)</td>
<td>39.6 (7.1) 22.8 (4.3) 12.1 (2.2)</td>
</tr>
</tbody>
</table>

aIncludes three patients from the RRI–CKD study with stage 2 CKD at time of PWV testing (due to improvement).
bSince stage of CKD was determined based solely on the eGFR criterion, patients with eGFR ≤ 60ml/min/1.73m² may or may not have CKD.
cMultiple causes of CKD are possible. For the 'higher GFR group', because CKD had not been previously diagnosed, reported comorbidities are given.
dBody mass index measurements are missing on three stage 2 patients in the University of Michigan (UM)-Other Studies.

Table 2. Associations between variables of interest (from Table 1) and pulse wave velocity (PWV) in the RRI–CKD study and the other three University of Michigan (UM) studies

<table>
<thead>
<tr>
<th></th>
<th>Higher GFR group (UM-Other Studiesa, n = 149)</th>
<th>Lower GFR group (RRI–CKD study, n = 264)</th>
<th>Combined group (n = 413)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in PWVb P value Partial R²</td>
<td>Change in PWVb P value Partial R²</td>
<td>Change in PWVb P value Partial R²</td>
</tr>
<tr>
<td>Age (per 10years)</td>
<td>1.12 &lt;0.0001 0.25</td>
<td>0.83 &lt;0.0001 0.21</td>
<td>0.82 &lt;0.0001 0.19</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10mmHg)</td>
<td>0.52 &lt;0.0001 0.17</td>
<td>0.39 &lt;0.0001 0.10</td>
<td>0.47 &lt;0.0001 0.15</td>
</tr>
<tr>
<td>Pulse pressure (per 10mmHg)</td>
<td>0.56 &lt;0.0001 0.12</td>
<td>0.47 &lt;0.0001 0.11</td>
<td>0.53 &lt;0.0001 0.13</td>
</tr>
<tr>
<td>Diabetes (DM)</td>
<td>3.34 &lt;0.0001 0.19</td>
<td>1.93 &lt;0.0001 0.06</td>
<td>2.59 &lt;0.0001 0.11</td>
</tr>
<tr>
<td>Body mass index (per 5kg/m²)</td>
<td>0.71 &lt;0.0001 0.16</td>
<td>0.45 0.0001 0.04</td>
<td>0.59 &lt;0.0001 0.09</td>
</tr>
<tr>
<td>Hypertension (HTN)</td>
<td>1.66 &lt;0.0001 0.13</td>
<td>0.68 0.1087 0.01</td>
<td>1.56 &lt;0.0001 0.08</td>
</tr>
<tr>
<td>Resting heart rate (per 10b.p.m.)</td>
<td>0.74 &lt;0.0001 0.09</td>
<td>0.51 0.0005 0.03</td>
<td>0.65 &lt;0.0001 0.06</td>
</tr>
<tr>
<td>Diastolic blood pressure (per 10mmHg)</td>
<td>0.56 0.0003 0.06</td>
<td>0.19 0.1031 0.01</td>
<td>0.40 &lt;0.0001 0.03</td>
</tr>
<tr>
<td>eGFRd (per 10ml/min/1.73m²)</td>
<td>−0.25 0.0296 0.02</td>
<td>−0.14 0.2839 0.00</td>
<td>−0.23 &lt;0.0001 0.04</td>
</tr>
</tbody>
</table>

All associations are adjusted for age and one of the sites. The partial $R^2$ represents the additional contribution of each predictor to the model $R^2$ after controlling for age and site (the PWV measurements from one of the sites of the RRI–CKD study [‘lower GFR group’] were significantly lower than other sites due to operator effects).

aIncludes three patients from the RRI–CKD study with stage 2 CKD at time of PWV testing (due to improvement).
bThe linear regression coefficient. For dichotomous variables (e.g. DM), it is the difference in mean PWV between the two groups (e.g. mean PWV is 1.93 m/s higher among diabetics compared to non-diabetics in the RRI–other sites due to operator effects). cBMI measurements are missing on three stage 2 patients in the University of Michigan (UM)-Other Studies.

dGlomerular filtration rate (GFR) was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula.

