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Original Paper

Albuminuria is Associated With Subendocardial Viability Ratio in Chronic Kidney Disease Patients

Robert Ekart[a] Sebastjan Bevc[b] Nina Hojs[b] Maša Knehtl[b] Benjamin Dvoršak[b] Radovan Hojs[b]

[a]Department of Dialysis, [b]Department of Nephrology, University Medical Centre Maribor, Clinic for Internal Medicine, Maribor, Slovenia

Key Words
Albuminuria • Chronic kidney disease • Pulse-wave analysis

Abstract
Background/Aims: Albuminuria is a well-established marker of subclinical organ damage. Pulse-wave analysis (PWA) employs the technique of applanation tonometry to obtain a peripheral pulse pressure waveform, from which central hemodynamic data are derived by application of the transfer function. Using PWA we can measure the subendocardial viability ratio (SEVR) and ejection duration (ED). SEVR or the Buckberg index is a non-invasive estimate of myocardial workload, oxygen supply and perfusion and a measure of the ability of the arterial system to meet the heart`s energy requirements. ED is the duration of ventricular ejection. The objective of this study was to evaluate the relationship between albuminuria and PWA parameters in chronic kidney disease (CKD) patients. ***Methods:*** We studied 86 CKD patients aged 59.8±13.5 years, 56 (65.1%) were male. PWA analysis and 24-hour ambulatory blood pressure (24hABP) monitoring were performed. The following parameters were calculated: (1) aortic augmentation index with and without correction for a heart rate of 75 (Aix and AIx@HR75), (2) SEVR, calculated as the ratio of the diastolic pressure time index and the systolic pressure time index, (3) ED, (4) estimated central aortic systolic and diastolic pressure and (5) central aortic pulse pressure calculated as the difference between estimated aortic systolic and diastolic BP. Blood samples and urine albumin-to-creatinine ratio (UACR) were analyzed; UACR values were natural log transformed (lnUACR). ***Results:*** Using CKD-EPI creatinine-cystatin C formula the eGFR in patients was 7-130 ml/min/1.73m^2 (mean 32.6; SD±24.6). We found statistically significant correlation between lnUACR and cystatin C (r=0.308; *P*=0.004), eGFR (r=-0.219; *P*=0.04), hemoglobin (r=-0.255; *P*=0.02), phosphorus (r=0.222; *P*=0.04), iPTH (r=0.268; *P*=0.01), SEVR (r=-0.254; *P*=0.02) and ED (r=0.315; *P*=0.003). No statistically significant correlations between lnUACR and cardiac biomarkers TnI, NT-proBNP, central aortic BP and 24h ABP values were found. Using multiple regression analysis statistically significant association was found between SEVR as dependent variable and lnUACR (β=-0.223, *P*=0.039),

Assoc. Prof. Robert Ekart, MD, PhD
University Medical Centre Maribor, Clinic for Internal Medicine, Department of Dialysis, Ljubljanska 5, SI-2000 Maribor (Slovenia), Tel. + 386 2 321 27 25, Fax + 386 2 331 23 93
E-Mail robert.ekart2@guest.arnes.si

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sex (β=-0.216, *P*=0.035), and diabetes (β=0.332, *P*=0.001). Multiple regression analysis with ED as dependent variable has shown statistically significant association with lnUACR (β=0.242, *P*=0.031) and diabetes (β=-0.275, *P*=0.01). Patients were stratified into tertiles according to the lnUACR. Statistically significant differences in serum creatinine (*P*=0.001), cystatin C (*P*=0.012), hemoglobin (*P*=0.03), calcium (*P*=0.036), iPTH (*P*=0.008), SEVR (*P*=0.007) and ED (*P*=0.004) were found between tertiles. In post hoc analysis we found statistically significant differences between first and third tertile in SEVR (*P*=0.002; 95% CI:10.5-45) and in ED (*P*=0.001; 95% CI:-6.89-(-1.87)). ***Conclusions:*** Nondialysis CKD patients with higher levels of albuminuria have lower SEVR and higher ED and our results have shown the importance of central hemodynamic parameters like are SEVR and ED as a better or earlier noninvasive hemodynamic indexes in these patients.

