ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Predictors for the prolonged R wave peak time among patients with arterial hypertension

Arteriyal hipertansiyon hastalarında uzamış R dalgası pik süresi prediktörleri

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ABSTRACT

Objective: Hypertension (HT) is prevalent in the general population and is associated with significant cardiovascular adverse events. Major structural and electrical remodeling occurs in the ventricular myocardium in response to the pressure overload. Increased left ventricular mass (LVM) and myocardial fibrosis contribute to the prolongation of the R wave peak time (RWPT), which may indicate electrical remodeling in patients with HT. We evaluated predictors for prolonged RWPT among patients with a previous diagnosis of HT.

Methods: Consecutive patients who had a previous diagnosis of arterial HT and presented to the cardiology clinic for routine visit were included in the study. The standard 12-lead surface electrocardiography (ECG) and transthoracic echocardiography (TTE) was performed on all the patients included in the study for evaluating RWPT and the epicardial fat tissue (EFT). The upper limit for the RWPT was accepted as 40 milliseconds (ms).

Results: Between February 2019 and February 2020, 453 patients were screened; and of these, 237 were included in the study. The mean age was 62.1±11.2 years, and 41.8% of the included patients were men. The mean RWPT of the study population was 41.9±10.8. The RWPT was prolonged in 55 patients, and the remaining 172 patients had normal RWPT. In the univariate analysis, EFT (Odds ratio [OR] 1.222; 95% confidence interval [CI] 1.077-1386; p=0.002), the left ventricular mass index (LVMI) (OR 1.011; 95% CI 1.001-1.021; p=0.026), and fragmented QRS (fQRS) (OR 2.679; 95% CI 1.433-5.004; p=0.002) were associated with a prolonged RWPT. Multivariate analysis revealed that only EFT (OR 1.211; 95% CI 1.061-1.383; p=0.005) and fQRS (OR 2.796; 95% CI 1.459-5.359; p=0.002) predicted prolonged RWPT.

Conclusion: Among the patients with HT, EFT and fQRS predicted prolonged RWPT. These findings may suggest that compared with increased LVM, myocardial fibrosis had a more significant impact on ventricular activation time.

ÖZET

Amaç: Hipertansiyon (HT) toplumda oldukça yaygın görülen bir hastalık olup önemli kardiyovasküler sonlanım noktaları ile ilişkilidir. Artan basınç yükü sonrası ventrikül miyokard dokusunda ciddi yapısal ve elektriksel yeniden şekillenme ortaya çıkmaktadır. Hipertansif hastalarda elektriksel yeniden şekillenmenin göstergelerinden biri R dalgası pik süresi uzamasıdır (RWPT) ve bu durumun nedenleri arasında artmış sol ventrikül miyokard kitlesi ile miyokardial fibroz yer almaktadır. Çalışmamızda daha önce HT tanısı bulunan hastalarda uzamış RWPT öngördüren parametreleri araştırmayı amaçladık.

Yöntemler: Hipertansiyon tanısı bulunan kardiyoloji polikliniğine rutin kontrol için gelen ardışık hastalar çalışmaya dahil edilmiştir. Standart 12 derivasyonlu yüzey elektrokardiyografi (EKG) ve transtorasik ekokardiyografi (TTE) çalışmaya dahil edilen hastalara RWPT ve EFT değerlendirilmesi amacıyla uygulandı. RWPT için üst sınır 40 milisaniye (ms) olarak belirlendi.