In 253 of these 264 subjects, we also examined the relationship between PWV and urine albumin/creatinine ratio. A weak relationship was observed in age-adjusted analyses ($\beta = 0.003$ per 10mg/g, $P = 0.046$). However, this relationship was nullified after adjustment for traditional risk factors including diabetes, SBP, BMI and hypertension.
For each model, the method of all possible subset selection was used to determine the 'best' model, with model 4 selected as the model most predictive of PWV. The model $R^2$ represents the predictive ability of the model and the partial $R^2$ represents the amount of variability in PWV explained by each predictor given the other variables in that model (e.g. 44% of the variation in PWV is explained by model 1 and given age and blood pressure are in the model; 2% of the variation in PWV is explained by eGFR). Models were controlled for site 2 (the PWV measurements from one of the sites of the RRI study [lower GFR group] were significantly lower than other sites due to operator effects).

Glomerular filtration rate (GFR) was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula.

Further adjusting for DBP did not further contribute to the model $R^2$ and was not significant ($P = 0.10$).

### 'Higher GFR group'

Of these 149 patients, 60% had hypertension, 25% had diabetics and 81% were over age 60. Seventeen percent had an eGFR between 30 and 60 ml/min/1.73 m², 72% were between 60 and 90 ml/min/1.73 m² and 10% between 90 and 100 ml/min/1.73 m² (Table 1).

In age-adjusted analyses, PWV was significantly associated with blood pressure, BMI and HR (all $P < 0.001$; Table 2); on average, PWV was 3.4 and 1.7 m/s greater in diabetics and hypertensives, respectively ($P < 0.0001$). eGFR did correlate with PWV ($\beta = -0.25$ m/s per 10 ml/min/1.73 m², $P = 0.03$; Table 2), explaining 2% of PWV variation. However, the PWV–eGFR relationship was not identified in any subgroup: hypertensives ($P = 0.09$); diabetics ($P = 0.88$); normotensives ($P = 0.57$).

In multiple regression analysis, the PWV–eGFR relationship remained significant after adjusting for age and SBP ($\beta = -0.24$ m/s per 10 ml/min/1.73 m², $P = 0.02$; Table 3), but not after adjusting for age, SBP and diabetes status ($\beta = -0.14$ m/s per 10 ml/min/1.73 m², $P = 0.17$). Further, adjusting for BMI and HR had no effect on the PWV–eGFR relationship ($\beta = -0.15$ m/s per 10 ml/min/1.73 m², $P = 0.11$). The traditional cardiovascular risk factors remained highly significant in all models ($P < 0.001$).
To examine the PWV–eGFR relationship over a broad range of kidney function, the ‘higher GFR group’ and ‘lower GFR group’ were combined. Of the 413 patients, 79% had hypertension, 28% had diabetes and 62% were over age 60. Eight percent had an eGFR <15ml/min/1.73m², 63% were 15–60ml/min/1.73m² and 30% were 60–100ml/min/1.73m².

In age-adjusted analysis of the combined group, GFR significantly correlated with PWV, but the predictive value (partial $R^2$) was much smaller than traditional risk factors (diabetes, SBP, DBP, hypertension status, BMI, resting HR and PP; Table 2). Figure 3 depicts a scatter plot of the unadjusted PWV–eGFR relationship showing, on average, higher PWV in diabetics ($P<0.0001$). Although the overall PWV–eGFR relationship was significant ($P<0.0001$), this relationship was not significant among diabetics ($P=0.97$) or among non-diabetics ($P=0.13$). As seen in Figure 4, no ‘stepwise’ relationship was identified between PWV and GFR stage among diabetics, hypertensives or normotensives ($P=0.15$).

The multivariable models in Table 3 accounted for 39–53% of the variability in PWV. A 10ml/min/1.73m² lower eGFR predicted only a 0.16m/s higher PWV, after adjusting for just age and SBP (Table 3, Model 1). Importantly, the contribution of eGFR to the model $R^2$ continued to decrease from 2% to 0.6% with additional adjustment for diabetes, BMI and HR. After these adjustments, a 10ml/min/1.73m² lower eGFR predicted only a 0.08m/s higher PWV (Table 3, Model 4). Similar results were found when DBP (or PP) was used in place of SBP in each of the models.

Figure 5 summarizes the relationship between model estimates of PWV versus age by diabetic status and illustrates the minimal additional predictive value of eGFR (for values of 15, 45 and 75ml/min/1.73m²).

