Progression of Aortic Pulse Wave Velocity in Patients With Chronic Kidney Disease

Susanne Tholen, MD;[1] Katharina Klofat, MD;[1] Cheng Rui Pan, PhD;[2] Christoph Schmaderer, MD;[1] Jens Lutz, MD;[3] Uwe Heemann, MD;[1] Marcus Baumann, MD, PhD[1]

From the Department of Nephrology, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany;[1] Centre for Epidemiological Studies and Clinical Trials, Ruijin Hospital, Medical School, Shanghai Jiaotong University, Shanghai, China;[2] and Department of Nephrology, Klinikum der Johannes-Gutenberg-Universität Mainz, Mainz, Germany[3]

Aortic pulse wave velocity (aPWV) is elevated in patients with chronic kidney disease (CKD) and predicts cardiovascular risk. However, the natural progression of arterial stiffness in these patients remains uncertain. Therefore, the main aim of this study was to investigate the development of aPWV and to identify potential factors associated with its progression. aPWV measurement was carried out in 70 CKD patients at baseline and after 12 months. Correlations to several variables, in particular annual glomerular filtration rate reduction and diabetes mellitus, were studied. In the cohort, aPWV significantly increased in 1 year by 1.1 m/s ($P<.01$). Dividing the group into patients with stable and progressive aPWV, factors associated with accelerated progression were age, systolic blood pressure, and diabetes, whereas loss of renal function had no significant impact. The annual aPWV progression in CKD patients reached 1 m/s, which predicts an increased cardiovascular risk. Variables involved with progressive arterial stiffness need further evaluation. *J Clin Hypertens (Greenwich).* 2013;15:833–838.

The aortic pulse wave velocity (aPWV) is established as a blood pressure (BP)–independent risk factor for cardiovascular disease in the general population.[1,2] It provides the possibility to noninvasively measure arterial stiffness. Several studies have shown elevated aPWV and, thus, aortic stiffness in patients with chronic kidney disease (CKD).[3–5] The largest known study in this context demonstrated a significant negative correlation between aPWV and the level of kidney function estimated by estimated glomerular filtration rate (eGFR) in 2564 CKD patients.[6]

Endothelial dysfunction,[7] oxidant stress,[8] inflammation,[9] and activation of the renin-angiotensin system,[10] which are frequently evident in CKD patients, have been discussed as potential factors in connection with increased arterial stiffness.

With respect to prospective studies, aPWV is a predictor for cardiovascular morbidity and mortality in end-stage renal disease patients.[11] Likewise, Ford and colleagues[12] showed in 133 CKD stage 3 and 4 patients that aortic stiffness was independently associated with the rate of decline in renal function. These data provide evidence for a relationship between arterial stiffness and CKD. Moreover, arterial stiffness can predict cardiovascular survival and decline in renal function. By contrast, no data are available that investigate the natural progression of arterial stiffness in CKD patients and thus potential factors resulting in its accelerated progression. This is of particular interest for clinical routine procedures to assess timelines for reevaluation of arterial stiffness in CKD patients.

Therefore, it was the aim of this study to investigate the development of aPWV patterns over time and to identify parameters that may promote an accelerated progression of arterial stiffness in CKD. For this reason, the study examined aPWV in a cohort of 70 patients with CKD after 1 year to assess the natural progression of arterial stiffness and to define clinical parameters potentially associated with accelerated progression of arterial stiffness.

METHODS

Patient Recruitment: Inclusion and Exclusion Criteria

This prospective cohort study was initiated in autumn 2007 and the recruitment of patients for the follow-up examination took place from October 2008 to February 2009. The follow-up period was 12±1 months. All patients provided written consent to their participation and the study protocol was approved by the local ethics committee. Of the 70 patients with CKD, 34 were recruited from a kidney center in Weißenburg, Germany. The remaining 36 patients were treated in the outpatient unit of the Department of Nephrology of the Klinikum rechts der Isar Munich, Germany. The same examination procedures and devices were used for examinations both at baseline and at follow-up. The main criterion for inclusion of patients was the diagnosis of CKD, confirmed either by clinical data or biopsy.