Introduction

Albuminuria is a common finding in chronic kidney disease (CKD) and is one of the earliest markers of glomerular diseases. It is often associated with underlying diabetic glomerulosclerosis, hypertension, obesity, and vascular disease, where the underlying renal pathology is not known [1]. CKD is associated with numerous complications directly or indirectly related to the cause of CKD, decreased glomerular filtration rate (GFR) or albuminuria. Population-based studies have demonstrated an increased risk of death, and cardiovascular mortality as GFR falls below 60 ml/min/1.73 m^2 or when albuminuria is present [1, 2]. The presence of higher levels of proteinuria increases the risk of death, acute myocardial infarction and progression to kidney failure independently of the degree of estimated GFR (eGFR) [2]. Increased urine albumin-to-creatinine ratio (UACR) has also been related to extracardiac vascular changes, such as increased carotid wall thickness and carotid-femoral pulse wave velocity (cfPWV), which are expression of atherosclerosis and aortic stiffness, respectively [3]. Arterial stiffness describes the rigidity of the arterial walls and is a general term for the elasticity (or compliance) of the arteries. Pulse wave analysis (PWA) employs the technique of applanation tonometry to obtain a peripheral pulse pressure waveform, from which central haemodynamic data are derived by application of the transfer function. Measurements obtained from PWA have been shown to be reproducible both in healthy subjects and patients with known cardiovascular risk factors [4-6]. PWA allows the measure of several hemodynamic indexes that have been used to assess global cardiovascular risk. The subendocardial viability ratio (SEVR) or the Buckberg index is a non-invasive estimate of myocardial workload, oxygen supply and perfusion. SEVR is a measure of the ability of the arterial system to meet the heart`s energy requirements and is usually high, 130-200% [7, 8]. Ejection duration (ED) is the time period (in milliseconds) from the beginning of the rise of the central pulse pressure until the incisura in the pressure curve, reflecting the closing of the aortic valve [7]. The ratio of the duration of systolic ejection to the total duration of a cardiac cycle is the ejection duration index [9]. Patients with systolic dysfunction have been found to have a higher ED than those with diastolic dysfunction [10]. In patients with CKD stage 3-4, a reduction of SEVR predicted cardiovascular mortality in a multicenter, prospective study [11]. In type 1 diabetes patients lower SEVR was associated with renal damage, albuminuria and history of cardiovascular disease [12, 13].

The purpose of our study was to evaluate the relationship between UACR and different PWA parameters in CKD patients.

Materials and Methods

Study population

The study population consisted of 86 CKD patients aged 59.8±13.5 years, 56 (65.1%) were male, all Caucasian, from our outpatient clinic. Only subjects with age > 18 years and criteria for CKD (markers

of kidney damage or/and decreased GFR) according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition and classification of CKD [1] were included in this analysis. According to the Sphygmocor Clinical Guide instructions, patients with atrial fibrillation and aortic valve stenosis were excluded [7]. If the radial pulse is modified due to severe obstruction of any part of the brachial artery system or arrhythmia, PWA device Sphygmocor cannot be used in these situations to derive aortic pressure [7]. Primary causes of CKD were: 36 hypertensive nephropathy, 19 diabetic nephropathy, 12 chronic glomerulonephritis, 6 polycystic kidney disease, 13 others. The study was approved by the National Ethics Committee (N° 42/01/11) and adhered to the Declaration of Helsinki. All patients gave written informed consent.

Pulse wave analysis

All patients were studied in the morning, between 8 a.m. and 11 a.m. Prior to the measurement, subjects were under similar conditions (abstained from coffee, cigarettes, heavy meals, and exercise). Each patient waited for 5-10 min in a quiet room before blood pressure (BP) recordings and PWA analyses were taken. Radial artery pressure waveforms were recorded using applanation tonometry (SphygmoCor, AtCor Medical, Ltd., Sydney, Australia). A single examiner performed all measurements. An average radial pressure waveform was generated for at least 10 seconds of sequential radial pressure waveforms. The SphygmoCor PWA System derives a calibrated BP waveform at the ascending aorta from a peripheral pressure waveform, recorded non-invasively at the radial artery. During the procedure, the patients were seated comfortably beside a table with their arm resting on the table and their palm facing upward. The following values for quality indices were considered acceptable: operator index ≥ 80 %, average pulse height ≥ 80 %, pulse height variation ≤ 5 %, diastolic variation ≤ 5 %.

The following parameters were calculated: (1) aortic augmentation index with and without correction for a heart rate of 75 (Aix and AIx@HR75), computed as the difference between the first and the second systolic shoulders divided by the pulse pressure, (2) SEVR, calculated as the ratio of the diastolic pressure time index and the systolic pressure time index, (3) ED, the duration of ventricular ejection, (4) estimated central aortic systolic and diastolic pressure (CASP and CADP) and (5) central aortic pulse pressure (CAPP) calculated as the difference between estimated aortic systolic and diastolic BP.