Due to the difference in enrolment criteria with respect to age, an additional analysis was performed to examine the PWV–eGFR relationship in the combined group after excluding those under age 60. This sub-analysis included 268 individuals with eGFR values: >60 ($n=100$), 60–30

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**Combined group**

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(n = 96) and <30 (n = 72) ml/min/1.73m². The results of this subgroup analysis were similar to that of the combined group.

Discussion

This study’s main findings are: (i) Traditional risk factors of arterial stiffness remain predictive across the range of renal impairment. (ii) The predictive value of eGFR on PWV is ‘statistically’ significant, but the effect is very small (partial \( R^2 \) <1%) above and beyond conventional determinants of arterial stiffness including age, SBP, diabetes and obesity [5,12,18]. These results suggest that the previously reported renal impairment–arterial stiffness relationship is largely attributable to the common underlying risk factors.

This study both confirms and extends the findings of two previous studies that reported a renal impairment–arterial stiffness relationship in more homogeneous populations. Briet et al. compared 95 individuals with CKD (mean \( {\text{Cr}}=\text{EDTA} \) GFR of 36 ± 16ml/min/1.73m²) to 121 hypertensives and 57 normotensives (mean GFR 86 ± 24 and 92 ± 21ml/min/1.73m²), respectively [9]. As in the present study, they identified a significant relationship between carotid-femoral PWV and GFR. However, in multivariable analyses (n = 273), where the dependent variable was carotid-femoral PWV (as in our study), only 2% of the variation in PWV was explained by GFR. This value was similar to the one reported in the present study (2.4%) after adjustment for only two covariates (age and SBP). No adjustment was made in the Briet study for diabetes, however. In the present study that includes a more representative proportion of diabetes (28%), we found that diabetes strongly influences PWV. Diabetics had a 1.6m/s greater PWV than non-diabetics, independent of all other factors. It is very likely that, after adjustment for diabetes, the authors of the previous study would have seen further attenuation of the PWV–eGFR relationship.

Ohyya et al. measured carotid-femoral PWV in over 3000 subjects presenting for a health checkup program [10]. An independent PWV–creatinine clearance relationship was reported after adjustment for age, SBP, proteinuria, fasting plasma glucose, gender and total cholesterol. Similar to our results, creatinine clearance (the surrogate used for GFR) explained only 0.3% of the variance in PWV after adjusting for traditional vascular risk factors in a multivariable model. Although the sample was large, it included predominately higher renal function subjects with only 183 subjects having creatinine clearance of <60ml/min, few with stage 4 and none with stage 5 CKD. The present study extends these findings by analyzing arterial stiffness across the spectrum of GFR (ranging from 10 to 100ml/min/1.73m²).

Recently, Hermans et al. measured carotid-femoral transit time and augmentation index (other indices of central artery stiffness) in a prospective study of 767 individuals including normals and those with impaired glucose tolerance and diabetes [23]. The prevalence of diabetes was more representative of the typical nephrology practice than in the Briet or Ohyya studies; however, their study included only stages 2–3 CKD patients. In contrast to these other studies, no relationship was identified between eGFR and central arterial stiffness. When our sample was limited to this smaller range of GFR, we also did not identify an independent GFR–PWV relationship. It is likely that the weak relationship between kidney function and central arterial stiffness was at least partially due to the narrow range of renal function. Like the Hermans study, our study suggested a relationship between central arterial stiffness and albuminuria in age-adjusted analyses. However, after further adjustment for diabetes, hypertension and other cardiovascular risk factors, this relationship was no longer significant in either study.

The present study combined with prior studies suggests that the association between arterial stiffness and renal function per se is weak at best, especially when compared to the established risk factors for arterial stiffness. Cardiovascular risk factors thought to exert an important influence on arterial stiffness include age, diabetes, blood pressure, dyslipidemia and components of the metabolic syndrome [20]. Additionally, we did not observe any significant relationship between the degree of albuminuria and PWV in the stages 3–5 CKD patients. We believe that the higher PWV observed among CKD patients is primarily due to the cardiovascular risk factors that both CKD and arterial stiffness have in common, rather than their renal impairment or degree of albuminuria per se.

