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The relationship between R wave peak time and left ventricular mass index in patients with end-stage renal disease on hemodialysis

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Abstract

Purpose Cardiovascular complications have been reported to be the main cause of mortality in patients with end-stage renal disease (ESRD). Although left ventricular hypertrophy is the most common clinical presentation of cardiac remodeling, cardiovascular complications may also include disturbances of the heart conduction system. The R wave peak time (RWPT) has been previously associated with left ventricular hypertrophy and myocardial ischemia. In this study, we aimed to investigate the relationship between RWPT and echocardiographic parameters in patients with ESRD.

Methods This study enrolled 66 patients (29 females, age 57.2 ± 12.8 years) with ESRD, and 72 controls (37 females, age 55.3 ± 10.1 years) with similar risk factors. All patients underwent electrocardiography and transthoracic echocardiography. The RWPT was defined as the interval between the onset of the QRS complex and the peak of the R or R′ wave.

Results There was no significant difference in terms of clinical and demographic parameters between ESRD patients and controls. Left ventricular ejection fraction was similar between the groups. However, left atrial diameter, interventricular septal thickness, posterior wall thickness, left ventricular mass (LVM) and left ventricular mass index (LVMI) were significantly higher in patients with ESRD. Among electrocardiographic parameters, P wave and QRS complex durations and RWPT were significantly higher in patients with ESRD. Prolonged RWPT, increased LVM and LVMI were identified as associates of ESRD. Furthermore, RWPT correlated well with LVM and LVMI.

Conclusion The present study demonstrated that RWPT prolonged significantly in patients with ESRD. Furthermore, prolonged RWPT has been associated with increased LVM and LVMI.

Keywords Echocardiography · Electrocardiography · End-stage renal disease · R wave peak time

Introduction

Patients with end-stage renal disease (ESRD) often experience cardiovascular complications which are the main cause of mortality in these patients [1]. The pathogenesis of cardiovascular complications in ESRD patients is complex and multifactorial including vascular changes, degeneration of cardiomyocytes, left ventricular hypertrophy and arrhythmia as well as traditional risk factors such as hypertension, dyslipidemia and diabetes mellitus [2–4]. The most common clinical presentation of cardiac impairments in the course of ESRD is probably the left ventricular hypertrophy [5]. However, it should be noted that cardiovascular complications in patients with ESRD may also include disturbances of the heart conduction system. Electrolyte disturbances including hypocalcemia can lead to disturbed transmission of electrical impulses in cardiomyocytes [6]. These conduction problems in the uremic heart may lead to delayed ventricular depolarization and subsequently prolonged ventricular activation time on surface electrocardiography (ECG).

The R wave peak time (RWPT), also known as ventricular activation time, represents the time for the conduction of the electrical activity from the endocardium to the epicardium in the ventricles [7]. RWPT has been reported to be prolonged in the presence of ventricular hypertrophy or dilatation as

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well as the disorders in the conduction system [8]. RWPT is also prolonged in myocardial ischemia due to the conduction delay in the Purkinje fibers and the myocytes [9]. In previous studies, RWPT was associated with an increased risk of impaired left ventricular systolic function and adverse events in patients with ischemic heart diseases [10, 11]. Left ventricular hypertrophy, myocardial ischemia, and conduction system disturbances have been reported to be common cardiovascular complications in patients with ESRD [12, 13]. Thus, prolonged RWPT may be an obvious sign of cardiac remodeling in patients with ESRD and, to our knowledge, no previous study has examined RWPT in these patients.

In this study, we hypothesized that RWPT may be prolonged in patients with ESRD and this prolongation may be related to echocardiographic indices of left ventricular hypertrophy. Thus, we aimed to investigate the relationship between RWPT and echocardiographic parameters in patients with ESRD.

Methods

Study population

This single-center study enrolled 66 patients (29 females, mean age 57.2 ± 12.8 years) with ESRD (glomerular filtration rate < 15 ml/min/1.73 m^2), along with 72 age- and sex-matched controls (37 females, mean age 55.3 ± 10.1 years). Patients with coronary artery disease, myocardial infarction, left ventricular dysfunction (left ventricular ejection fraction < 50%), moderate to severe heart valve disease, cardiomyopathy, arrhythmia, high degree atrioventricular block, complete bundle branch block, active infection, connective tissue disease, and liver or thyroid dysfunction were excluded from the study. All patients underwent transthoracic echocardiography (TTE) and 12-lead high-resolution surface ECG. All demographic, electrocardiographic and echocardiographic parameters were recorded into a dataset and compared between ESRD patients and controls. All patients provided a written informed consent and the study protocol was approved by the local ethics committee of the hospital in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Echocardiography

All patients underwent TTE performed by the same cardiologist using Vivid 5 echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway), and 3.2 mHz adult probe with the patient in the left lateral decubitus position. In all patients, left atrial diameter (LAD), interventricular septal thickness (IVST), posterior wall thickness (PWT), left ventricular end-systolic (LVESD) and end-diastolic diameters (LVEDD) were measured on the parasternal long-axis view. Left ventricular ejection fractions (LVEF) of the patients were calculated by using biplane Simpson's method. Left ventricular mass (LVM) was calculated based on Devereux formula [$LVM = 0.8\ (1.04\ (IVST + LVEDD + PWT)^3 - (LVEDD)^3) + 0.6$], and body surface area was estimated using Mosteller formula [body surface area = (height (cm) × body weight (kg)/3600)$^{1/2}$]. Left ventricular mass was divided by body surface area to estimate left ventricular mass index (LVMI).