Office and ambulatory blood pressure measurements

Before the PWA analysis office brachial diastolic and systolic BP values have been obtained from the portable bedside monitoring automatic BP device (Dash 4000, General Electric Healthcare, Dallas, TX, USA). After PWA analysis ambulatory BP (24hABP) monitoring was done for 24-hour using a Schiller BR-102 plus monitor (Schiller, Switzerland). BP was recorded every 20 minutes during the day and every 30 minutes during the night. The cuff of the BP monitor was applied to the upper portion of the arm, and the patients were instructed to attend to their usual activities and medications.

Laboratory variables

Blood samples for serum creatinine, cystatin C, total cholesterol, triglycerides, hemoglobin, high-sensitive C-reactive protein (hsCRP), intact parathyroid hormone (iPTH), cardiac biomarkers (troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP)) were drawn from the vein at the beginning of the study. Urine albumin concentration was analyzed by an immunonephelometric method (Dimension Vista, Siemens Healthcare Diagnostics, Newark, DE, USA). UACR was calculated by the formula: urine albumin (mg/L) × 8.84/urine creatinine (mmol/L) and expressed in mg/g. eGFR was calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C formula [14].

Statistical analysis

All data are presented as mean values and range or SD, whereas UACR data were natural log transformed (lnUACR) because of the skewed nature of the data. Correlation (Pearson and Spearman coefficient) between different variables was performed. A multiple regression analysis was used to assess the influence of independent variables that could have an effect on SEVR and/or ED as a dependent variable. As independent variables age, sex, eGFR, diabetes, smoking, lnUACR and mean ABP were considered. The association between lnUACR and other factors that are supposed that could have an influence on lnUACR was further tested by stratifying patients into tertiles according to the lnUACR values. One way ANOVA test for multiple groups was used. For all tests, a P value of <0.05 was considered as statistically significant. All of the statistical analyses were performed with the Statistical Package for Social Sciences for Windows version 22.0 (SPSS Inc, Chicago, IL, USA).

Results

The baseline characteristics of the study population are shown in Table 1. The mean age was 59.8 years, 65.1% were male. Data on arterial hemodynamics are shown in Table 2. The mean SEVR was 151%, which is comparable with normal conditions (~130- 200%). The mean augmentation index which is an important measurement of arterial compliance and increases with age was 29, which is higher than normal population in age 60 years (mean 26.1; lower 5% confidence interval 7.5 and upper 5% confidence interval 47.7). Average brachial systolic (but not diastolic) BP values were higher (146/80 mmHg) than mean central aortic systolic pressure values (135/81 mmHg).

According to the CKD stage most of the patients (69.8%) had CKD stage 3 and 4, stage 5 had 17.4%, stage 1 had 5.8% and stage 2 had 7% patients.

Table 1. Characteristics of the study population

N=86	Mean/range
Age (years)	59.8 (22-88)
Gender – male (N, %)	56 (65.1)
Body mass index (kg/m^2)	28.4 (19-42)
Smokers (N, %)	38 (44.2)
Serum creatinine (μmol/L)	259 (71-669)
Cystatin C (mg/L)	2.1 (0.7-4.2)
eGFR (ml/min/1.73 m^2)	33 (7-130)
Troponin I (ng/mL)	0.02 (0.02-0.12)
NT-proBNP (pg/mL)	122 (1-921)
Total cholesterol (mmol/L)	5 (2.7-9)
Triglycerides (mmol/L)	2.04 (0.4-8)
hsCRP (mg/L)	6 (0.2-70)
Calcium (mmol/L)	2.2 (1.9-2.7)
Phosphorus (mmol/L)	1.2 (0.7-2.5)
iPTH (pg/mL)	140 (20-535)
UACR (mg/g)	940 (2-7641)
lnUACR	5.86 (0.7-8.9)

Abbreviations: eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; hsCRP, high sensitive C-reactive protein; iPTH, intact parathyroid hormone; UACR, urine albumin-to-creatinine ratio; lnUACR, natural log transformed urine albumin-to-creatinine ratio