The results of these studies are at variance with a report by Wang et al. that suggested a strong ‘stepwise’ association between CKD stage and PWV. In that analysis, an independent PWV–eGFR association was reported in 102 individuals with varying degrees of renal impairment [19]. A 10ml/min/1.73m² lower eGFR predicted a 2.36m/s higher PWV. This value is over 20 times the beta coefficient in our study, and was much larger than the estimates for established risk factors of arterial stiffness such as age, hypertension or diabetes (none of which reached statistical significance). Moreover, although not significant, the presence of diabetes, history of CVD and the presence of cardiovascular risk factors actually predicted a lower PWV. We believe that this was probably an overestimation of eGFR’s predictive value due to the higher prevalence of conventional risk factors such as pre-existent CVD, diabetes, hypertension and older age in their patients with stages 3–5 CKD. In keeping with this higher prevalence of conventional risk factors and increasing age, PWV increased according to the stage of CKD. This study also had a relatively small sample size, amplifying the effects of any influential points. Thus, while CKD stage superficially appeared to strongly correlate with PWV, traditional predictors of PWV likely influenced the results.

The factors responsible for the small (partial \( R^2 = 0.6% \)) but statistically significant effect of GFR on PWV are unclear. A number of possible mechanisms have been invoked to explain how impaired renal function may lead to arterial stiffness. These include the accumulation of advanced glycation end products, elastin fragmentation and replacement with collagen, increased lipid peroxidation, deposition of materials in the arterial wall including calcium, hyperplasia of smooth muscle cell, enhanced renin–angiotensin system activity, increased inflammatory mar-
kers and excess fluid volume [9,10]. However, none of these are unique to renal impairment. An equally plausible hypothesis is that decreasing GFR may be accounting for the duration of exposure to the common risk factors; thus, diabetic patients with stage 5 CKD have, in general, been exposed to diabetes longer than those with stage 1.

An analysis of the Cardiovascular Health Study group compared traditional and novel risk factors as predictors of cardiovascular mortality, and may be relevant to the interpretation of our findings [21]. The authors found that traditional Framingham risk factors predicted cardiovascular mortality but ‘novel’ risk factors did not add to these models. Our study similarly suggests that, in patients across the spectrum of CKD, PWV is determined primarily by these traditional risk factors. Figure 5 displays the minor predictive value of eGFR in a modeled relationship between age and PWV by diabetes status.

It is important to note that higher PWV (irrespective of its genesis) has pathophysiological implications for CKD patients. Faster PWV produces earlier reflection of the incident pulse wave from points of structural and/or functional discontinuity. The resulting replacement of pulse wave augmentation of diastole by augmentation of systole increases afterload. Such changes in ventricular–vascular coupling may play a role in the genesis of ventricular hypertrophy, which is highly prevalent in CKD.

Our study has limitations, which should be considered when interpreting its results. Individuals with stiffer arteries may have died before reaching later stages of CKD, leaving healthier individuals (with lower PWV) in the later stages. This possibility can only be assessed in a prospective study with repeated PWV measurements. Antihypertensive medications have been shown to modulate arterial stiffness measurement [24–26]. All participants with hypertension in this study were on stable treatment with antihypertensive medications and SBP was adjusted for in the models. Still, it is likely that medications have differential effects on arterial stiffness and renal function. Further studies are needed to examine the relationship between medications and arterial stiffness in patients with CKD. Furthermore, while a heterogeneous group was necessary to ensure adequate representation of a range of GFR in normotensive, hypertensives and diabetics, both statistical adjustment and subgroup analyses were needed to control for these comorbidities. However, regardless of the subgroup examined, PWV never explained >2% of the variation in eGFR, and statistical adjustment only served to further decrease the strength of the PWV–eGFR relationship. We recognize that the diabetics in the ‘higher GFR group’ (study B in Figure 2) were not ‘well controlled’, possibly contributing to a higher PWV. However, after excluding diabetics, the PWV in these patients (n = 61) was not significantly different (P = 0.18) than the PWV in stages 4–5 (combined). Finally, urine albumin was only available in the RRI–CKD group, creatinine was measured in different laboratories (at individual study sites) and GFR was estimated (not measured). However, the MDRD equation correlates well with isotope clearance methods particularly in stage 3 CKD and below [22].

In summary, the relationship between the degree of renal impairment and arterial stiffness is statistically significant but quite small, especially compared to traditional cardiovascular risk factors. These cardiovascular risk factors remain strongly predictive across a wide range of kidney function and are likely more important in the pathogenesis of arterial stiffness than the level of renal function per se. Longitudinal studies are needed to further unravel the pathogenesis of progressive vascular disease in CKD.

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References


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