Electrocardiographic analysis

A 12-lead high-resolution electrocardiography (ECG), which was recorded at a speed of 25 mm/s and a voltage of 10 mm/mV, was obtained from all patients after a 10-min rest (Nihon Kohden Cardiofax ECG-9132). Patients were allowed to breathe freely but not to speak or cough during recordings. All ECG papers were scanned, loaded to a computer, magnified sufficiently and analyzed with a digital image processing software (http://www.imagej.nih.gov). Measurements were calibrated on the underlying standard ECG graph paper. All measurements were calculated by two independent cardiologists blinded to other patients' clinical information. The onset and the end of the P waves were marked with the cursor on a high-resolution computer screen in order to calculate P wave duration in all leads. The beginning of the P wave was defined as the point where the initial deflection of the P wave crossed the isoelectric line, and the end of the P wave was defined as the point where the final deflection of the P wave crossed the isoelectric line. The PR interval was defined as the period that extends from the beginning of the P wave until the beginning of the QRS complex. The QRS duration was defined as the interval from the start of the QRS complex until J point; and RWPT was defined as the interval from the onset of the QRS complex until the peak of the R or R′ wave (Fig. 1). QT interval was defined as the interval from the onset of the QRS complex to the end of the T wave. The R–R interval was measured and used to compute the heart rate and to correct QT interval (QTc) with the Bazett's Formula. ($QTc = QT/\sqrt{R\text{–}R}$ interval in seconds). All durations were calculated in milliseconds and the mean values were calculated from 12 leads.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp. Armonk, NY). Descriptive statistics are reported as mean ± standard deviation for continuous variables with normal distribution or median (25th–75th percentiles) values for continuous variables without normal distribution and as frequency with percentages for the categorical variables. The Shapiro–Wilk

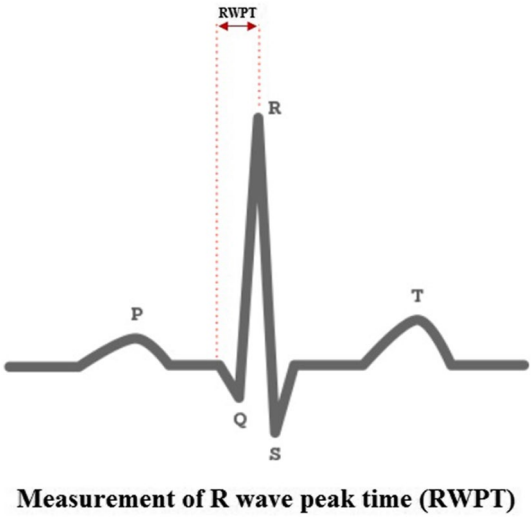

Fig. 1 The measurement of R wave peak time on electrocardiography

and Kolmogorov–Smirnov tests are used to test the normality of the distribution of continuous variables. Categorical variables are compared with Chi square or Fisher exact tests. Student *t* test or Mann–Whitney *U* test is used to compare continuous variables as appropriate. The significance level is accepted as $p < 0.05$ in all statistical analyses. A logistic regression analysis is performed in order to identify any independent echocardiographic and electrocardiographic associates of ESRD. A receiver operating characteristic (ROC) curve analysis is performed to evaluate the sensitivity, specificity, area under the curve (AUC), and confidence interval (CI) of parameters associated with ESRD. Bland–Altman analysis (MedCalc software for Windows) is used to compare ROC curve analysis results for RWPT, LVM, and LVMI.

Results

The clinical and demographical characteristics of patients with ESRD and controls are presented in Table 1. Age and gender distribution were similar between patients and controls. There was also no significant difference between the groups in terms of body mass index, systolic and diastolic blood pressures, the frequencies of diabetes mellitus, hypertension, dyslipidemia and smoking status.

The echocardiographic parameters including LVEF, LVESD, and LVEDD were found to be similar between the groups. However, LAD, IVST, PWT, LVM, and LVMI (Fig. 2a) were significantly higher in the ESRD group as compared to controls (Table 1).

A comparison of electrocardiographic parameters yielded that there was no significant difference in terms of heart rate, PR interval, QT interval and calculated QTc between the groups. However, P wave duration, QRS duration and RWPT (Fig. 2b) were significantly higher in patients with ESRD as compared to controls (Table 1).

The univariate correlates of ESRD were taken into multiple logistic regression analysis. Prolonged RWPT, increased LVM and LVMI were identified as associates of ESRD (Table 2).