Table 2. Arterial hemodynamics of the study population

N=86	Mean / range / SD
Subendocardial viability ratio (%)	151 (79-235) / 34.1
Augmentation index	29 (-3-56) / 11.1
Augmentation index @HR75	25 (1-48) / 9.4
Ejection duration (%)	35 (27-48) / 5
Central aortic systolic blood pressure (mmHg)	135 (96-217) / 22.6
Central aortic diastolic blood pressure (mmHg)	81 (44-118) / 11.9
Central aortic pulse pressure (mmHg)	54 (24-99) / 19.1
24h ambulatory mean arterial pressure (mmHg)	97 (71-130) / 10.8
24h ambulatory heart rate (beats per min)	71 (54-97) / 8.1

We found a statistically significant correlation between lnUACR and cystatin C (r=0.308; *P*=0.004), eGFR (r=-0.219; *P*=0.04), hemoglobin (r=-0.255; *P*=0.02), phosphorus (r=0.222; *P*=0.04), iPTH (r=0.268; *P*=0.01), SEVR (r=-0.254; *P*=0.018) and ED (r=0.315; *P*=0.003). Figure 1 shows that with the increasing of albuminuria (lnUACR) the SEVR is decreasing. No statistically significant correlations between lnUACR and cardiac biomarkers troponin I (r=-0.09; *P*=0.421), NT-proBNP (r=0.06; *P*=0.574), central aortic systolic BP (r=0.1; *P*=0.364), central aortic diastolic BP (r=0.08; P=0.451) and 24hABP (r=0.14; *P*=0.19) values were found.

Using multiple regression analysis statistically significant association between SEVR as dependent variable and sex (β=-0,216, *P*=0.035), diabetes (β=0.332, *P*=0.001), and lnUACR (β=-0.223, *P*=0.039) as independent variables were found (Table 3). In multiple regression analysis with ED as dependent variable only lnUACR (β=0.242, *P*=0.031) and diabetes

Table 3. Multiple regression analysis of factors related to subendocardial viability ratio (SEVR) and ejection duration (ED) as dependent variable

	SEVR		ED	
Variables	β	P	β	P
Age	-0.124	0.259	-0.089	0.436
Sex	-0.216	0.035	0.145	0.171
eGFR	-0.075	0.489	0.085	0.452
Diabetes	0.332	0.001	-0.275	0.01
Smoking	-0.167	0.089	0.156	0.128
lnUACR	-0.223	0.039	0.242	0.031
Mean 24hABP	-0.01	0.919	0.004	0.967

Abbreviations: eGFR, estimated glomerular filtration rate; lnUACR, natural log transformed urine albumin-to-creatinine ratio; ABP, ambulatory blood pressure

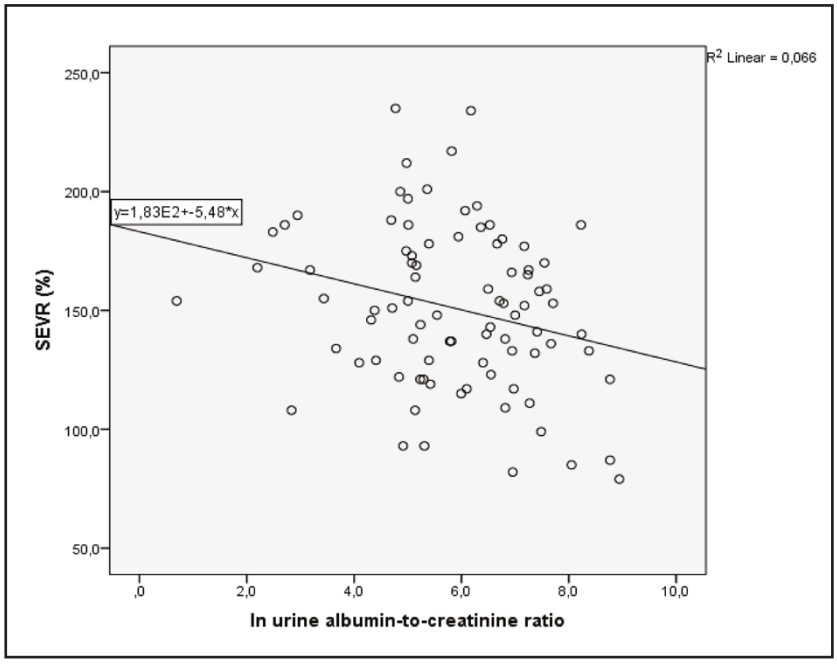

Fig. 1. Scatter plot of subendocardial viability ratio (SEVR) and log transformed urine albumin-to-creatinine ratio with the regression line showing the negative relationship between SEVR and log transformed urine albumin-to-creatinine ratio.

