10.5152/turkjnephrol.2020.3633

Original Article

Turkish Journal of Nephrology

Subclinical Cardiovascular Risk Factors in Chronic Kidney Disease: Abnormal Heart Rate Recovery

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Abstract

Objective: Chronic kidney disease (CKD) is associated with increased mortality and high cardiovascular (CV) risk. Slow heart rate recovery (HRR) is an index of cardiac autonomic dysfunction and also a prognostic tool for cardiac and all-cause mortality in high-risk groups. In this study, we aimed to investigate the subclinical CV risk factor in different stages of CKD.
Materials and Methods: Fifty-one patients with stage 1–5 CKD (mean age, 42.5±8.1 years) and 42 healthy individuals (mean age, 36.0±7.9 years) were included in the study. The HRR was calculated by subtracting the heart rates in the 1st, 2nd, and 3rd minute of the recovery period from the maximum heart rate attained during the exercise stress test.
Results: The HRR in the 1st minute was significantly slower in the CKD group compared with that in the control group (22.4±11.3 and 32.4±11.1, respectively; p<0.001). The HRR in the 2nd and 3rd minute was also slower in the patient group, but the difference was not statistically significant. Seventeen patients with the 1st minute HRR ≤18 beats/min were mainly distributed in CKD stages 4 and 5.
Conclusion: Patients with CKD with no known cardiac disease and no structural cardiac changes were at risk of CV events with a slow HRR in the exercise test. Clinicians should be careful not to underestimate CV events in this group of patients.
Keywords: Cardiovascular risk, chronic kidney disease, heart rate recovery

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Received: 25.10.2018 **Accepted:** 27.01.2019

Cite this article as: Turgut D, Coşkun Yenigün E, Kundi H, Özkayar N, Dede F. Subclinical Cardiovascular Risk Factors in Chronic Kidney Disease: Abnormal Heart Rate Recovery. Turk J Nephrol 2020; 29(1): 28-32.

INTRODUCTION

Chronic kidney disease (CKD) is strongly associated with increased all-cause mortality and is mainly related to cardiovascular (CV) causes. Early estimation of CV risks in this group is vital. There is a combination of conventional CV risk factors, kidney-specific risk factors, and heart problems related to structural changes (1). In addition, cardiac autonomic dysfunction (CAnD) is a major complication of CKD that likely contributes to the high incidence of CV mortality in this patient population (2). New variables such as exercise capacity and heart rate recovery (HRR) provide an easy method to analyze CAnD (3).

The decrease in heart rate after exercise is known as HRR. HRR is associated with the balance between sympathetic withdrawal and parasympathetic reactivation after a graded exercise and is a good predictor of cardiac autonomic activity (2). It is evident that a slower HRR is not just an index of autonomic dysfunction but also a powerful prognostic tool for cardiac and all-cause mortality in high-risk groups (3). The HRR at 1 to 5 min detected during the treadmill stress test exercise has been established as a valid method (4). The 1st minute of recovery (HRR1) (fast phase) characterizes a period in which there is an abrupt and rapid decrease in HR. After the 1st minute (slow phase), it takes 2 to 5 min for HR to return to its resting values (5).

In patients with CKD, reduced exercise capacity is associated with poor survival (6). All CV risks and CAnD increase the mortality risk not only in symptomatic pa-

tients but also in asymptomatic patients. An abnormal HRR after a graded exercise is also used to estimate subclinical CV risks in patients with CKD (7). In this study, we aimed to estimate HRR abnormalities in different stages of CKD with respect to the normal population.

