Razmerje subendokardne viabilnosti, ambulantno merjenje krvnega tlaka in serumski označevalci srčno-žilnih bolezni pri bolnikih s kronično ledvično boleznijo

Subendocardial viability ratio, ambulatory blood pressure monitoring and serum biomarkers for cardiovascular disease in chronic kidney patients

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Izvleček

Namen: *Kronična ledvična bolezen je povezana z visoko prevalenco srčnožilnih bolezni. Tehnika meritve pulznega vala nam poda informacije o aortnih tlakih in temelji na neinvazivnih meritvah perifernega pulza. Razmerje subendokardne viabilnosti miokarda kot del analize perifernega pulznega vala je neinvazivna meritev mikrovaskularne prekrvavitve miokarda.*

Metode: *V naši raziskavi smo pri bolnikih s kronično ledvično boleznijo analizirali povezavo med razmerjem subendokardne viabilnosti miokarda, 24-urnimi meritvami krvnega tlaka in serumskimi označevalci za srčnožilne bolezni. S pomočjo aplanacijske tonometrije smo analizirali periferni pulzni val pri 86 bolnikih s kronično ledvično boleznijo. Pri bolnikih, ki smo jih razde-*

Abstract

Purpose: *Chronic kidney disease (CKD) is associated with a higher prevalence of cardiovascular diseases. The pulse wave analysis measures the aortic pressure waveform based on noninvasive peripheral pressure recording. The subendocardial viability ratio, as part of the pulse wave analysis, is a noninvasive measure of microvascular coronary perfusion.*

Methods: *In the present study, we investigated the relationship between the subendocardial viability ratio, 24-h ambulatory blood pressure measurements, and serum biomarkers to determine the risk for cardiovascular disease in patients with CKD. A pulse wave analysis using applanation tonometry was performed in 86 patients with CKD. Serum biomarkers were measured in pati-*

lili v dve skupini glede na mediano razmerja subendokardne viabilnosti miokarda, smo merili tudi serumske označevalce srčnožilnih bolezni.

Rezultati: *Povprečna starost bolnikov je bila 60±13 let, 65% je bilo moških, povprečna vrednost razmerja subendokardne viabilnosti miokarda je bila 151±34%. Bolniki s kronično ledvično boleznijo v skupini z nižjimi vrednostmi razmerja subendokardne viabilnosti miokarda (<151%) so imeli statistično značilno nižji hemoglobin (p=0.002) ter višje vrednosti NT-proBNP (p=0.034), serumskega fosforja (p=0.04), augmentacijskega indeksa (p=0.003), 24h pulza (p=0.004) in 24h pulznega tlaka (p=0.003).*

Zaključek: *Bolniki s kronično ledvično boleznijo, ki imajo vrednosti razmerja subendokardne viabilnosti miokarda pod 151%, imajo višje tveganje za srčnožilne bolezni.*

ents, and the patients were grouped according to the median value of the subendocardial viability ratio.

Results: *The mean age of the patients was 60 ± 13 years; 65% of the patients were men, and the mean subendocardial viability ratio was 151% ± 34%. Patients with CKD in the lower subendocardial viability ratio group (<151%) had significantly lower hemoglobin (p=0.002) and higher NT-proBNP (p=0.034), serum phosphorus (p=0.04), augmentation index (p=0.003), 24-h pulse (p=0.004), and 24-h pulse pressure (p=0.003).*

Conclusion: *Our findings suggest that patients with CKD with a subendocardial viability ratio below 151% have a higher cardiovascular risk.*

INTRODUCTION

Patients with chronic kidney disease (CKD) are prone to develop cardiovascular complications. To assess cardiovascular risk in the general population and in patients with CKD, we can use 24- to 48-h ambulatory blood pressure measurements (ABPM), arterial stiffness measurements using pulse wave analysis (PWA) or carotid femoral pulse wave velocity (cfPWV), and cardiac biomarkers such as troponin I, amino-terminal fragment of B-type natriuretic peptide prohormone (NT-proBNP), and many other biomarkers. Arterial hypertension constitutes a very relevant cardiovascular and renal risk factor in all patients. To assess this risk, the best approach is ABPM, as it allows to detect masked hypertension, masked untreated hypertension, and dipping patterns (1).