(β=-0.275, *P*=0.01) were statistically significant (Table 3). Patients were stratified into tertiles according to the lnUACR. Using one way ANOVA statistically significant differences in serum creatinine (*P*=0.001), cystatin C (*P*=0.012), hemoglobin (*P*=0.03), calcium (*P*=0.036), iPTH (*P*=0.008), SEVR (*P*=0.007) and ED (*P*=0.004) between the tertiles were found (Table 4). Figure 2 presents PWA parameters SEVR and ED for patients divided into tertiles according to ln UACR and we found that SEVR in the third tertile was almost 30% lower than in the first tertile. The mean ED in all three tertiles was similar (33-37%), despite them we found statistically significant difference between all three groups.

Table 5 shows statistically significant differences (post hoc analysis, LSD) between the first and the third and the first and the second tertiles according to the lnUACR.

We also formed three groups of patients with most frequent primary renal disease in our cohort. Patients with diabetic nephropathy (group 1), hypertensive nephropathy (group 2) and chronic glomerulonephritis (group 3) were compared. Using one way ANOVA statistically significant differences between groups in age, eGFR, UACR, lnUACR, NT-proBNP, SEVR, ED, CASP, CAPP and 24h APP were found (Table 6).

Table 7 shows statistically significant differences (post hoc analysis, LSD) between the first and the third and the first and the second group according to the group of primary renal disease.

Table 4. Baseline clinical and biochemical characteristics of 86 chronic kidney disease patients divided into tertiles according to lnUACR

Variable	Tertile 1 (n=30)	Tertile 2 (n=29)	Tertile 3 (n=27)	P-value
Age (years)	64±11	57±15	58±13	0.063
Smoking (N/%)	14(47)	13(45)	11(41)	0.904
Body mass index (kg/m^2)	29 ±5.6	28 ±4.8	28 ±5.2	0.372
Serum creatinine (μmol/L)	198±88	272±150	325±128	0.001
Cystatin C (mg/L)	1.8±0.7	2.1±0.9	2.5±0.9	0.012
eGFR (ml/min/1.73 m^2)	37±20	36±32	24±17	0.085
Hemoglobin (g/L)	135±14	128±22	123±15	0.03
Total cholesterol (mmol/L)	4.7±1.1	5.1±1.5	5.3±1.3	0.334
Triglycerides (mmol/L)	1.6±0.7	2.3±1.7	2.2±1.2	0.097
NT-pro-BNP (pg/mL)	112±173	120±165	134±199	0.889
Troponin I (ng/mL)	0.02±0.01	0.02±0.02	0.02±0.002	0.479
High sensitive CRP (mg/L)	8.1±15.8	7.1±11	2.6±3	0.176
Calcium (mmol/L)	2.3±0.1	2.3±0.2	2.2±0.1	0.036
Phosphorus (mmol/L)	1.2±0.3	1.2±0.4	1.3±0.3	0.222
Intact-PTH (pg/ml)	93±59	151±121	180±125	0.008
SEVR (%)	163±34	153±33	135±31	0.007
ED (%)	33±4.8	35±4.9	37±4.6	0.004
Augmentation index	33±11	26±13	29±9	0.071
Augmentation index@HR75	26±10	24±9	27±8	0.341
CASP (mmHg)	134±25	131±20	140±22	0.276
CADP (mmHg)	80±15	82±9	82±11	0.753
CAPP (mmHg)	54±20	49±17	58±19	0.171
24h ASBP (mmHg)	131±18	136±15	139±20	0.247
24h ADBP (mmHg)	74±11	77±7	76±9	0.412
24h AMAP (mmHg)	95±12	98±8	99±12	0.303
24h APP (mmHg)	57±16	59±12	62±16	0.397
24h ambulatory heart rate	69±8	71±7	73±9	0.167

Abbreviations: eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; PTH, parathyroid hormone; SEVR, subendocardial viability ratio; ED, ejection duration; CASP, central aortic systolic pressure; CADP, central aortic diastolic pressure; CAPP, central aortic pulse pressure; ASBP, ambulatory systolic blood presssure; ADBP, ambulatory diastolic blood pressure; AMAP, ambulatory mean arterial pressure; APP, ambulatory pulse pressure; lnUACR, natural log transformed urine albumin-to-creatinine ratio

Discussion

In our study associations between albuminuria and central hemodynamic parameters SEVR and ED in nondialysis CKD patients were found. To our knowledge, this is the first study that showed that a lower SEVR and higher ED are associated with higher levels of albuminuria in nondialysis CKD patients. We found no significant relationships between albuminuria and other PWA parameters, including aortic augmentation index with and without correction for a heart rate of 75, CASP, CADP, and CAPP.