Bulgular: Şubat 2019 ile Şubat 2020 arasında 453 hasta çalışma için taranmış olup bunlardan 237'si çalışmaya dahil edilmiştir. Hastaların ortalama yaşının 62.1±11.2 ve %41.8'i erkek olarak görüldü. Çalışmaya dahil edilen hastaların ortalama RWPT değeri 41.9±10.8 olarak bulundu. RWPT 55 hastada uzamış olarak saptanırken kalan 172 hastada normal bulundu. Tek değişkenli analizde EFT (OR, 1.222; 95% CI, 1.077-1386; p=0.002), sol ventrikül kitle indeksi (LVMI) (OR, 1.011; 95% CI, 1.001-1.021; p=0.026) ve fragmente QRS (fQRS) (OR, 2.679; 95% CI, 1.433-5.004; p=0.002) parametrelerinin uzamış RWPT ile ilişkili olduğu bulundu. Çok değişkenli analizde ise EFT (OR, 1.211; 95% CI, 1.061-1.383; p=0.005) ve fQRS (OR, 2.796; 95% CI, 1.459-5.359; p=0.002) parametrelerinin uzamış RWPT'i predikte ettiği gösterildi.

Sonuç: Hipertansif hastalarda, EFT ve fQRS uzamış RWPT'ı predikte etmektedir. Bu sonuçlar ventriküler aktivasyon süresi uzamasına miyokardial fibrozun, artmış sol ventrikül kitlesine göre daha etkili olduğunu düşündürebilir.

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Hypertension (HT) is a major public health problem causing significant morbidity and mortality. Approximately, half of all cardiovascular (CV) mortality is attributable to HT.[1] Elevated systemic pressure overload causes pathologic structural and electrical remodeling in the left ventricle (LV), which is defined as hypertensive heart disease (HHD). It is characterized by left ventricular hypertrophy (LVH), left atrial enlargement (LAE), and LV systolic and diastolic dysfunction.[2] In particular, development of LVH is an adaptive mechanism for the increased wall tension secondary to the pressure overload, and it allows LV to maintain mechanical function. Prior reports demonstrated that LVH correlated with CV risk factors in patients with HT and was associated with poor prognosis.[3] Myocardial remodeling associated with HHD is not just dependent on hypertrophy but involves interplay of complex mechanisms. Among them, inflammation contributes to a cascade of events leading to structural changes.[4]

The R wave peak time (RWPT), which is also defined as the ventricular activation time, represents the conduction of electrical activity from the endocardium to the epicardium in the ventricles.[5] Previous studies reported that RWPT had several clinical implications, and its prolongation was frequently observed in the context of LVH, myocardial ischemia, and conduction system abnormalities.[5-7] Prolonged RWPT in the left ventricular myocardium among patients with HT can be attributed to increased left ventricular mass and accumulation of inflammatory cells leading to myocardial fibrosis and ischemia.

Recently, epicardial fat tissue (EFT) was demonstrated to act as an endocrine organ, secreting several biological active molecules including plasminogen activator inhibitor type I, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6).[8] Importantly, EFT was shown as a reliable indicator for visceral adiposity and had stronger value for predicting CV adverse events compared with traditional adiposity measures, such as body mass index (BMI) and waist circumference.[9] Paracrine effects of EFT are of particular importance owing to its close proximity to the cardiac myocardium and the lack of any anatomical barrier.[10] EFT may act as a local mediator for cardiac fibrosis.

In this study, we evaluated the predictors for prolonged RWPT among patients with a prior diagnosis of HT.

METHODS

Study population

Between February 2019 and February 2020, consecutive patients who had a prior diagnosis of arterial HT and presented to our outpatient cardiology clinic for routine clinical visits were screened for eligibility to the study. A prior diagnosis of HT was determined by the presence of HT diagnosis code in our hospital's electronic database system and/or the use of any antihypertensive medications as indicated by the current European Society of Cardiology guideline on the management of arterial HT for at least 12 months' duration.[11] Antihypertensive medications included angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), calcium channel blockers (CCB), beta-blockers (BB), and diuretics. Patients with secondary HT, any structural heart disease other than LVH, paced electrocardiography (ECG) rhythm, bundle branch or fascicular block, second or higher atrioventricular block, and poor ECG recording or echocardiographic window which prevented optimal evaluation were excluded from the study. Written informed consent was obtained from all the included patients, and the local ethics committee approved the study.