Arterial stiffness can be measured noninvasively by using reproducible and relatively nonexpensive technology such as applanation tonometry (2). Radial artery PWA is a simple method to measure different hemodynamic parameters in the central aorta that have been used to assess cardiovascular risk. Buckberg et al. demonstrated that the ratio of the area of the diastolic phase to that of the systolic phase in the central aortic profile has a close correlation with the blood supply to the subendocardium (3). This ratio was designated as the subendocardial viability ratio (SEVR), which is related to the functioning of the heart and oxygen consumption, and the energy supply to the heart (4,5). Recent studies have shown the association between SEVR and albuminuria, extreme dipper profile, and cardiovascular mortality (6-8).

Different circulating serum biomarkers are involved in the pathogenesis of cardiovascular complications in patients with CKD. One of these biomarkers is NT-proBNP, which is an indirect marker of symptomatic and asymptomatic ventricular dysfunction. It is released by the ventricles in response to volume expansion and increased wall stress. Patients with CKD had higher levels of NT-proBNP due to advanced atherosclerosis and decreased renal clearance (9).

The purpose of our present study was to investigate the relationship between SEVR, 24-h ABPM, and serum biomarkers to determine the risk for cardiovascular disease in nondialysis patients with CKD.

STUDY DESIGN AND METHODS

Study population

Patients were recruited from the Nephrology Outpatient Clinic University Clinical Centre, Maribor, Slovenia. All subjects were free of any acute illnesses at the time of the study. The inclusion criteria were as follows: age > 18 years; presence of CKD based on criteria (markers of kidney damage and/or decreased glomerular filtration rate (GFR)) according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition and classification of CKD; asymptomatic regarding heart failure and acute coronary syndrome; and not hospitalized at the time of the study. According to the Sphygmocor® Clinical Guide instructions, patients with atrioventricular block of second or third degree, pacemaker, atrial fibrillation, and aortic valve stenosis were excluded (5).

Pulse wave analysis measurements

All subjects were examined in the morning hours, between 8 a.m. and 12 a.m. Before the measurement, patients were kept under similar conditions, that is, calm and relaxed and asked to abstain from heavy meals, cigarettes, coffee, and exercise. During the procedure, the subjects were seated comfortably beside a table with their arm resting on the table and their palms facing upward. Radial artery pressure waveforms were recorded by applanation tonometry (SphygmoCor®, AtCor Medical, Ltd., Sydney, Australia). The SphygmoCor® Central Blood Pressure Assessment System uses a high-fidelity Millar pressure transducer to noninvasively record the pressure wave at the radial artery. This is achieved by partially flattening the radial artery against the underlying bone in the wrist. Key measurements of cardiovascular risk and heart function were obtained from this aortic pressure waveform. A single examiner performed all measurements. Aortic augmentation index with and without corrections for a heart rate of 75 (AIx and AIx@HR75, respectively), computed as the difference between the first and second systolic shoulders divided by the pulse pressure, and SEVR, which was calculated as the ratio of the diastolic pressure time index and the systolic pressure time index, were analyzed.

Office and 24-h ambulatory blood pressure measurements

Before the PWA, office brachial diastolic and systolic blood pressure (BP) values were obtained from the portable bedside monitoring automatic BP device (Dash 4000, General Electric Healthcare, Dallas, TX, USA). After PWA measurements, 24-h ABPM was performed using a Schiller BR-102 plus monitor (Schiller AG, Baar, Switzerland). BP was recorded every 20 min during the day and every 30 min during the night. The cuff of the BP monitor was fitted to the upper portion of the arm, and the patients were instructed to attend to their usual activities and medications. Hypertension was defined as office systolic and/or diastolic blood pressure ≥140/90 mmHg, and/or current antihypertensive medication use, according to the guidelines.

Laboratory variables

In patients with CKD, blood samples were drawn from the vein in the morning after an overnight fast of at least 12 h. The estimated GFR (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C formula.