Albuminuria is a potential marker for arteriosclerosis. Albuminuria caused by glomerular damage seems to be associated with endothelial injury of the glomeruli, which led us to the idea that albuminuria can be used as a variable for arteriosclerotic changes in other arteries. A possible explanation of our results is that lower SEVR and higher ED

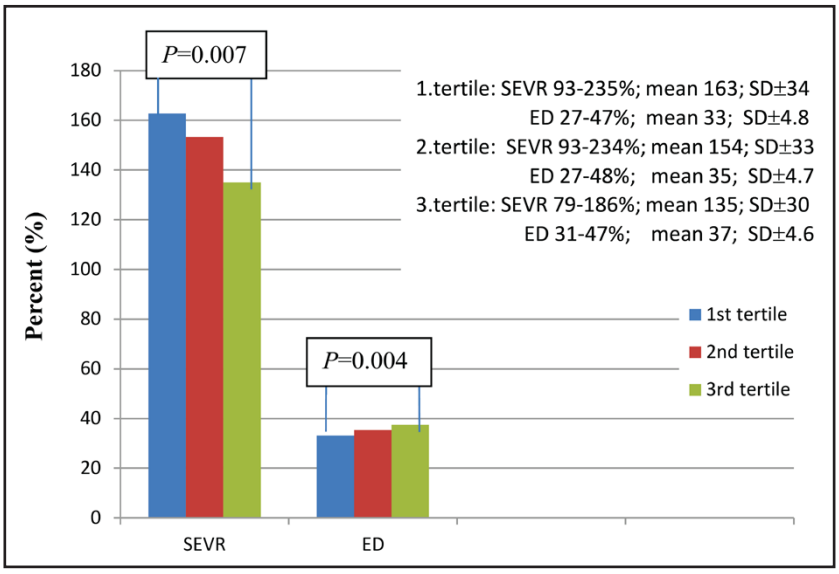

Fig. 2. Pulse wave analysis parameters (SEVR and ED) for patients divided into tertiles according to log transformed urine albumin-to-creatinine ratio. Abbreviations: SEVR, subendocardial viability ratio; ED, ejection duration.

Table 5. One way ANOVA test for multiple groups - post hoc analysis (LSD) differences between the tertiles according to the lnUACR values

Variable	P value and 95% CI between the first and the second tertile	P value and 95% CI between the second and the third tertile	P value and 95% CI between the first and the third tertile
Age	*P*=0.04; 95% CI: 0.24-13.7	*NS*	*P*=0.04; 95% CI: 0.16-13.9
SEVR	*NS*	*NS*	*P*=0.006; 95% CI: 7.2-42.1
ED	*NS*	*NS*	*P*=0.002; 95% CI: -6.53-(-1.55)
Serum creatinine	*P*=0.04; 95% CI: -134.2-(-3.8)	*NS*	*P*=0.001; 95% CI: -184.8-(-52.2)
Cystatin C	*NS*	*NS*	*P*=0.02; 95% CI: -1.1-0.08
Hemoglobin	*NS*	*NS*	*P*=0.016; 95% CI: 2.2-21.2
iPTH	*P*=0.048; 95% CI: -108.8-(-0.6)	*NS*	*P*=0.004; 95% CI: -136.6-(-26.5)

Abbreviations: CI, Confidence Interval; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; SEVR, subendocardial viability ratio; ED, ejection duration; lnUACR, natural log transformed urine albumin-to-creatinine ratio

represent impaired, shortened perfusion of the subendocardial myocardium relative to the cardiac workload mainly due to a reduction in diastolic perfusion time. These patients may have asymptomatic disturbances in myocardial perfusion or arteriosclerotic changes of coronary arteries. For this reason, they could have a higher risk for cardiovascular morbidity and mortality. As no correlation between albuminuria and cardiac biomarkers troponin I and NT-pro-BNP were found, our finding may emphasize the role of central hemodynamic parameters SEVR and ED as better or earlier noninvasive hemodynamic indexes.