In the ROC curve analysis, RWPT longer than 29.9 ms associated with the presence of ESRD with a sensitivity of 74% and a specificity of 66% (AUC 0.808; 95% CI 0.737–0.878; $p < 0.001$), LVM higher than 170 g associated with the presence of ESRD with a sensitivity of 77% and a specificity of 73% (AUC 0.753; 95% CI 0.670–0.836; $p < 0.001$) and LVMI higher than 94.8 g/m^2 associated with the presence of ESRD with a sensitivity of 78% and a specificity of 74% (AUC 0.799; 95% CI: 0.723–0.875; $p < 0.001$) (Fig. 3). When compared with Bland–Altman analysis, there was no significant difference between the AUCs of ROC curves for RWPT and LVM ($z = 1.452$; $p = 0.146$), also between RWPT and LVMI ($z = 0.231$; $p = 0.817$) (Fig. 4a, b, respectively).

Correlation analyses were performed between electrocardiographic and echocardiographic parameters. There was a significant and moderate positive correlation between RWPT and LVM ($r = 0.684$, $p < 0.001$) (Fig. 5a) and also a significant and moderate positive correlation between RWPT and LVMI ($r = 0.681$, $p < 0.001$) (Fig. 5b).

Discussion

In this case–control study, we have focused on the relationship between electrocardiographic and echocardiographic parameters in patients with ESRD. Echocardiographic parameters related to left ventricular hypertrophy and left atrial dilatation have been found to be significantly increased in the ESRD group. Among electrocardiographic parameters, P wave and QRS complex durations along with RWPT were significantly higher in patients with ESRD. Prolonged RWPT was associated with increased LVM and LVMI in patients with ESRD. The novel finding of this study was that prolonged RWPT may be an obvious sign of cardiac remodeling in patients with ESRD and, to our knowledge, this was the first study that examined this association.

Chronic kidney disease is strongly associated with an increased incidence of cardiovascular diseases, and patients with ESRD are 10–20 times more likely to die from cardiovascular events than the general population [14]. It was reported previously that 87% of adult patients have cardiovascular diseases diagnosed at the time of ESRD onset, and approximately 50% of deaths are attributed to cardiovascular events [15]. In addition to the traditional risk factors such

Table 1 The comparison of demographic, echocardiographic and electrocardiographic parameters between patient and control groups

Variables	ESRD group ($n=66$)	Control group ($n=72$)	p value
Demographic parameters			
Age (years)	57.2 ± 12.8	55.3 ± 10.1	0.231
Gender, female, *n* (%)	29 (43.9)	37 (51.4)	0.382
Body mass index (kg/m^2)	27.9 ± 4.7	28.6 ± 3.6	0.388
Hypertension, *n* (%)	33 (45.8)	39 (59.1)	0.119
Diabetes mellitus, *n* (%)	23 (34.8)	19 (26.4)	0.281
Dyslipidemia, *n* (%)	11 (15.3)	12 (18.2)	0.647
Smoking status, *n* (%)	20 (27.8)	13 (20)	0.288
Systolic blood pressure (mmHg)	129.9 ± 16.1	127.3 ± 11.5	0.287
Diastolic blood pressure (mmHg)	81.4 ± 12.3	79.2 ± 9.1	0.251
Echocardiographic parameters			
LV EF (%)	60.6 ± 5.8	61.9 ± 6.2	0.196
LAD (mm)	35.8 ± 4.3	32.6 ± 3.4	< 0.001
LVEDD (mm)	44.8 ± 7.9	43.5 ± 5.8	0.263
LVESD (mm)	31.1 ± 6.2	29.8 ± 6.1	0.228
IVST (mm)	12.1 ± 2.2	10.4 ± 1.8	< 0.001
PWT (mm)	11.8 ± 2.1	10.2 ± 1.8	< 0.001
LVM (g)	197.1 ± 75.5	158.9 ± 59.3	< 0.001
LVMI (g/m^2)	116.2 ± 37.9	85.5 ± 28.1	< 0.001
Electrocardiographic parameters			
Heart rate (beats/min)	79.2 ± 14.4	76.6 ± 12.1	0.246
P wave duration (ms)	107.8 ± 12.8	102.8 ± 13.8	0.029
PR interval (ms)	174.9 ± 46.7	169.2 ± 38.1	0.425
QRS duration (ms)	99.7 ± 16.4	92.8 ± 9.7	0.003
QT interval (ms)	371.2 ± 43.7	369.9 ± 37.3	0.864
Corrected QT interval (ms)	422.6 ± 44.1	415.2 ± 37.4	0.285
R wave peak time (ms)	33.8 ± 5.3	27.3 ± 4.9	< 0.001

ESRD end stage renal disease, *IVST* ınterventricular septal thickness, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end systolic diameter, *LVEDD* left ventricular end diastolic diameter, *LVM* left ventricular mass, *LVMI* left ventricular mass index, *PWT* posterior wall thickness