Statistical analysis

Study variables are expressed as the mean ± SD, and as the range for continuous variables or as counts or proportions for categorical variables. Univariate correlations between SEVR and the measured parameters were performed with Pearson's correlation. To compare the mean values from two groups according to the median value of SEVR, the independent sample t-test was used. A chi-squared test was used to compare the differences between two independent groups when the dependent variable was ordinal (smoking, diabetes, gender, dipping, treated hypertension, previous coronary heart disease, cerebrovascular insult, and treated dyslipidemia). A one-way ANOVA test for multiple groups was used to compare different CKD groups, with NT-proBNP as the dependent variable. For all tests, a p-value of <0.05 was considered to be statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences for Windows version 24.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

The study population included 86 patients with CKD. All patients were Caucasian and in the age range of 23-88 years (mean age: 60 ± 13 years); 56 (65%) of them were males. Thirty-eight (44%) patients were smokers, and 21 (24%) patients had diabetes. The primary cause of CKD was hypertensive nephropathy in 36 (42%) patients, diabetic nephropathy in 19 (22%) patients, chronic glomerulonephritis in 12 (14%) patients, polycystic kidney disease in six (7%) patients, and other causes in 13 (15%) patients. Eighty-two (95%) patients had treated hypertension, 10 (12%) patients had previous coronary heart disease (stable or unstable angina pectoris, myocardial infarction, coronary artery by-pass graft), six (7%) patients had previous cerebrovascular insult, and 33 (38%) patients had treated dyslipidemia.

The mean SEVR in patients with CKD was 151% ± 34% (range 79-235%). The demographic, biochemical, and clinical characteristics of all patients are shown in Table 1. According to the CKD stage, most of the patients had CKD stage 3 (30.2%) and 4 (40.7%). Fifteen (17.4%) patients had CKD stage 5, but were not yet on dialysis. The SEVR did not significantly differ between smokers and nonsmokers (p = 0.096).

Comparison of the two groups of patients according to the median of SEVR

The patients were categorized into two groups according to the median value of SEVR (151%). Patients in the group with lower SEVR had significantly lower hemoglobin and higher serum phosphorus, NT-pro-BNP, beta-2 microglobulin (B2M), AIx@HR75, ejection duration, office systolic BP, 24-h pulse pressure, and 24-h ambulatory heart rate (Figure 1 and Table 2). The chi-square test revealed significant differences in both groups regarding sex (p < 0.041), diabetes (p < 0.002), and cerebrovascular insult (p < 0.026).