Address for correspondence: Susanne Tholen, MD, Department of Nephrology, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 Munich, Germany
E-mail: susanne.tholen@tum.de

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Data Collection

The evaluation of anthropometric data included height, weight, and body mass index (BMI) of each patient, the underlying illness deemed to have caused the CKD, and other comorbidities such as diabetes mellitus. In addition, information with respect to medication, in particular lipid-lowering and antihypertensive drugs, was obtained from each patient. Laboratory tests included values for hemoglobin, glucose, glycated hemoglobin (HbA_{1c}), lipid profile (triglycerides and total, high-density lipoprotein, and low-density lipoprotein cholesterol), serum creatinine, and the protein/creatinine ratio (P/C ratio). The eGFR for patients with elevated serum creatinine levels was determined via the Modification of Diet in Renal Disease (MDRD) formula created by Levey and colleagues.[13] For patients with serum creatinine levels <1.1 mg/dL, the Mayo Clinic formula was used for this purpose, as described previously.[14] In order to calculate the mean annual GFR decrease, the serum creatinine values of the years 2005 until 2008 were transformed into GFR values using the MDRD formula and then allocated using the following formula: Delta GFR (mL/min/1.73 m²)=[(GFR 05 – GFR 06)+(GFR 06 – GFR 07)+(GFR 07 –GFR 08)]/3.

BP measurements were performed in a standardized manner. The patient had to lie down and remain in a resting state for 5 minutes. Three measurements were performed within 4 minutes on the right upper arm using the automatic hemodynamometer boso medicus PC (Bosch and Sohn GmbH u. Co. KG, Jungingen, Germany). The average of the systolic BP (SBP) and diastolic BP (DBP) was transformed to the mean BP (MBP) value: MBP (mm Hg)=DBP+1/3 (SBP – DBP).

The measurement of the aPWV was carried out 10 minutes after the BP measurement with the Complior SP device (Alam Medical, Paris, France)[15] using the subtraction of the carotid-femoral distance. The testing conditions were based on the recommendations by Laurent and colleagues.[16] The patients had been requested to refrain from nicotine or caffeine for at least 3 hours before the examination, as these substances may alter aPWV.[17] They were also told to avoid alcohol 10 hours before the measurement. The pressure transducers were placed on the pulse of the right common carotid artery and femoral artery. In order to calculate the distance between carotid and femoral pulse (ΔL in meters), the patients' height and weight had to be provided to the Complior SP device. The time interval (Δt in seconds) between the beginning of the carotid and femoral pulse wave is determined by the program as well. The ratio of ΔL to Δt, expressed in m/s, is referred to as aPWV. The measurement was repeated and if the two detected values did not differ by more than 1 m/s, the results were averaged to arrive at the mean aPWV. In a second step, the absolute change of the aPWV was determined by calculating the difference between the PWV values at baseline and follow-up. The relative change over time in percentage was determined by the following formula:

$$\Delta\text{aPWV}(\%) = (\text{aPWV} - \text{aPWV at baseline})/\text{aPWV at baseline}.$$

Statistical Analysis

All statistical tests were performed using SPSS version 17.0 for Windows (SPSS Inc, Chicago, IL). Patient and group characteristics were obtained by means of descriptive statistics. Quantitative data are expressed as mean and standard deviation, except for parameters not normally distributed, which are presented as median together with 25th and 75th percentile. Qualitative data are given as number and in percent.

To determine the change of the aPWV after the annual interval, the difference between the aPWV at baseline and at follow-up was calculated with a paired *t*-test, chi-square, or Mann-Whitney *U*-test where appropriate. Subgroup analysis of the 3 groups describing natural progression of arterial stiffness was performed with the analysis of variance and post hoc Bonferroni correction.