Baseline demographic characteristics and medical/family histories of the study population were recorded. Physical examination was performed by the attending cardiologist. Blood samples were obtained in the fasting state for analyzing complete blood count, routine biochemistry, and lipid panel. Weight and height of the included patients were measured using a standardized protocol

Abbreviations:

2D	*Two-dimensional*
ACEI	*Angiotensin converting enzyme inhibitors*
ARB	*Angiotensin II receptor blockers*
BB	*Beta-blockers*
BMI	*Body mass index*
BP	*Blood pressure*
CCB	*Calcium channel blockers*
CI	*Confidence interval*
CV	*Cardiovascular*
DM	*Diabetes mellitus*
ECG	*Electrocardiography*
EFT	*Epicardial fat tissue*
HHD	*Hypertensive heart disease*
HL	*Hyperlipidemia*
HT	*Hypertension*
IL-6	*Interleukin-6*
LAE	*Left atrial enlargement*
LV	*Left ventricle*
LVH	*Left ventricular hypertrophy*
LVM	*Left ventricular mass*
LVMI	*Left ventricular mass index*
OR	*Odds ratio*
PICP	*Propeptide of type I procollagen*
RWPT	*R wave peak time*
TNF-α	*Tumor necrosis factor-α*
TTE	*Transthoracic echocardiography*

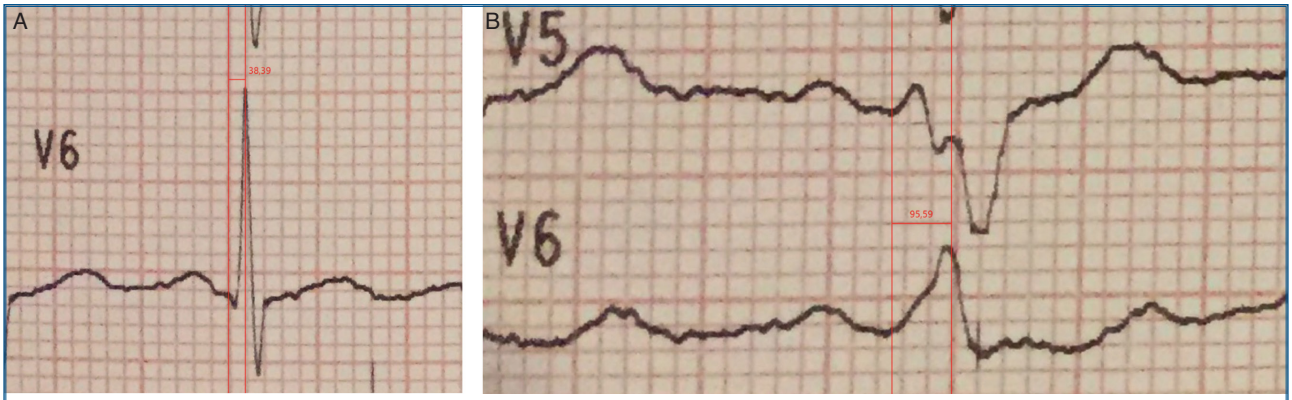

Figure 1. Measurement of R wave peak time (RWPT) from the 12-lead ECG recording in a patient with normal **(A)** and prolonged **(B)** RPWT.

and recorded. BMI was calculated by weight in kg divided by height in meters (kg/m^2). Waist circumference was measured in the horizontal plane midway between the lowest rib and the iliac crest when the patient was standing with bare midriff following a normal exhalation. Diagnosis of diabetes mellitus (DM) was made by any of the following; fasting glucose level ≥126 mg/dL, random glucose level ≥200 mg/dL, or the use of any oral anti-diabetic medication and/or subcutaneous insulin for the treatment of DM. Criteria for the diagnosis of hyperlipidemia (HL) was any of the following; low density lipoprotein level ≥70 mg/dL or the use of any lipid lowering medications for the treatment of HL. Patients were considered as smokers in case they smoked ≥1 cigarette per day.