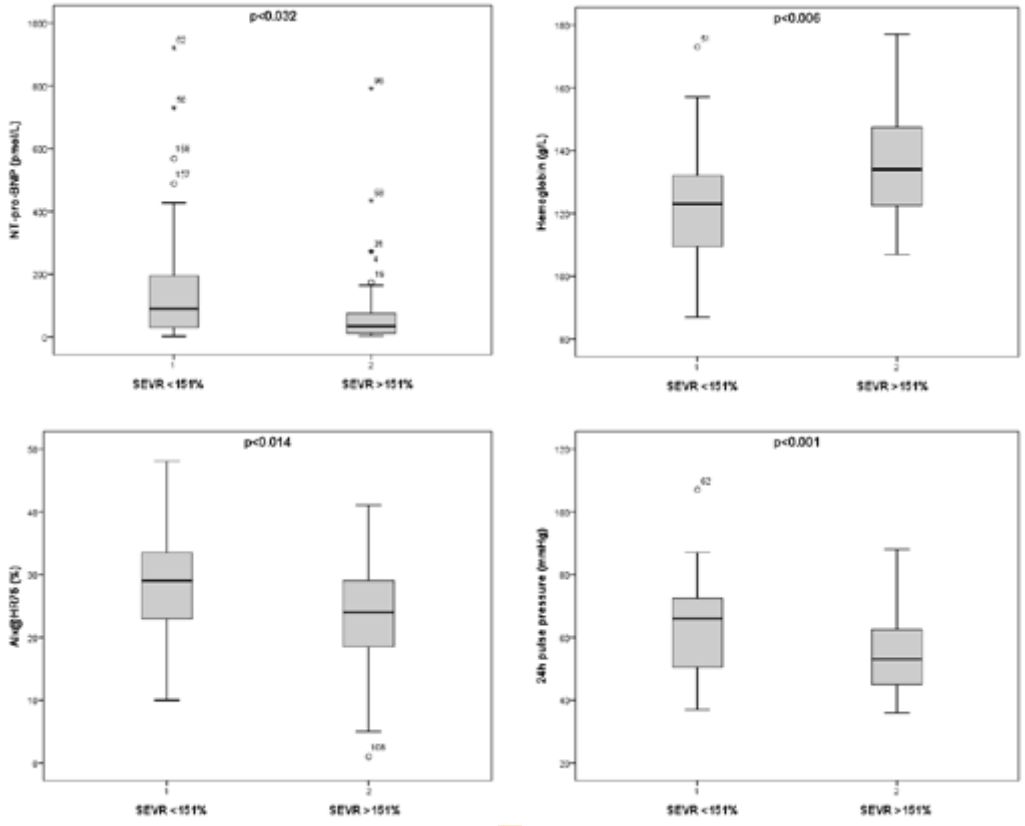

Figure 1. *The difference in NT-pro-BNP, hemoglobin, AIx@HR75, 24h pulse pressure between two groups according to the median of SEVR. Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide; AIx@HR75, aortic augmentation index with correction for a heart rate of 75; SEVR, subendocardial viability ratio;*

Table 1: *Descriptive data of all patients;*

Characteristic	All patients (N=86) Results presented as mean and (range)
Age (years)	60.4 (23-88)
Gender-male (N, %)	56 (65)
Body mass index (kg/m^2)	28.6 (19-42)
Smokers (N, %)	38 (44)
Diabetics (N, %)	21 (24.4)
Serum creatinine (µmol/L)	263 (81-669)
Cystatin C (mg/L)	2.1 (0.7-4.2)
eGFR (ml/min/1.73 m^2)	31.7 (7-113)
Hemoglobin (g/L)	129 (87-177)
Ferritin (µg/L)	164 (11-586)
hsCRP (mg/L)	6.1 (0.2-70)
Calcium (mmol/L)	2.23 (1.89-2.72)
Phosphorus (mmol/L)	1.22 (0.73-2.49)
Troponin I (ng/mL)	0.022 (0.02-0.12)
NT-proBNP (pg/mL)	121.6 (2-921)
Uric acid (mmol/L)	399 (131-595)
25-hydroxyvitamin D (nmol/L)	54.9 (7.5-149.7)
Beta-2 microglobulin (mg/L)	6.14 (1.6-16.1)
Homocysteine (µmol/L)	25 (8.5-50)
Interleukin-6‡ (pg/ml)	4.76 (2-21.3)
FGF23‡ (AE/ml)	264.5 (40-1500)
Total cholesterol (mmol/L)	5.06 (2.67-9)
Low-density cholesterol (mmol/L)	3.08 (1.2-6)
High-density cholesterol (mmol/L)	1.22 (0.57-2.17)
Triglycerides (mmol/L)	2.04 (0.4-8)
Lipoprotein (a) (g/L)	0.32 (0.02-1.56)
Apolipoprotein A1 (g/L)	1.76 (0.86-19.4)
Apolipoprotein B (g/L)	0.98 (0.36-2.02)
SEVR (%)	151 (79-235)
Augmentation index (AIx) (%)	30 (2-56)
Augmentation index (AIxŽHR75) (%)	26 (1-48)
Ejection duration (%)	35 (27-48)
Office SBP (mmHg)	146 (103-227)
Office DBP (mmHg)	80 (53-117)
24h ASBP (mmHg)	135 (100-180)
24h ADBP (mmHg)	76 (45-104)
24h MAP (mmHg)	97 (71-130)
Dippers (N, %)	23 (26.7)
24h pulse pressure (mmHg)	59 (36-107)
24h ambulatory heart rate (beats per min)	71 (54-97)

Abbreviations: ASBP, ambulatory systolic blood pressure; ADBP, ambulatory diastolic blood pressure; DPB, diastolic blood pressure; e-GFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; hsCRP, high-sensitive C-reactive protein; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; SEVR, subendocardial viability ratio; ‡: N=85

Table 2: *The relationship between all patients divided according to the median value of SEVR in two groups;*