RESULTS

A total of 70 patients were included. The demographic data are provided in Table I. The mean age of the cohort was 65.8±11.8 years and 60% of the patients were men. In this cohort, 64.3% (n=45) had diabetes. Of those, 27.5% (n=11) had insulin-dependent diabetes. The main cardiovascular parameters are shown in Table II. There was a significant increase in arterial stiffness throughout the cohort comparing baseline aPWV (10.9 m/s) and follow-up (11.9 m/s). This corresponded to an increase in aPWV of approximately 11% (Table III). The CKD patients were characterized according to their aPWV progression. The patients were divided into 3 subgroups according to their aPWV at baseline and its change during the follow-up period. The threshold for the aPWV of 10 m/s was chosen since it has been validated as a transitional value between

TABLE I. Characteristics of Patients

Parameters	All Patients (N=70)
Age, y	65.8±11.8
Male/female sex, No. (%)	42 (60.0)/28 (40.0)
BMI, kg/m²	28.7±5.7
Hb, g/dL	12.9±1.7
Glucose, mg/dL	118.1±32.2
HbA_{1c}, %	6.5±1.0
Diabetes mellitus/ insulin, No. (%)	45 (64.3)/11 (27.5)
Triglycerides, mg/dL	150.0 (112.5; 212.3)
Total cholesterol, mg/dL	199.0±48.2
LDL cholesterol, mg/dL	112.5±46.0
HDL cholesterol, mg/dL	48.1±12.5
Statin therapy, No. (%)	29 (44.6)

Abbreviations: BMI, body mass index; Hb, hemoglobin; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein Insulin, number of insulin-dependent diabetics; LDL, low-density lipoprotein.

normal and pathological patterns in several studies.[17,18] The first group consisted of patients with an aPWV <10 m/s at baseline and follow-up. The second group included patients who had values <10 m/s at baseline, but proceeded to higher values at follow-up. Patients who showed aPWV values >10 m/s at baseline and follow-up constituted the third group. Hereafter, the 3 subgroups are referred to as group 1, 2, and 3 (Table IV). Corresponding to the chosen threshold of 10 m/s, the mean aPWV at baseline was 8.3 m/s in group 1, 9.1 m/s in group 2, and 13.5 m/s in group 3. The greatest change in the aPWV after 1 year was 2.1 m/s (24.5%) in group 2, whereas the patients in group 1 and group 3 showed only smaller changes of 0.1 m/s (1.6%) and 1.2 m/s (11%), respectively. The difference between aPWV measured at both time points varied significantly between groups 1 and 2 ($P<.01$) and between groups 1 and 3 ($P<.05$).

Patients' age significantly differed between the groups. Age was lowest in group 1 (57.8 years) and significantly higher in group 2 (66.8 years; $P<.05$) and 3 (70.2 years; $P<.001$). SBP significantly differed between the groups. SBP was lowest in group 1 (130.7 mm Hg). In group 2, SBP was nonsignificantly increased as compared with group 1 (133.1 mm Hg). Group 3 had significantly higher SBP values (148.9 mm Hg; $P<.01$). Level of HbA_{1c} was lowest in group 1 and significantly higher in group 3 ($P<.01$). Correspondingly, the number of diabetic CKD patients was significantly lower in group 1 (41%) as compared with group 2 (72%) and group 3 (77%).

In order to further examine the relationship between diabetes mellitus and the progression of aPWV over time, patients were divided into "diabetic" and

TABLE II. Cardiovascular Parameters (Blood Pressure Measurement was Conducted in Supine Positioning)

Cardiovascular Parameters	All Patients (N=70)
SBP, mm Hg	140.5±18.2
DBP, mm Hg	76.7±9.3
MBP, mm Hg	98.0±10.8
HR, min^{-1}	64.0±9.6
RAS blocker, No. (%)	57 (86.4)

Abbreviations: DBP, mean diastolic blood pressure; HR, heart rate; MBP, mean blood pressure; RAS blocker, renin-angiotensin-aldosterone system antagonists; SBP, mean systolic blood pressure.