Moreover, the linkage between albuminuria and central hemodynamic parameters may explain the association between albuminuria and the development of extrarenal complications in CKD patients. The risks of mortality, myocardial infarction, and progression

Table 6. Baseline clinical and biochemical characteristics of 67 chronic kidney disease patients divided into three groups according to primary renal disease

Variable	Hypertensive nephropathy (n=36)	Diabetic nephropathy (n=19)	Chronic glomerulonephritis (n=12)	P-value
Age (years)	65±13	65±9	48±11	0.0001
UACR (mg/g)	516±762	1679±2196	1458±1856	0.017
lnUACR	4.75±1.7	6±1.5	6.3±1.1	0.004
eGFR (ml/min/1.73 m^2)	31±25	27±16	52±35	0.022
NT-pro-BNP (pg/mL)	102±143	198±215	29±44	0.013
SEVR (%)	155±30	124±31	155±29	0.001
ED (%)	34±4.7	38±5.5	36±4.9	0.02
CASP (mmHg)	138±24	148±18	120±14	0.003
CAPP (mmHg)	56±20	68±15	40±10	0.0001
24h APP (mmHg)	56±20	71±13	50±12	0.0001

Abbreviations: lnUACR, natural log transformed urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; SEVR, subendocardial viability ratio; ED, ejection duration; CASP, central aortic systolic pressure; CAPP, central aortic pulse pressure; APP, ambulatory pulse pressure

to kidney failure associated with a given level of eGFR are independently increased in patients with higher levels of proteinuria [2]. Patients with massive proteinuria but without overtly abnormal eGFR have worse clinical outcomes than those with moderately reduced eGFR without proteinuria [2]. In the study of Hemmelgarn et al., the risk of all-cause mortality was markedly higher among participants with eGFR of 30 to 44.9 mL/min/1.73 m^2 [2]. In our study, the patients with the highest albuminuria level had mean eGFR 24 mL/min/1.73 m^2, and these patients had lower SEVR than other patients. According to our results we could make a hypothesis that CKD patients with higher levels of albuminuria, lower SEVR, and higher ED had more impaired perfusion of subendocardial myocardium, which could lead to an increased risk of cardiovascular complications and death. It is well known that many CKD patients die before they start with renal replacement therapy. Impaired kidney function may be a merely marker for severity of vascular disease, including atherosclerosis that is not yet clinically evident [15].

Mosimann et al. have shown that SEVR and aortic augmentation index are associated with ankle-brachial arterial pressure in a study of 65 patients with peripheral arterial disease [16]. Prince et al. reported significantly lower SEVR in association with ankle-brachial arterial pressure index in 144 patients with type 1 diabetes [17]. Theilade et al. found in a cohort of 636 type 1 diabetes patients that decreased SEVR was independently associated with albuminuria and history of cardiovascular disease [13]. The eGFR in these patients was much higher (83 vs. 33 ml/min/1.73m^2) than in our patients. Prince et al. found in a cohort of 133 type 1 diabetes patients that higher augmentation pressure and lower SEVR were associated with microalbuminuria and poor renal function [12]. Di Micco et al. performed PWA in 212 patients with CKD stage 3-4 and found that a greater reduction of SEVR values significantly predicts cardiovascular mortality [11]. The results of our present study and all mentioned studies show that SEVR could be a valuable tool for the assessment of renal and cardiovascular risk.

Our study has some limitations due to its observational nature. The main limitation is a small sample size. Furthermore only Caucasian patients were included, it is a single-center cohort study and no follow-up was performed. The lack of a control group with normal renal function also constitutes a limitation. The strength of our study is that we performed PWA measurements, 24hABP and laboratory measurements of cardiovascular risk factors, which

Table 7. One way ANOVA test for multiple groups - post hoc analysis (LSD) differences between the groups according to the primary renal disease: diabetic nephropathy (group 1), hypertensive nephropathy (group 2) and chronic glomerulonephritis (group 3)

Variable	P value and 95% CI between the diabetic and the hypertensive nephropathy group	P value and 95% CI between the hypertensive and the chronic glomerulonephritis group	P value and 95% CI between the diabetic nephropathy and the chronic glomerulonephritis group
Age	NS	P=0.0001; 95% CI: 9.2-24.4	P=0.0001; 95% CI: 7.8-24.8
Body mass index	P=0.04; 95% CI: 0.01-5.7	NS	NS
eGFR	NS	NS	P=0.01; 95% CI: -44.7-(-5.4)
Total cholesterol	NS	NS	P=0.048; 95% CI: -2-(-0.011)
NT-pro-BNP	P=0.02; 95% CI: 15.2-189	NS	P=0.004;95% CI: 55.3-283.3)
Calcium	NS	NS	P=0.02; 95% CI: -0.2-(-0.02)
lnUACR	P=0.007; 95% CI: 0.35-2.1	P=0.01; 95% CI: 2.75-2.35	NS
SEVR	P=0.0001; 95% CI: -50.3-(-15.9)	NS	P=0.007; 95% CI: -54.2-(-9)
ED	P=0.004; 95% CI: 1.35-6.9	NS	NS
CASP	NS	P=0.01; 95% CI: 4.25-31.9	P=0.001; 95% CI: 12.4-43.1
CAPP	P=0.01; 95% CI: 2.34-21.3	P=0.006; 95% CI: 4.6-27	P=0.0001; 95% CI: 15.2-40.2
24hAPP	P=0.003; 95% CI: 3.9-19.1	P=0.048; 95% CI: 0.06-17.9	P=0.0001; 95% CI: 10.6-30.4