Characteristic	Patients below median value of SEVR (N=43)	Patients above median value of SEVR(N=43) mean±SD	P value
Age (years)	62.8±12.3	57.9±13.1	0.08
Body mass index (kg/m^2)	28.2±5.4	28.8±5.1	0.82
Serum creatinine (µmol/L)	285±140	242±124	0.14
Cystatin C (mg/L)	2.3±0.83	1.97±0.85	0.06
eGFR (ml/min/1.73 m^2)	28±22.9	35.4±21.4	0.13
Hemoglobin (g/L)	123.2±18.5	135±16.3	**0.002**
Ferritin (µg/L)	176±117	153±88	0.3
hsCRP (mg/L)	6±9.3	6.2±13.5	0.93
Calcium (mmol/L)	2.22±0.15	2.24±0.13	0.34
Phosphorus (mmol/L)	1.3±0.42	1.15±0.27	**0.04**
Troponin I (ng/mL)	0.025±0.02	0.02±0.00	0.09
NT-proBNP (pg/mL)	161.8±201.1	81.3±140.6	**0.034**
Uric acid (mmol/L)	409±92	388±101	0.32
25-hydroxyvitamin D (nmol/L)	54.9±31.2	55±24	0.99
Beta-2 microglobulin (mg/L)	6.9±3.2	5.4±2.8	**0.022**
Homocysteine (µmol/L)	25.6±10.3	24.3±8.9	0.56
Interleukin-6 (pg/ml)	5.4±4.1	4.2±3.2	0.13
FGF23‡ (AE/ml)	318.3±322	209.5±212.5	0.07
Total cholesterol (mmol/L)	4.9±1.3	5.2±1.4	0.24
Low-density cholesterol (mmol/L)	2.9±1	3.2±1.1	0.18
High-density cholesterol (mmol/L)	1.3±0.4	1.2±0.3	0.29
Triglycerides (mmol/L)	1.9±1.3	2.2±1.2	0.26
Lipoprotein (a) (g/L)	0.39±0.42	0.25±0.26	0.08
Apolipoprotein A1 (g/L)	1.97±2.7	1.55±0.24	0.32
Apolipoprotein B (g/L)	0.95±0.32	1±0.3	0.44
SEVR (%)	124.1±19.8	178.4±20.6	**0.0001**
Augmentation index (AIx) (%)	30.2±10.5	29.6±10.7	0.605
Augmentation index (AIx@HR75) (%)	28.8±7.9	23.2±9.1	**0.003**
Ejection duration (%)	38.5±4.4	31.8±2.6	**0.0001**
Office SBP (mmHg)	154±24	138±19	**0.001**
Office DBP (mmHg)	80±13	81±10	0.77
24h ASBP (mmHg)	139±17	132±17	0.07
24h ADBP (mmHg)	75±9	77±9	0.21
24h MAP (mmHg)	98±11	96±11	0.59
24h pulse pressure (mmHg)	64±15	54±13	**0.003**
24h ambulatory heart rate (beats per min)	73±9	68±6	**0.004**

Abbreviations: ASBP, ambulatory systolic blood pressure; ADBP, ambulatory diastolic blood pressure; DPB, diastolic blood pressure; e-GFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; hsCRP, high-sensitive C-reactive protein; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; SEVR, subendocardial viability ratio; ‡: N=85

Relationship between SEVR and gender

In patients with CKD, SEVR was significantly higher in males than in females (157% ± 33% vs 140% ± 33%, respectively, $p < 0.03$).

Relationship between SEVR and diabetes

SEVR was significantly lower in CKD patients with diabetes than in CKD patients without diabetes (128% ± 33% vs 159% ± 31%, respectively, $p < 0.0001$).

Relationship between SEVR and previous cardiovascular disease

No significant difference in SEVR was observed for treated hypertension (152% ± 33% vs 138% ± 44%, $p = 0.44$), treated dyslipidemia (148% ± 35% vs 153% ± 34%, $p = 0.53$), and previous cerebrovascular insult (176% ± 29% vs 149% ± 34%, $p = 0.06$). Significant differences in SEVR were observed only for patients with previous coronary heart disease (176% ± 29% vs 148% ± 33%, $p < 0.012$).

Association between SEVR and serum biomarkers for cardiovascular disease

SEVR was correlated with hemoglobin ($r = 0.27$; $p < 0.013$), high-density lipoprotein ($r = -0.23$; $p < 0.036$), and apolipoprotein A1 ($r = -0.24$; $p < 0.026$). One-way ANOVA showed significant differences in NT-pro-BNP between patients with CKD 5 and all other CKD groups ($p < 0.01$). We found that NT-proBNP increased from CKD stage 1-5 (Figure 2).