Arterial blood pressure (BP) measurements were performed using automatic sphygmomanometers with appropriate cuff size and after five minutes of rest in a quiet environment. Patients were advised to avoid smoking, exercise, and consuming coffee and tea for at least 30 minutes before the BP measurement. Three measurements were performed one to two minutes apart, and the mean was recorded. Additional measurements were performed in case the first two differed by more than 10 mmHg.

12-lead surface ECG recordings

A standard 12-lead surface ECG (Schiller, Cardiovit AT-10 plus) (Filter 150 Hz, 25 mm/s, 10 mm/mV) was recorded for all the included patients. ECG recordings were analyzed by a cardiologist who was blinded to other data. Semi-automatic digital calipers were used for the analysis of ECG recordings, which were scanned and amplified eight times for detailed evaluation. RWPT was defined as the duration from the onset of the QRS complex until the peak of the R or R′wave and measured from three consecutive QRS complexes in precordial leads V5-V6[5] (Figures 1A and 1B). The longest duration was recorded. According to previous evidence in the literature, RWPT > 40 ms was defined as prolongation.[5] Fragmented QRS (fQRS) was defined as any of following; presence of an additional R wave (R′), notching in the nadir of the S wave, notching in the R wave, and presence of and additional R′ wave in at least two contiguous leads corresponding to a myocardial territory.[12]

Transthoracic echocardiographic evaluation and EFT analysis

The study patients underwent a standard two-dimensional (2D) transthoracic echocardiographic (TTE) evaluation using a GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway). TTE was performed by a cardiologist who was blinded to other data.

Standard 2D, M-mode, pulsed, and continuous Doppler measurements were performed in accordance with the current guideline on chamber quantification.[13] LVEF was assessed using the modified Simpson's biplane method. Left ventricular mass (LVM) was calculated with the linear method using the Cube formula. Left ventricular mass index (LVMI) was calculated by indexing LVM to the body surface area.

EFT visualization and quantification was assessed in accordance to the method proposed and validated by Iacobellis et al.[14] Measurement of EFT was per-

formed on the right ventricular free wall at the parasternal long-axis view using the aortic annulus as the anatomical reference. EFT was identified as an echo-free space under the visceral pericardial layer on 2D TTE and was measured perpendicularly in front of the right ventricular free wall at end-systole in three cardiac cycles.

Statistical analysis

Continuous variables were presented as mean±standard deviation or median (25^{th}-75^{th}) percentiles, and the categorical variables were expressed as number of cases with percentages. The normality distribution patterns of variables were evaluated using histograms, probability plots, and analytical methods (Kolmogorov-Smirnov). The variables were compared using a two-tailed Student's t test for continuous variables of normal distribution or the Mann-Whitney U test for the continuous variables of non-normal distribution. The chi-squared test was used for the categorical variables. The effects of the various variables on RWPT were calculated by univariate and multivariate (enter method) regression analysis. All the statistical tests were two-tailed, and a p value <0.05 was considered significant. All the analyses were carried out using the SPSS v22.0 (IBM Corp.; Armonk, NY, USA).

RESULTS

Between February 2019 and February 2020, 453 patients were screened for eligibility to include in the study. Among them, 95 did not give consent, 70 had structural heart diseases other than LVH, 23 had bundle branch or fascicular block, 26 had poor ECG recordings or echocardiographic window that prevented optimal evaluation, and two had paced ECG rhythm. These patients were excluded, and the study population comprised of the remaining 237 patients.

The mean age was 62.1±11.5 years, and 40.5% of the included patients were men. DM and HL was present among 32.2% and 63% of the patients, respectively. The mean LVMI and EFT were 84.3±30.5 g/m^2 and 5.6±2.4 mm, respectively. fQRS was identified among 33.5% of the patients. The mean RWPT of the included patients was 41.9±10.8 ms.