MATERIALS AND METHODS

Study Population

The study population comprised 51 patients with CKD (29 men and 22 women; mean age, 42.5±8.1 years) and 42 healthy individuals (21 men and 21 women; mean age, 36.0±7.9 years). Patients with CKD were between stages 1 to 5 and without any renal replacement treatment (RRT). Regarding the primary kidney diseases in patients, 29 (56.8%) were of unknown origin, 13 (25.4%) had diabetic nephropathy, and 9 (17.8%) had cystic kidney diseases. CKD and stages were defined based on eGFR according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of CKD. No patient had known heart failure, and none of the treated coronary artery diseases (CAD) were accepted. Patients with symptoms of heart failure (NYHA III-IV) as well as patients with electrocardiogram (ECG) abnormalities, atrial fibrillation, or uncontrolled hypertension were excluded. Hypertension, diabetes mellitus, and dyslipidemia (recent total cholesterol value ≥250 mg/dL, triglyceride ≥150 mg/dL, and HDL <40 mg/dL) were defined by history and/or medication use. All included patients were able to perform exercise testing. The patients were advised to remain on a low sodium diet (100 mmol/day) and protein reduction to 0.6-0.8 g/kg/day, and they were encouraged to cease smoking and exercise regularly. The control group was selected from healthy volunteers with no known drug use and disease whose GFR was >90 mL/min/1.73 m^2 with normal urine protein excretion (<150 mg/day).

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ankara Numune Education and Research Ethics Committee. All subjects provided written informed consent prior to participating in the study.

Table 1. Demographic properties of patient and control groups

	CKD Group (n=51)	Control Group (n=42)	p
Age (year) (±SD)	42.5±8.1	36.0±7.9	0.071
Female / Male n (%)	22/29 (43%/57%)	21 /21 (50%/50%)	
Body Mass Index (kg/m^2) (±SD)	28.36±1.3	25.4±2.2	0.063
Diabetes n (%)	17 (33%)	-	
Hypertension n (%)	40 (78%)	-	
Dyslipidemia n (%)	18 (35%)	-	

bpm: beats per minute; HRR1: 1st minute heart rate recovery; HRR2: 2nd minute heart rate recovery; HRR3: 3rd minute heart rate recovery

Protocol for Exercise Stress Test

The patients underwent a standard maximal graded exercise treadmill test according to the standard Bruce protocol. Continuous 12-lead ECG monitoring was performed throughout testing. The participants exercised until the HR was >95% of the estimated maximal HR (220-age). The patients underwent the stress test without a cool-down period. HRR values were calculated by subtracting the HR at the 1st, 2nd, and 3rd minute of the recovery period from the HR attained at peak exercise. A HRR of ≤18 beats/min was considered abnormal (8). The exercise capacity was calculated as total metabolic equivalent units (METs) achieved at peak exercise.

Statistical Analysis

Continuous variables were expressed as the mean±standard deviation, and categorical variables were expressed as percentages. Comparisons of categorical and continuous variables between the two groups were performed by using the x2 test and unpaired t-test, respectively. The correlation between various parameters was evaluated using the Pearson correlation test. p<0.05 was considered statistically significant. The Statistical Package for the Social Sciences (SPSS) (IBM Corp.; Armonk, NY, USA) version 23.0 statistical package was used for all analyses.

RESULTS

Our patient population comprised 51 patients with CKD stage 1-5 and 42 healthy controls. CKD stages were as follows: stages 1-2, 5 (9%) patients; stage 3, 29 (56%) patients; and stage 4-5, 17 (33%) patients. None of the patients were on RRT. There was no difference in terms of age, gender, and body mass index between the groups. Eleven (21%) patients were on Angiotensin converting enzyme inhibitor (ACEI) medication, and 26 (50%) patients were using Anjiotensin receptor blocker (ARB). Only one patient was administered erythropoietin, and only one patient was a smoker. The baseline characteristics of patients and the controls are shown in Table 1.

The pre-exercise stress test (EST) and cardiac autonomous function-related findings for the patient and control groups are summarized in Table 2. Although mean ejection fractions of the patients were lower in the patient group (62±2 and 65±3, p<0.001), maximum left ventricular wall thickness, basal systolic blood pressure (SBP), maximum SBP, basal diastolic blood pressure (DBP), maximum DBP, and basal heart rate (HR) were similar in both groups. However, maximum HR was significantly lower in patients with CKD (p<0.001). In an analysis of exercise capacity, all study groups achieved a MET score >10. However, the patient group had a statistically lower MET score than the control group (11.2±2.5 and 14.2±3, respectively; p<0.001).