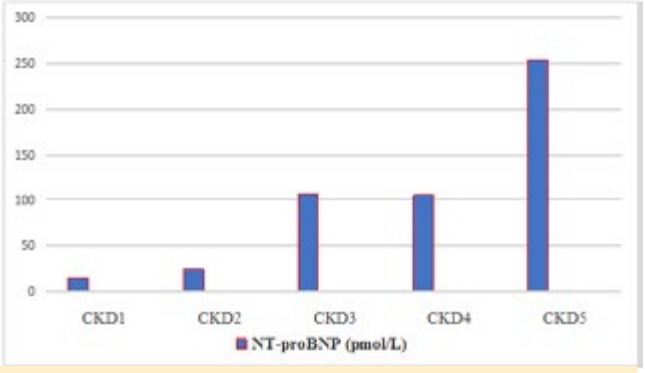

Figure 2. *NT-proBNP according to CKD stages*
Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide;

Association between SEVR and ABPM parameters

SEVR negatively correlated with 24-h pulse pressure ($r = -0.33$; $p < 0.002$), 24-h ambulatory heart rate ($r = -0.43$; $p < 0.0001$), and night-time heart rate ($r = -0.52$; $p < 0.0001$) (Figure 3). We did not find a correlation between SEVR and 24-h ambulatory systolic and diastolic BP and 24-h mean arterial pressure. Sixty-three (73.3%) patients were nondippers. We also did not find any statistically significant difference in SEVR and serum biomarkers between dippers and nondippers.

DISCUSSION

We examined the associations between PWA parameters, 24-h ABPM parameters, and serum biomarkers in nondialysis CKD patients. Our study population included patients with CKD who were asymptomatic for cardiovascular or other acute diseases at the time of the study.

The main point of interest in our observational study was to analyze the association between SEVR and other cardiovascular parameters in patients with CKD. To our knowledge, this is the first study in which we found that CKD patients with SEVR below 151% had lower hemoglobin and higher serum phosphorus, NT-proBNP, B2M, vascular stiffness, 24-h heart rate, and 24-h pulse pressure. According to the results, these patients have a higher risk for cardiovascular disease. These results could be important for routine clinical practice. PWA measurements, especially SEVR, could give a valuable estimation of cardiovascular risk in this group of patients. According to our results, the combination of SEVR, hemoglobin, and NT-proBNP measurements could be a valuable tool for screening nondialysis CKD patients who are at risk to develop cardiovascular complications. Follow-up studies will answer whether CKD patients with lower SEVR, lower hemoglobin, and higher NT-proBNP are at risk for a higher degree of hospitalization, cardiovascular events, and death.

It is important to stress that our patients were asymptomatic for heart failure and other cardiovascular diseases. Despite this fact, we found higher NT-proBNP values in the group of patients with SEVR below 151%. NT-proBNP is a good prediction marker of first cardiovascular events in the population as well as