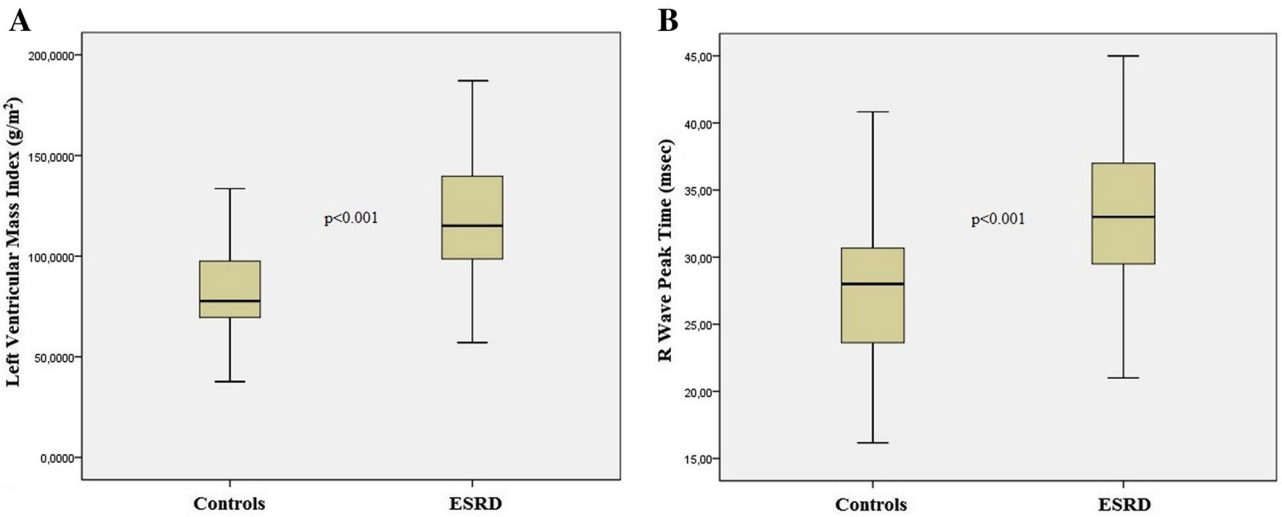

Fig. 2 The box-plot graph comparing the left ventricular mass index (**a**) and R wave peak time (**b**) values between patients with end-stage renal disease (ESRD) and controls

Table 2 The results for multivariate logistic regression analyses of univariate correlates of end stage renal disease

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
QRS duration	1.044	1.013–1.075	0.005	1.031	0.990–1.074	0.145
R wave peak time	1.284	1.171–1.408	< 0.001	1.219	1.074–1.384	0.002
P wave duration	1.029	1.002–1.057	0.033	1.029	0.996–1.063	0.088
Left atrial diameter	1.235	1.119–1.363	< 0.001	1.079	0.943–1.234	0.268
Interventricular septal thickness	1.479	1.225–1.786	< 0.001	1.110	0.494–2.495	0.801
Posterior wall thickness	1.523	1.251–1.853	< 0.001	0.791	0.324–1.930	0.606
Left ventricular mass	1.015	1.009–1.021	< 0.001	1.098	1.037–1.143	0.006
Left ventricular mass ındex	1.037	1.023–1.050	< 0.001	1.165	1.042–1.387	0.001

CI confidence Interval, *OR* odds ratio

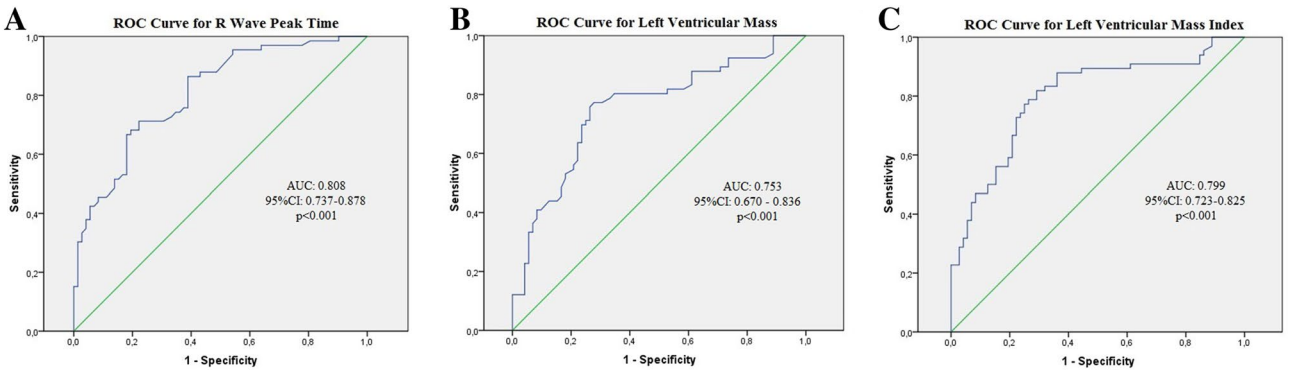

Fig. 3 Receiver operating characteristic curve revealing the area under the curves for R wave peak time (**a**), left ventricular mass (**b**) and left ventricular mass index (**c**) to be associated with the presence of end-stage renal disease (*AUC* area under curve, *CI* confidence interval)