Abbreviations: CI, Confidence Interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; lnUACR, natural log transformed urine albumin-to-creatinine ratio; SEVR, subendocardial viability ratio; ED, ejection duration; CASP, central aortic systolic pressure; CAPP, central aortic pulse pressure; APP, ambulatory pulse pressure

could have an influence on albuminuria, all at the same time. The study was conducted in patients with different CKD etiology and not only in diabetic patients such as in some others studies [12, 13].

Conclusion

We have shown that in nondialysis CKD patients higher levels of albuminuria are associated with lower SEVR and higher ED. These findings suggest the importance of PWA measurements, which is a simple, easily reproducible, and not time consuming method, which could help us as a clinical tool in detecting CKD patients with a higher risk for cardiovascular morbidity.

Further prospective studies are needed to test the influence of eGFR, albuminuria and various other factors on PWA variables SEVR and ED.

Disclosure Statement

The authors declare that there is no conflict of interest.

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References

1 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013;3:1-150.

2 Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M: Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010;303:423-429.

3 Viazzi F, Pontremoli R: Blood pressure, albuminuria and renal dysfunction: the 'chicken or egg' dilemma. Nephrol Dial Transplant 2014;29:1453-1455.

4 Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ: Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998;16:2079-2084.

5 Siebenhofer A, Kemp C, Sutton A, Williams B: The reproducibility of central aortic blood pressure measurements in healthy subjects using applanation tonometry and sphygmocardiography. J Hum Hypertens 1999;13:625-629.

6 Filipovsky J, Svobodova V, Pecen L: Reproducibility of radial pulse wave analysis in healthy subjects. J Hypertens 2000;18:1033-1040.

7 Sandy Skinner and contributors. Sphygmocor clinical Guide, pulse wave analysis. AtCor Medical Pty Ltd (formerly PWV Medical) ABN 11 062 279 985. Head Office: West Ryde Corporate Centre, 11/1059-1063 Victoria road, West Ryde, NSW 2114, Australia. Available at: www.atcormedical.com.

8 Buckberg GD, Fixler DE, Archie JP, Hoffman JI: Experimental subendocardial ischemia in dogs with normal coronary arteries. Circ Res 1972;30:67-81.

9 Crilly M, Coch C, Bruce M, Clark H, Ailliams D: Indices of cardiovascular function derived from peripheral pulse wave analysis using radial applanation tonometry: a measurement repeatability study. Scand J Clin Lab Invest 2007;67:413-422.

10 Nichols WW, O'Rourke MF: McDonald's blood flow in arteries: theoretical, experimental and clinical principles, 5thedition. Hodder Arnold; Oxford University Press, pp. 1-624, 2005.

11 Di Micco L, Salvi P, Bellasi A, Sirico ML, Di Iorio B: Subendocardial viability ratio predicts cardiovascular mortality in chronic kidney disease patients. Blood Purif 2013;36:26-28.

12 Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ: Augmentation pressure and subendocardial viability ratio are associated with microalbuminuria and with poor renal function in type 1 diabetes. Diab Vasc Dis Res 2010;7:216-224.

13 Theilade S, Hansen TW, Rossing P: Central hemodynamics are associated with cardiovascular disease and albuminuria in type 1 diabetes. Am J Hypertens 2014;27:1152-1159.

14 Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS: Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20-29.

15 Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX: Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006;17:2034-2047.

16 Mosimann K, Jacomella V, Thalhammer C, Meier TO, Kohler M, Amann-Vesti B, Husmann M: Severity of peripheral arterial disease is associated with aortic pressure augmentation and subendocardial viability ratio. J Clin Hypertens (Greenwich) 2012;14:855-860.

17 Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ: Pulse wave analysis and prevalent cardiovascular disease in type 1 diabetes. Atherosclerosis 2010;213:469-474.