When the HRR results were analyzed, in the 1st minute, the HRR was significantly slower in the CKD group than in the control group (22.4±11.3 and 32.4±11.1, respectively; p<0.005). Although the HRR in the 2nd and 3rd minutes was faster in the control group than in the patient group, the difference was not statistically significant (p=0.122 and p=0.22, respectively) (Figure 1). When we analyzed 17 patients with HRR1≤18 beats/min, it was demonstrated that patients were mainly distributed in CKD stages 4 and 5. These results are summarized in Table 3.

Table 2. Analysis of pre-exercise stress test and cardiac autonomous function related findings

	CKD Group (n=51)	Control Group (n=42)	p
LVEF (%) (±SD)	62±2	65±3	<0.001
LV wall thickness (mm) (± SD)	4.9±0.4	4.6±0.5	0.112
Basal SBP (mmHg) (min-max)	130 (100-180)	120 (90-130)	0.208
Max. SBP (mmHg) (min-max)	150 (125-220)	140 (100-200)	0.068
Basal DBP (mmHg) (min-max)	80 (55-119)	80 (60-90)	0.131
Max. DBP (mmHg) (min-max)	70 (40-120)	80 (60-100)	0.421
METs (mL/kg/min) (±SD)	11.2±2.5	14.2±3	<0.001
Basal HR (bpm) (±SD)	93.4±15.5	92.7±15.7	0.084
Max. HR (bpm) (±SD)	148.2±14.3	167.7±14.2	<0.001
HRR1 (bpm) (±SD)	22.4±11.3	32.4±11.1	<0.001
HRR2 (bpm) (±SD)	47.2±13.6	52.2±12.6	0.122
HRR3 (bpm) (±SD)	51.8±14.2	58.7±15.1	0.22

bpm: beats per minute; DP: diastolic blood pressure; HR: heart rate; HRR1: 1st minute heart rate recovery; HRR2: 2nd minute heart rate recovery; HRR3: 3rd minute heart rate recovery; LVEF: left ventricular ejection fraction; LV: left ventricule; METs: metabolic equivalents; SBP: systolic blood pressure.

Table 3. Abnormal heart rate recovery in patient group

	CKD Group (n=51)	Control Group (n=42)
HRR≤18/min; n (%)	17 (33 %)	1 (2%)
	CKD Stage 1-2: 0 (0%)	
	CKD Stage 3: 2 (3%)	
	CKD Stage 4-5: 15 (87%)	
HRR>18/min; n (%)	34 (69 %)	41 (98%)

CKD: Chronic kidney disease

DISCUSSION

Our study showed that patients with CKD had a slower HRR after EST, especially in the 1st minute of recovery. An abnormal HRR1 (≤18 beats/min) is mainly observed in progressive kidney disease.

Many studies have reported an increase in HR during EST and a decrease in HR during the recovery period mainly due to changes in the tone balance between the sympathetic and the parasympathetic nervous systems (9). Any alteration in this system mainly favoring increased activity of sympathetic system and decreased parasympathetic system refers to CAnD (10). It is documented that CAnD is a result of inflammation, endothelial dysfunction, atherosclerosis, and arrhythmia (11). The exact mechanisms contributing to CAnD in CKD are unclear, but many studies have shown that there is an increased risk of premature death and direct detrimental effects on the clinical prognosis of renal failure (12-14). Sympathetic overactivity and abnormalities in CV reflexes are some of the causes of CAnD in CKD (2, 15).