TABLE III. Change of the aPWV Over Time

aPWV, m/s	All Patients (N=70)
aPWV at baseline, m/s	10.9±3.1
aPWV at follow-up, m/s	11.9±4.2[a]
Delta aPWV, m/s	1.1±2.0
Delta aPWV, %	11.0±20.1

Abbreviations: aPWV, aortic pulse wave velocity; Delta aPWV, difference of the aortic pulse wave velocity. [a]$P<.01$.

TABLE IV. Subgroup Analysis: Demographic and Cardiovascular Parameters in the 3 Groups Depending on the aPWV at Baseline and Its Change Over Time

	All Patients (N=70)		
	Group 1 (n=22)	Group 2 (n=18)	Group 3 (n=30)
Age, y	57.8±9.1	**66.8±9.3[a]**	**70.2±12.1[b]**
BMI, kg/m^2	27.1±5.5	27.5±5.7	28.3±4.7
Hb, g/dL	12.8±1.2	13.4±1.4	13.0±2.0
Glucose, mg/dL	110.8±30.8	119.4±31.2	119.4±34.9
HbA_{1c}, %	5.9±0.7	6.5±0.8	**6.9±1.0[c]**
Diabetes mellitus, No. (%)	9 (41.0)	13 (72.0)	**23 (77.0)[a]**
SBP, mm Hg	130.7±18.4	**133.1±15.9[c]**	**148.9±13.0[b]**
SBP at follow-up, mm Hg	130.6±16.4	135.9±17.3	149.3±12.8
DBP, mm Hg	73.7±9.1	77.7±7.3	77.3±10.2
DBP at follow-up, mm Hg	76.1±9.2	79.8±6.1	77.9±10.2
MBP, mm Hg	92.7±11.4	96.2±9.1	**101.1±9.6[c]**
HR, min/min	60.8±8.4	64.8±10.7	66.1±9.5
aPWV at baseline, m/s	8.3±1.1	**9.1±0.8[b]**	**13.5±2.7[b]**
Delta aPWV, m/s	**0.1±1.4[c]**	2.1±1.6	**1.2±2.2[a]**
Delta aPWV, %	**1.6±18.5[c]**	24.5±19.4	**11.0±18.0[a]**
Creatinine, mg/dL	2.0±1.9	1.4±0.6	2.0±1.4
eGFR, $mL/min/1.73\ m^2$	56.9±32.4	61.1±25.5	52.7±34.1
Delta eGFR, $mL/min/1.73\ m^2$	2.5±7.7	0.8±3.6	3.7±8.0
P/C ratio, g/g Krea	0.4±0.8	0.1±0.1	0.3±0.2

Abbreviations: aPWV, aortic pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; Delta aPWV, difference of the aortic pulse wave velocity; Delta eGFR, mean annual eGFR-decrease; Hb, hemoglobin; HbA_{1c}, glycated hemoglobin; HR, heart rate; MBP, mean blood pressure; SBP, systolic blood pressure; P/C ratio, protein/creatinine ratio. Group 1: aPWV <10 m/s at baseline and follow-up. Group 2: aPWV <10 m/s at baseline, >10 m/s at follow-up. Group 3: aPWV >10 m/s at baseline and follow-up. [a]$P<0.05$. [b]$P<.001$. [c]$P<.01$. Bold values indicate significance.

"nondiabetic." "Nondiabetic" CKD patients (n=25) had a baseline aPWV of 9.8 m/s. The follow-up aPWV was 10.2 m/s. This corresponds to an increase of 0.4 m/s (5.1%). The diabetic CKD patients (n=45) had significantly higher baseline aPWV (11.4 m/s). The follow-up aPWV in this group was significantly higher (13.0 m/s; $P<.05$), reflecting an annual increase of 1.5 m/s (15.1%). The difference between groups of baseline aPWV and follow-up aPWV, as well as the annual aPWV increase, was significant (baseline aPWV, $P<.05$; follow-up aPWV, $P<.01$; Delta aPWV, $P<.05$ [Table V]).