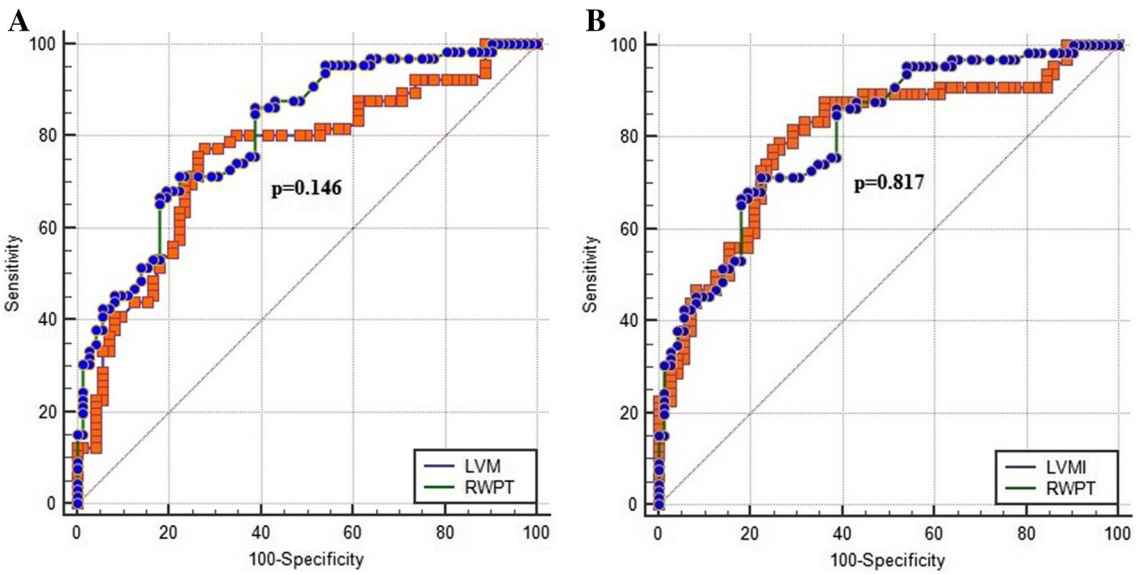

Fig. 4 Comparison of receiver operating characteristic curves of R wave peak time with that of left ventricular mass (**a**) and left ventricular mass index (**b**) to be associated with the presence of end-stage renal disease

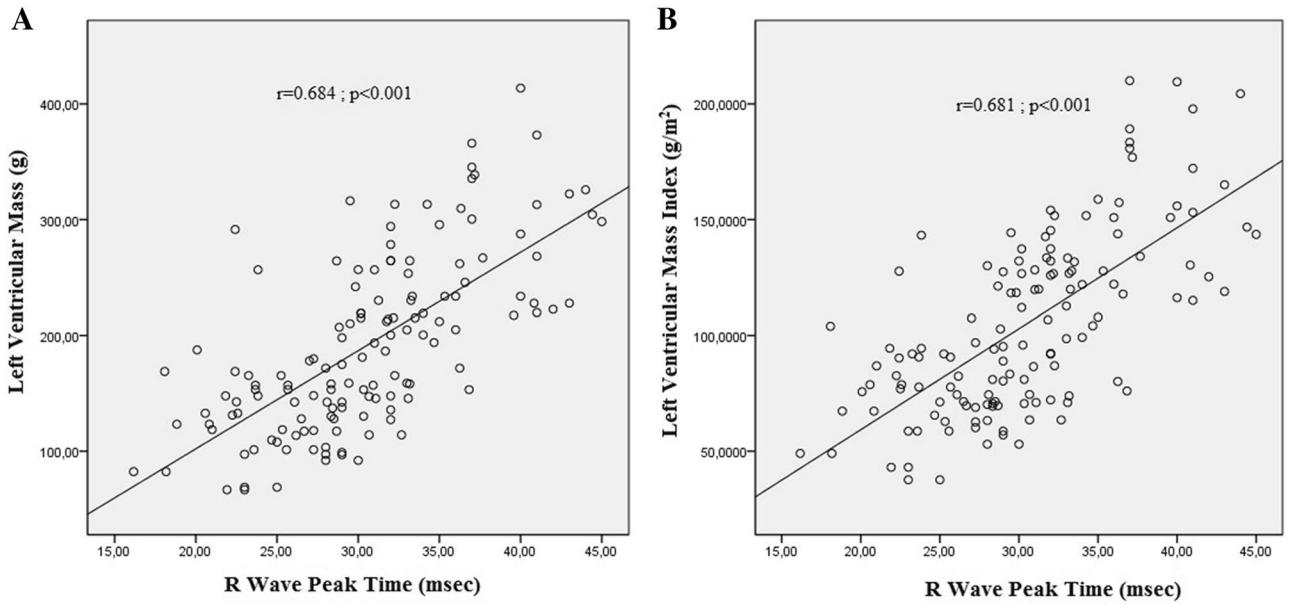

Fig. 5 The scutter dot graphs revealing the moderate positive correlation between R wave peak time and left ventricular mass (**a**), and also between R wave peak time and left ventricular mass index (**b**)

as hypertension, dyslipidemia and diabetes mellitus, non-traditional risk factors such as anemia [16], overhydration [17], endothelial dysfunction [18], hypocalcemia [19] and hyperparathyroidism [20] related mechanisms have been implicated.

Left ventricular hypertrophy is a common pathology in ESRD patients. Cardiac hypertrophy is a response of the myocardium to an increased workload. Initial cardiac hypertrophy constitutes an adaptive mechanism, but prolonged and severe hypertrophy is a risk factor for arrhythmias, sudden death and heart failure [21]. Increased accumulation of collagen due to left ventricular hypertrophy may result in myocardial fibrosis and decreased cardiac reserve. Thus, cardiac conduction disorders may occur [22]. ESRD patients with left ventricular hypertrophy have an increased risk of cardiovascular events and, specifically, an increased risk of sudden cardiac death [23–25]. There is also evidence that concentric remodeling of the left ventricle may increase cardiovascular risk [26]. Thus, the abnormal left ventricular structure has been suggested as a therapeutic target [27]. In the present study, ESRD patients had a significantly higher prevalence of left ventricular hypertrophy as compared to controls with similar cardiovascular risk factors.