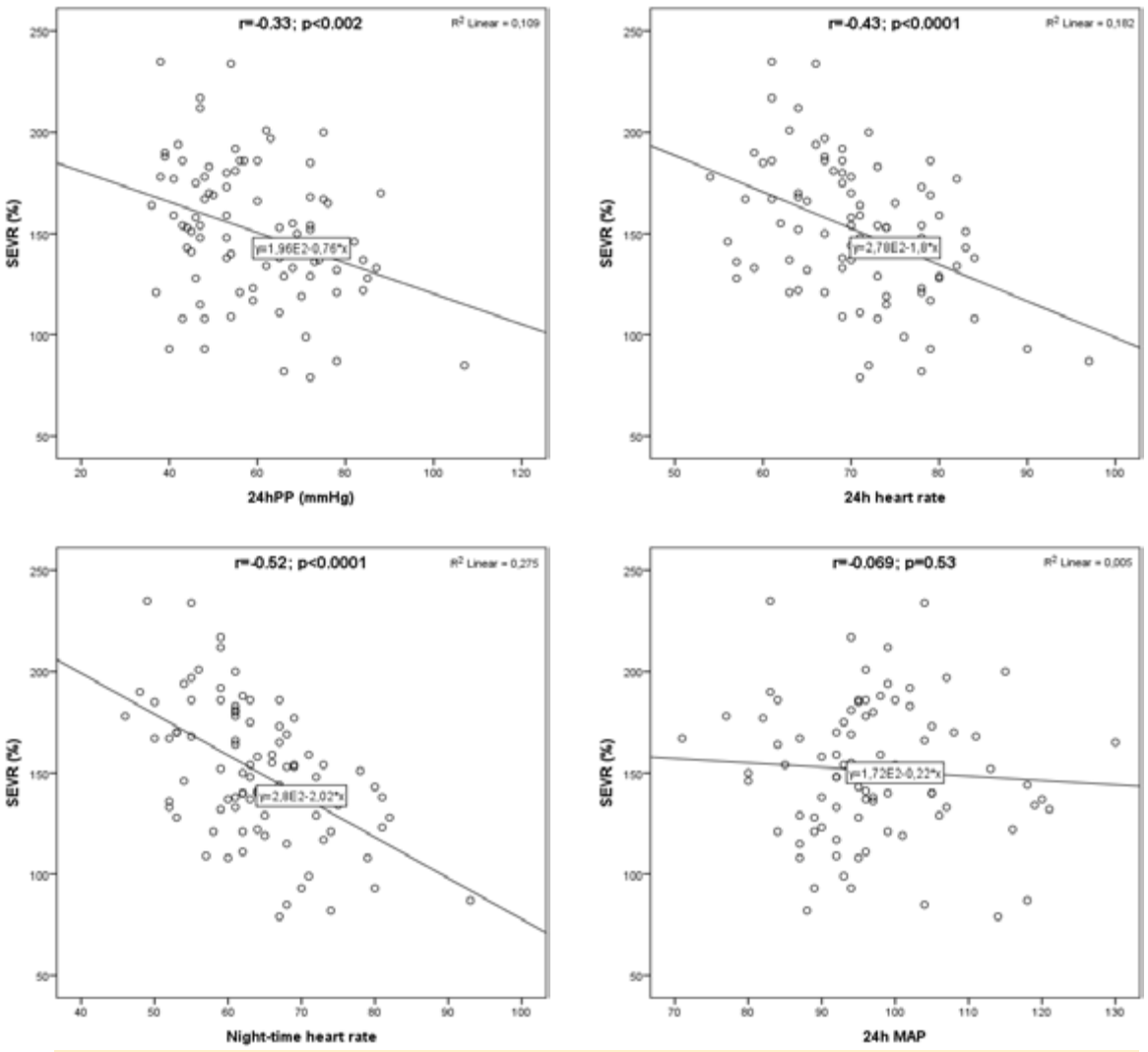

Figure 3. *The relationship between SEVR and 24hABPM parameters.*
Abbreviations: 24hPP, 24h pulse pressure; MAP, mean arterial pressure; SEVR, subendocardial viability ratio;

to determine the risk of stroke in patients with atrial fibrillation. Impaired renal function is associated with elevated plasma levels of both BNP and NT-proBNP (9). In our study, the values of NT-proBNP progressively increased from CKD stage 1-5 (Figure 3). Because it is uncertain whether NT-proBNP is completely renally excreted, markedly elevated levels of NT-proBNP in patients with diminished renal function could be due to either decreased clearance or increased cardiac production (10). Several studies have confirmed that NT-proBNP is a useful marker of cardiovascular risk in patients with CKD and have reported correlations between eGFR and NT-proBNP (11-13). Because our patients with SEVR below the median value of 151% had significantly higher NT-proBNP values, we could use SEVR as an important cardiovascular marker. We should stress that despite categorizing the patients according to the median of SEVR in different groups, eGFR values between both groups of patients with CKD were not significantly different. NT-proBNP was also an independent predictor of death in a heart failure population with eGFR < 60 mL/min/1.73 m2 (14). In a recent study, BNP and NT-proBNP values were found to be significant in predicting the need for dialysis in CKD stage 4 and 5 patients (15). In the CRIC study, elevated levels of highly sensitive troponin T and NT-proBNP

were strongly associated with incident heart failure, even after adjusting for a broad range of traditional and novel cardiovascular risk factors, and these elevated levels may indicate early subclinical changes in volume and myocardial stress that subsequently contribute to clinical heart failure (16). Bansal et al. observed that even modest elevations in NT-proBNP levels were associated with significantly increased rate of incident heart failure (16). Although we measured troponin I in our patients, we did not find an association between SEVR and troponin I. There was also no significant difference in troponin I between the groups of patients categorized according to the median value of SEVR.

Anemia is common in patients with CKD and is known to worsen their prognosis. Patients with CKD frequently retain fluid and have excessively high cardiovascular mortality. Previous studies on patients with advanced heart failure have shown that approximately half of the patients with anemia have hemodilution rather than a true decrease in red blood cell mass (17). Our previous study revealed that in CKD patients, SEVR is independently associated with hemoglobin and that lower levels of hemoglobin were associated with lower SEVR values (18). We hypothesize that lower hemoglobin, higher NT-proBNP, and lower SEVR are part of the same cardiovascular process called cardio-renal syndrome in patients with CKD.