To assess the role of renal function decline, the GFR difference between baseline and follow-up was determined. The cohort was divided according to median GFR decrease after the annual interval (delta GFR=1.66 mL/min/1.73 m²). There is no significant difference in demographic and cardiovascular parameters or aPWV and its change over time between the two groups (Table VI).

In the final analysis, the study focused on the potential protective effect of a renin-angiotensin-aldosterone system antagonists (RAS) blocker on aPWV and its progression (Table VII). For this purpose, patients were divided into two subgroups according to their RAS medication status. There was no significant difference in aPWV progression between patients taking RAS medication and those not taking RAS blockers. By contrast, groups differed significantly with respect to the aPWV levels at baseline and follow-up. Patients taking RAS medications showed significantly higher aPWV levels at both time points.

TABLE V. Subgroup Analysis: Demographic and Cardiovascular Parameters in the Diabetes and Nondiabetes Group

	All Patients (N=70)		
	Diabetes Mellitus		Significance
	No (n=25)	Yes (n=45)	(2-Sided)
Age, y	63.7±13.0	66.9±11.2	.277
BMI, kg/m²	**26.3±5.2**	**30.0±5.6**	**.008**
Glucose, mg/dL	107.8±30.8	123.6±32.0	.070
HbA_{1c}, %	**5.7±0.5**	**6.9±1.0**	**<.001**
P/C ratio, g/g Krea	0.3±0.2	0.2±0.3	.097
SBP, mm Hg	135.6±18.6	143.3±17.6	.089
DBP, mm Hg	74.4±9.8	77.9±8.9	.124
MBP, mm Hg	94.8±11.3	99.7±10.2	.065
HR, min^{-1}	**59.0±6.8**	**66.9±9.8**	**.001**
aPWV at baseline, m/s	**9.8±2.6**	**11.4±3.1**	**.033**
aPWV at follow-up, m/s	**10.2±2.9**	**13.0±4.5**	**.009**
Delta aPWV, m/s	**0.4±2.0**	**1.5±1.9**	**.031**
Delta aPWV, %	5.1±21.5	15.1±18.3	.061

Abbreviations: aPWV, aortic pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; Delta aPWV, difference of the aortic pulse wave velocity; HR, heart ratio; HbA_{1c}, glycated hemoglobin; MAP, mean blood pressure; P/C ratio, protein/creatinine ratio; SBP, systolic blood pressure. Bold values indicate significance.

DISCUSSION

In the current study, the natural progression of aPWV over a period of 12 months in a cohort of 70 CKD patients was investigated. Throughout the cohort, aPWV increased after 1 year by 1.1 m/s. CKD patients with accelerated progression of arterial stiffness were characterized by higher age and SBP. In those patients, HbA_{1c} and diabetes mellitus were pronounced, but not to a level of statistical significance. Loss of renal function was not apparent in CKD patients with progressive arterial stiffness. The use of RAS blockers had no impact on aPWV progression.

The first major finding is that aPWV increased after 1 year by more than 1 m/s throughout the CKD cohort. Prospective cohort studies revealed that an increase in aPWV by 1 m/s results in a significant increase in cardiovascular morbidity and mortality, with a hazard ratio of 1.36 in patients with end-stage renal disease.[11,19] Therefore, the finding of increased aPWV in the CKD cohort suggests increased cardiovascular risk. However, the risk described in Blacher's study cannot be transferred to this study, as it did not evaluate end-stage renal disease.

TABLE VI. Subgroup Analysis: Demographic and Cardiovascular Parameters Depending on Delta GFR-Decrease (median = 1.66 mL/min/1.73 m²)

	Group 1 (GFR decrease <1.66)	Group 2 (GFR-decrease ≥ 1.66)	Sig. (2-sided)
Age, y	65.7±12.1	65.9±11.5	0.959
Diabetes mellitus, %	21 (62.0)	23 (68.0)	0.618
SBP, mmHg	138.9±19.1	141.2±17.0	0.604
DBP, mmHg	77.9±10.3	75.5±8.2	0.272
MBP, mmHg	98.3±11.7	97.4±9.9	0.732
aPWV, m/s	11.6±3.9	12.4±4.4	0.448
Delta aPWV, m/s	1.0±2.0	1.2±2.0	0.779
Delta aPWV, %	10.9±21.6	11.8±18.9	0.885
PP, mm Hg	60.5±16.2	65.0±14.4	> 0.05
aPP, mm Hg	50.0±14.9	57.3±22.2	> 0.05