Pathophysiologic factors involved in left ventricular hypertrophy in ESRD patients are generally related to increased preload and afterload [28]. Among the preload-related factors, the role of intravascular volume expansion has to be underlined, as well as secondary anemia and the presence of arteriovenous fistulas resulting in asymmetric left ventricular remodeling [29, 30]. Among the afterload-related factors, increased systemic arterial resistance, elevated arterial blood pressure, and reduced large-vessel compliance related with vascular calcifications result in myocardial cell thickening and concentric left ventricular remodeling often together with activation of the renin–angiotensin–aldosterone system [31–33]. The pathophysiologic factors involved in left ventricular hypertrophy and cardiac remodeling in ESRD patients are summarised in Fig. 6.

ECG is a simple, non-invasive and readily available tool in daily routine practice. A variety of ECG markers including ST-segment and T wave abnormalities have been utilized to assess myocardial ischemia. In addition, QRS duration has been considered an important prognostic marker, and the significance of QRS duration is well known in patients with heart failure or myocardial infarction [34, 35]. In recent studies, prolongation of QRS duration has been reported to be correlated with interventricular conduction delay because of myocardial ischemia [36, 37]. The QRS duration is also increased in patients with left ventricular hypertrophy. The increased QRS duration may be attributed to the increased thickness of the left ventricular wall and to myocardial fibrosis, which distorts and prolongs the transmural conduction of electrical activity.

In previous studies, P wave parameters have been investigated in several cardiac conditions such as hypertension, paroxysmal atrial fibrillation, mitral stenosis, aortic stenosis and dilated cardiomyopathy [38–41]. In our study, P wave duration was significantly higher in the ESRD group which also could be explained by mechanisms related to left atrial and ventricular mechanics. Left ventricular hypertrophy

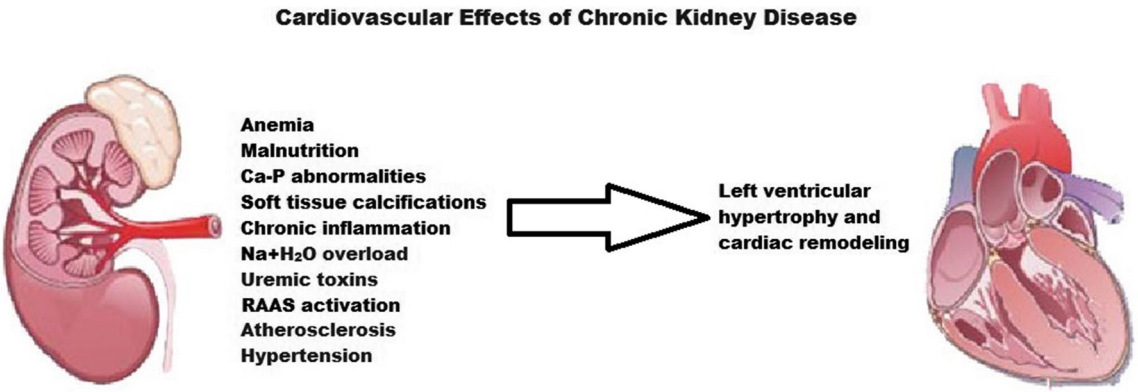

Fig. 6 The pathophysiologic factors involved in left ventricular hypertrophy and cardiac remodeling in patients with end-stage renal disease are summarised

may cause a decrease in left ventricular compliance with increased left ventricular end-diastolic pressure and left atrial pressure and thus, may increase the duration of the P wave in patients with ESRD [42].

RWPT is described as the duration from the onset of the QRS complex to the peak of the R wave. In addition to QRS duration, RWPT has also been reported to be prolonged in left ventricular hypertrophy, volume overload, conduction abnormalities, and coronary artery disease causing ischemia. In a previous study, Rencüzoğulları et al. demonstrated that the presence of prolonged QRS duration and RWPT were associated with the severity of coronary artery disease in patients with acute coronary syndrome [10]. In a different study, they also reported a significant association between no-reflow phenomenon and RWPT in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention [11]. In the present study, RWPT was significantly higher in the ESRD group as compared to controls. This prolongation may be attributed to increased muscle thickness between the endocardium to the epicardium in the ventricles. Since RWPT has been reported to be associated with increased cardiovascular events, increased RWPT in ESRD patients may also be a marker of increased cardiovascular risk. In this study, prolonged RWPT has been also associated with increased LVM and LVMI which are objective measures of left ventricular hypertrophy and cardiac remodeling. Since left ventricular hypertrophy has been associated with increased morbidity and mortality in these patients, measurement of RWPT on surface ECG may be an additional and easy diagnostic tool for risk stratification of patients with ESRD. Those with an increased RWPT may be particularly at risk for cardiovascular complications.