Dysfunctional vagal control of HR, known as slow HRR, is a new non-ECG measure that helps to assess and define CAnD (16). Decreased HRR has been associated with a higher incidence of all-cause mortality, sudden cardiac death, and CV events (7, 16, 17). The HRR has been calculated at the 1st, 2nd, 3rd, and 5th minute in different studies, but mainly at the 1st min. In the literature, there are various cut-off HRR values. In some studies, an HRR ≤12 beats/min is directly associated with mortality (8, 18, 19). However, in a study by Watanabe et al. (20), a total of 5438 patients were enrolled for 3 years, and HRR was defined as the difference in HR between the peak exercise and that after 1 min; a value ≤18 beats/min was considered abnormal. Furthermore, after adjusting for all confounding factors, an HRR ≤18 beats/min was found to be a powerful and independent predictor of death (20). In our study, we found that patients in stages 4 and 5 with the 1st minute HRR ≤18 beats/min were a majority,

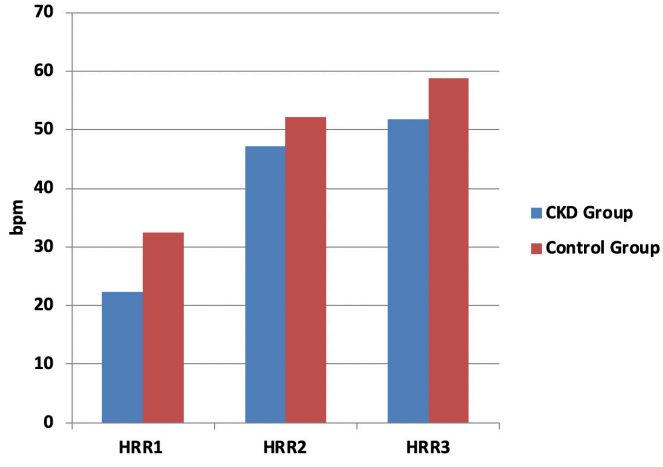

Figure 1. Heart rate recovery results in the 1st, 2nd, and 3rd minutes in patient and control groups.

although it was not statistically significant. With studies composed of large groups at different CKD stages, the HRR would be analyzed as an early predictor of CV risks in these vulnerable patients.

Lipinski et al. (21) retrospectively analyzed exercise treadmill and coronary angiographic data of 2193 men and found that the first 2 min of HRR predicted mortality and that the HR decrease during the 2nd minute of recovery predicted the presence of CAnD. In our study, we analyzed the 1st, 2nd, and 3rd minutes of HRR and found that the 1st minute HRR in patients with CKD was significantly slower. The 2nd and 3rd minute HRR were also slower in the CKD group, but it was not statistically significant. The correlation with HRR should be analyzed with large patient groups composed of homogenous stages 1-5 CKD in future studies.

CKD is a known risk factor for increasing the progression of CV problems. However, without any known cardiac illness, it is not certain whether CKD is associated with functional or structural cardiac changes. Nelson et al. (22) analyzed 840 patients with a GFR >60 mL/min and 93 patients with stage 3 CKD. Patients were assessed for their cardiopulmonary exercise as a marker of autonomic function. It was concluded that maladaptive CV/autonomic dysfunction in stage 3 CKD may suggest subclinical cardiopulmonary dysfunction preceding end-stage kidney disease (ESKD)-related cardiac problems. In our study, all patients were without any known cardiac disease with a preserved LVEF. Although our patients mainly had stage 3-5 CKD, our findings provide functional and physiological data. Without any known cardiac disease and no structural cardiac changes, patients with CKD are under risk of CV events with a slow HRR in the exercise test.

CONCLUSION

The most important limitation of our study is that it was a cross-sectional study with a small population, and we could not analyze the mortality. Also, patients were not homogenous considering the CKD stages. However, it is evident that patients with CKD without a diminished cardiac function should be carefully followed to prevent cardiac related deaths.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethics Committee of Ankara Numune Training and Research Hospital.

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.T., E.Y, F.D.; Design – D.T., E.Y., F.D.; Supervision – F.D., N.Ö., E.Y; Resource – E.Y., D.T., F.D.; Materials – H.K., E.Y., D.T; Data Collection and/or Processing – D.T., H.K., E.Y.; Analysis and/or Interpretation – D.T., E.Y, N.Ö.; Literature Search – D.T., E.Y.; Writing – D.T., E.Y.; Critical Reviews – F.D, H, K, N.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

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