Abbreviations: aPP, aortic pulse pressure; aPWV, aortic pulse wave velocity; Delta aPWV, difference of the aortic pulse wave velocity; MBP, mean blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; PP, pulse pressure.

TABLE VII. Subgroup Analysis: Demographic and Cardiovascular Parameters in Patients with and without RAS Blocker

	All patients		
	RAS blocker		
	No	Yes	Sig. (2-sided)
SBP, mmHg	134.3±19.4	139.8±17.9	0.234
DBP, mmHg	76.4±10.4	77.8±8.8	0.549
eGFR, ml/min/1.73 m^2	60.0±31.9	48.8±24.0	0.094
Diabetes mellitus, %	0.5±0.5	0.5±0.5	0.620
aPWV at baseline, m/s	**9.1±2.6**	**11.5±4.1**	**0.019**
aPWV at follow-up, m/s	**9.1±1.8**	**10.5±2.9**	**0.037**
Delta aPWV, m/s	−0.0±1.8	1.1±3.1	0.127

Abbreviations: aPWV, aortic pulse wave velocity; DBP, diastolic blood pressure; Delta aPWV, difference of the aortic pulse wave velocity; RAS blocker, renin-angiotensin-aldosterone-system-antagonists; SBP, systolic blood pressure. Bold values indicate significance.

The extent of aPWV increase in the investigated time frame is noteworthy. A significant increase in arterial stiffness appeared during the course of 1 year. This demonstrates that the progression of arterial stiffness in CKD patients can develop quickly. This further implies that the length and frequency of observation with respect to arterial stiffness should be carefully considered. Based on the findings of this study, annual testing of arterial stiffness in CKD patients could give useful information about changes of cardiovascular risk.

According to this first finding, the study further differentiated the set of CKD patients with respect to the longitudinal development of arterial stiffness. Patients with low and stable arterial stiffness were compared with patients demonstrating low aPWV at baseline but elevated aPWV at follow-up and a third group with high arterial stiffness at both time points.

CKD patients demonstrating at baseline low but at follow-up elevated aPWV had the strongest increase in aPWV with more than 2 m/s. Comparing those with CKD patients with low and stable aPWV, age and SBP appeared higher. Likewise, HbA_{1c} level and the diagnosis of diabetes tended to differ between the groups. By contrast, renal function and loss of renal function did not differ in comparison. Because of the small cohort, a validation of these parameters as independent predictors for progressive arterial stiffness using multivariate regression analysis was not feasible. However, age, SBP, and diabetes are widely accepted confounders for arterial stiffness, suggesting a potential link between these factors and the progression of arterial stiffness.[20–22] The effect of renal function and loss of renal function has to be considered carefully. Although a relationship between arterial stiffness and renal function is evident,[6] the investigated range in this cohort is small, which raises difficulties. Similarly, the loss of renal function reflected at 1 year has to be considered as a limitation of the study. The potential effects of RAS blockers on aPWV and its progression should also be discussed carefully. Patients who were prescribed RAS blockers were already in more advanced stages of both CKD and cardiovascular disease. Therefore, and due to the short time interval, the effect of this medication might be underestimated in this cohort.

CONCLUSIONS

This study provides evidence that arterial stiffness in CKD patients is characterized by a significant increase in aPWV during the course of 1 year. The progression reaches a level that is known to significantly increase cardiovascular risk. Therefore, arterial stiffness in CKD patients should be further investigated for it to become an appropriate tool for cardiovascular risk stratification. Further studies are also needed to clarify whether age, SBP, and diabetes are independent predictors of this progression and what role renal function plays in this context.

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