Secondary hyperparathyroidism is an inevitable component of ESRD and serves as a significant causative factor for the changes in the heart structure and the problems in transmitting electrical impulses within the heart [6]. Serum calcium–phosphate imbalance in patients with ESRD may affect the metabolism of individual tissues and cells. Considerable intracellular calcium ion accumulation in various organs may lead to different clinical dysfunctions in the course of ESRD. Previously, Mitsnefes et al. suggested that increased serum phosphate concentrations could cause pathological alterations in the cardiovascular system [43]. Besides, it is commonly accepted that hypocalcemia can lead to defective muscle contractions and disturbed transmission of electrical impulses in cardiomyocytes [44]. The reason for this conduction failure is probably related to the fact that calcium depletion compromises the membrane calcium channel activity and the inward flow of calcium ions to cardiomyocytes, which is necessary for action potential and proper depolarization progress in the heart [45]. Although it is well-known that hypocalcemia only increases the QTc interval and does not affect the QRS complex, the above-mentioned calcium–phosphate metabolism disorders may be associated with the intraventricular conduction disturbances identified in patients with ESRD.

Study limitations

The primary limitation was that our study was a nonrandomized and single-center study with a relatively small number of patients. Unfortunately, the design of this case–control study was not prospective and, therefore, lacks data regarding the potential prognostic effect of RWPT in patients with ESRD.

Conclusion

The present study demonstrated that RWPT prolonged significantly in patients with ESRD. Furthermore, prolonged RWPT has been associated with increased LVM and LVMI.

Thus, prolonged RWPT may be an obvious sign of cardiac remodeling in patients with ESRD. This prolongation may be due to increased muscle thickness between the endocardium to the epicardium in the ventricles. Since left ventricular hypertrophy has been associated with increased morbidity and mortality, measurement of RWPT on surface ECG may be an additional and easy diagnostic tool for risk stratification of patients with ESRD. Those with an increased RWPT may be particularly at risk for cardiovascular complications.

Author contributions All of the authors contributed to planning, conduct, and reporting of the work. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with ethical standards

Conflict of interest All of the authors have no conflict of interest.

References

1. Parekh RS, Carroll CE, Wolfe RA, Port FK (2002) Cardiovascular mortality in children and young adults with end-stage kidney disease. J Pediatr 141:191–197
2. Saeed F, Arrigain S, Schold JD, Nally JV Jr, Navaneethan SD (2019) What are the risk factors for one-year mortality in older patients with chronic kidney disease? An analysis of the cleveland clinic CKD registry. Nephron 141(2):98–104
3. Wang AY (2007) Cardiovascular risk factors in peritoneal dialysis patients revisited. Perit Dial Int 27(Suppl 2):S223–S227
4. García-López E, Carrero JJ, Suliman ME, Lindholm B, Stenvinkel P (2007) Risk factors for cardiovascular disease in patients undergoing peritoneal dialysis. Perit Dial Int 27(Suppl 2):S205–S209
5. Hampl H, Riedel E (2009) Cardiac disease in the dialysis patient: good, better, best clinical practice. Blood Purif 27:99–113
6. Rodriguez M, Lorenzo V (2009) Progress in uremic toxin research: parathyroid hormone, a uremic toxin. Semin Dial 22:363–368
7. MacLeod AG, Wilson FN, Barker PS (1930) The form of the electrocardiogram. I. Intrinsicoid electrocardiographic deflections in animals and man. Exp Biol Med 27:586–587
8. Pérez-Riera AR, de Abreu LC, Barbosa-Barros R, Nikus KC, Baranchuk A (2016) R-peak time: an electrocardiographic parameter with multiple clinical applications. Ann Noninvasive Electrocardiol 21:10–19
9. Holland RP, Brooks H (1976) The QRS complex during myocardial ischemia. An experimental analysis in the porcine heart. J Clin Invest 57:541–550
10. Rencüzoğulları I, Çağdaş M, Karakoyun S et al (2018) The association between electrocardiographic R wave peak time and coronary artery disease severity in patients with non-ST segment elevation myocardial infarction and unstable angina pectoris. J Electrocardiol 51(2):230–235
11. Çağdaş M, Karakoyun S, Rencüzoğullari İ et al (2017) Relationship between R-wave peak time and no-reflow in ST elevation myocardial infarction treated with a primary percutaneous coronary intervention. Coron Artery Dis 28:326–331
12. Scharer K, Schmidt KG, Soergel M (1999) Cardiac function and structure in patients with chronic renal failure. Pediatr Nephrol 13:951–965
13. McCullough PA, Assad H (2012) Diagnosis of cardiovascular disease in patients with chronic kidney disease. Blood Purif 33:112–118
14. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351:1296–1305
15. Saran R, Robinson B, Abbott KC et al (2017) US renal data system 2016 annual data report: epidemiology of Kidney Disease in the United States. Am J Kidney Dis 69(3 Suppl 1):A7–A8
16. Eckardt KU (1999) Cardiovascular consequences of renal anaemia and erythropoietin therapy. Nephrol Dial Transpl 14:1317–1323
17. Juan-Garcia I, Puchades MJ, Sanjuan R et al (2012) Echocardiographic impact of hydration status in dialysis patients. Nefrologia 32:94–102
18. Poulikakos D, Ross L, Recio-Mayoral A et al (2014) Left ventricular hypertrophy and endothelial dysfunction in chronic kidney disease. Eur Heart J Cardiovasc Imaging 15:56–61
19. Ky B, Shults J, Keane MG et al (2013) FGF23 modifies the relationship between vitamin D and cardiac remodeling. Circ Heart Fail 6:817–824
20. London GM, Fabiani F, Marchais SJ et al (1987) Uremic cardiomyopathy: an inadequate left ventricular hypertrophy. Kidney Int 31:973–980
21. Berk BC, Fujiwara K, Lehoux S (2007) ECM remodeling in hypertensive heart disease. J Clin Invest 117:568–575
22. Kahan T, Bergfeldt L (2005) Left ventricular hypertrophy in hypertension: its arrhythmogenic potential. Heart 91:250–256
23. Paoletti E, De Nicola L, Gabbai FB et al (2016) Associations of left ventricular hypertrophy and geometry with adverse outcomes in patients with CKD and hypertension. Clin J Am Soc Nephrol 11:271–279
24. Eckardt KU, Scherhag A, Macdougall IC et al (2009) Left ventricular geometry predicts cardiovascular outcomes associated with anemia correction in CKD. J Am Soc Nephrol 20:2651–2660
25. Paoletti E, Specchia C, Di Maio G et al (2004) The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: a 10 year survey. Nephrol Dial Transpl 19:1829–1834
26. Tsao CW, Gona PN, Salton CJ et al (2015) Left ventricular structure and risk of cardiovascular events: a Framingham Heart Study cardiac magnetic resonance study. J Am Heart Assoc 4(9):e002188
27. Herzog CA, Asinger RW, Berger AK et al (2011) Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: improving global outcomes (KDIGO). Kidney Int 80:572–586
28. Ritz E (2009) Left ventricular hypertrophy in renal disease: beyond preload and afterload. Kidney Int 75:771–773
29. Martin LC, Franco RJ, Gavras I et al (2004) Association between hypervolemia and ventricular hypertrophy in hemodialysis patients. Am J Hypertens 17:1163–1169
30. McRae JM, Levin A, Belenkie I (2006) The cardiovascular effects of arteriovenous fistulas in chronic kidney disease. A cause for concern? Semin Dial 19:349–352
31. Gross ML, Ritz E (2008) Hypertrophy and fibrosis in the cardiomyopathy of uremia—beyond coronary heart disease. Semin Dial 21:308–318
32. Steigerwalt S, Zafar A, Mesiha N, Gardin J, Provenzano R (2007) Role of aldosterone in left ventricular hypertrophy among African–American patients with end-stage renal disease on hemodialysis. Am J Nephrol 27:159–163