In our study, SEVR was significantly higher in males than in females. Similar results were recently published in a study on patients with rheumatoid arthritis (19) and in a study by Gonzales and Hadri (20). Anyfanti et al. (19) did not report differences in SEVR between healthy men and women, but they reported only on SEVR difference in patients with rheumatoid arthritis. Amah et al. also found lower values of SEVR in women than in men in dippers and in extreme dippers (6). Women have lower SEVR than men, partly due to a faster resting heart rate, which reduces diastolic time (i.e., the time for myocardial perfusion) (20). We did not find any significant differences in the 24-h ambulatory heart rate between men and women (data not shown).

In our study, we found an association between SEVR and patients with previous coronary heart disease; however, the SEVR values were not correlated with troponin I level. Tsiachris et al. demonstrated that SEVR is independently associated with coronary flow reserve (21). Hypertensive patients with impaired coronary flow reserve and without significant stenosis in coronary angiography had decreased SEVR values, and this may potentially indicate the presence of impaired microcirculation (21).

Our patients with lower SEVR had higher AIx@HR75, 24-h ambulatory heart rate, and 24-h pulse pressure. We can therefore conclude that our patients with CKD had higher arterial stiffness. AIx is a measure of the contribution that wave reflection makes to the arterial pressure waveform and provides a measure of systemic arterial stiffness (22). Elevated AIx has been reported to be associated with coronary artery disease and cardiovascular events (23). Arterial stiffness and elevated blood pressure are key determinants of cardiovascular risk. The extent of arterial stiffness and the amount of obstruction in peripheral arteries are important determinants of the timing and amplitude of the arterial wall reflection that might be linked to AIx and SEVR (23). These hemodynamic changes in the central aorta unfavorably affect heart function by increasing cardiac afterload and decreasing myocardial perfusion due to a lower pressure during diastole (24). It has been demonstrated that SEVR has a close correlation with the blood supply to the subendocardium (3,25). Pulse pressure per se predicts cardiovascular events at all levels and independently of the mean arterial pressure (4). The importance of pulse pressure as a predictor of cardiovascular morbidity and mortality has been shown by several population-based and interventional studies. Heart rate is also an important risk factor, and higher heart rates are associated with cardiac events (4). With a high heart rate, the systolic pressure-time index increases and the diastolic pressure-time index decreases (4). Both these changes may be harmful: the systolic pressure-time index is the primary determinant of myocardial oxygen utilization; on the other hand, when the diastolic pressure-time index is low, coronary arteries may not perfuse the left ventricle adequately (4). On the basis of this hemodynamic explanation, we can understand why our study patients with a higher 24-h ambulatory heart rate have lower SEVR and higher NT-proBNP.

Central blood pressure measurements in the ascending aorta or the carotid artery are expected to be more useful

than conventional brachial pressure measurements for predicting cardiovascular events; this is because central pressure, not brachial pressure, is the pressure that targeted organs encounter (26). The transmission of the pulsatile pressure waves to microvascular circulation is increased in patients with increased arterial stiffness (6). This mechanism may play a role in renal microvascular damage and could explain the lower eGFR value in our patients with lower SEVR and higher AIx@HR75, despite the fact that the difference in eGFR in both groups was not statistically significant.

LIMITATIONS OF THE STUDY

This is a single-center observational study with a relatively small and exclusively Caucasian population. The cross-sectional, observational design of our current study precludes definitive conclusions regarding the causal relationship between SEVR and cardiovascular complications in patients with CKD. No echocardiography and no follow-up were performed. The strength of our study is the enrolment of patients with different CKD stages and different CKD etiology and not patients with diabetes as the lone population, as done in some others studies.

CONCLUSIONS

In conclusion, CKD patients with SEVR below 151% have lower hemoglobin, higher NT-proBNP, higher 24-h pulse pressure, and higher augmentation index corrected to heart rate, and therefore, have a higher cardiovascular risk.

In further studies, the predictive value of a combination of SEVR, NT-proBNP, hemoglobin and AIx@HR75 measurements for all-cause death and a composite endpoint of cardiovascular events in CKD patients would be valuable.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at the institutions where the studies were conducted (IRB approval No.: UKC-MB-KME-9-02/15), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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