33. Di Lullo L, Gorini A, Russo D, Santoboni A, Ronco C (2015) Left ventricular hypertrophy in chronic kidney disease patients: from pathophysiology to treatment. Cardiorenal Med. 5(4):254–266
34. Savard P, Rouleau JL, Ferguson J et al (1997) Risk stratification after myocardial infarction using signal-averaged electrocardiographic criteria adjusted for sex, age, and myocardial infarction location. Circulation 96:202–213
35. Shenkman HJ, Pampati V, Khandelwal AK et al (2002) Congestive heart failure and QRS duration: establishing prognosis study. Chest 122:528–534
36. Grant RP, Dodge HT (1956) Mechanisms of QRS complex prolongation in man; left ventricular conduction disturbances. Am J Med 20:834–852
37. Hamilin RL, Pipers FS, Hellerstein HK, Smith CR (1968) QRS alteration immediately following production of left ventricular free wall ischemia in dogs. Am J Physiol 215:1032–1040
38. Ozer N, Aytemir K, Atalar E et al (2000) P wave dispersion in hypertensive patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 23:1859–1862
39. Turhan H, Yetkin E, Senen K et al (2002) Effects of percutaneous mitral balloon valvuloplasty on P-wave dispersion in patients with mitral stenosis. J Cardiol 89(5):607–609
40. Turhan H, Yetkin E, Atak R et al (2003) Increased P-wave duration and P-wave dispersion in patients with aortic stenosis. Ann Noninvasive Electrocardiol 8(1):18–21
41. Senen K, Turhan H, Riza Erbay A et al (2004) P-wave duration and P-wave dispersion in patients with dilated cardiomyopathy. Eur J Heart Fail 6:567–569
42. Boles U, Almuntaser I, Brown A, Murphy RR, Mahmud A, Feely J (2010) Ventricular activation time as a marker for diastolic dysfunction in early hypertension. Am J Hypertens 23(7):781–785
43. Mitsnefes MM, Kimball TR, Kartal J et al (2005) Cardiac and vascular adaptation in pediatric patients with chronic kidney disease: role of calcium-phosphorus metabolism. J Am Soc Nephrol 16:2796–2803
44. Jono S, Nishizawa Y, Shioi A, Morii H (1997) Parathyroid hormone related peptide as a regulator of vascular calcification. Its inhibitory action on in vitro calcification by bovine vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 17:1135–1142
45. Lipscombe D (2002) L-type calcium channels. High and new lows. Circ Res 90:933–935