RWPT was prolonged in 55 patients, and the remaining 172 patients had normal RWPT (Table 1). The mean RPWT was 37.1±6.7 ms and 57.0±6.4 ms in the normal and prolonged RWPT groups, respectively. Compared with patients with normal RWPT, those with prolonged RWPT had higher LVMI, increased EFT, and were more likely to have fQRS in their ECG recordings (Table 1). Importantly, there were no significant differences in BMI and waist circumferences between the two groups.

In the univariate analysis, EFT (Odds ratio [OR] 1.222; 95% confidence interval [CI] 1.077-1386; p=0.002), LVMI (OR 1.011; 95% CI 1.001-1.021; p=0.026), and fQRS (OR 2.679; 95% CI 1.433-5.004; p=0.002) were associated with a prolonged RWPT (Table 2). Multivariate analysis revealed that only EFT (OR 1.211; 95% CI 1.061-1.383; p=0.005) and fQRS (OR 2.796; 95% CI 1.459-5.359; p=0.002) predicted prolonged RWPT (Table 2).

DISCUSSION

In this study, we found that among patients with a previous diagnosis of HT, increased EFT detected in TTE and the presence of fQRS independently predicted prolonged RWPT.

Long-term exposure to the increased pressure overload triggers a cascade of events leading to myocardial structural and electrical remodeling, which is defined as HHD. Hypertrophic changes include increases in the size and protein content of the cardiomyocytes and is considered as the primary response for reducing LV wall stress against the increased pressure overload.[15] However, LVH is only the tip of the iceberg in the evolution of HHD as the interplay of various pathways, which are involved in the systemic and local inflammation response, are the major contributors to myocardial remodeling. Injured myocytes release several active molecules leading to increased secretion of inflammatory mediators, including IL-1β, IL-6, macrophage chemoattractant protein-1, and TNF-α.[16] This creates a paracrin proinflammatory milieu and results in the activation and differentiation of extracellular matrix proteins and cells causing fibrosis. Furthermore, activation of the renin-angiotensin-aldosteron axis in patients with HT contributes to the development of myocardial fibrosis and myocardial remodeling. Extensive myocardial fibrosis is not only the harbinger of the LV systolic and diastolic function but also responsible for the electrical remodeling manifested as conduction abnormalities and reentrant ventricular arrhythmias.[17]

Table 1. Basal characteristics of study population

Variable	All patients (N=227)	Normal RWPT (<40 ms) (n=172)	Prolonged RWPT (≥40 ms) (n=55)	*p*
Age (years)	62.1±11.5	62.5±11.6	60.9±11.2	0.408
Sex (male) (%)	92 (40.5)	66 (38.4)	26 (47.3)	0.242
BMI (kg/m^2)	32.8±5.9	32.8±6.1	32.5±5.1	0.745
Waist circumference (cm)	105.8±11.7	106.2±11.7	105.1±12.1	0.562
Diabetes (%)	73 (32.2)	52 (30.2)	21 (38.2)	0.272
Hyperlipidemia (%)	143 (63)	106 (61.6)	37 (67.3)	0.450
Smoking (%)	102 (44.9)	74 (43)	28 (50.9)	0.306
Systolic BP (mmHg)	156.9±23.1	155.9±22.9	159.8±24.4	0.280
Diastolic BP (mmHg)	88.6±13.3	87.9±12.6	90.4±15.1	0.239
Glucose (mg/dL)*	104(94-124)	103.5(94-124)	106(91.5-124)	0.749
eGFR (mL/min/1.73 m^2)	87.4±18.9	87.5±18.9	87.3±18.9	0.947
Creatinine (mg/dL)	0.81±0.23	0.80±0.24	0.82±0.21	0.579
HbA1c (%)	6.0±1.3	5.9±1.2	6.2±1.4	0.326
CRP (mg/L)*	3 (2-6)	3 (2-6)	4 (2-8)	0.597
LVEF (%)	59.9±1.8	59.9±1.7	59.8±2.1	0.412
LVMI (g/m^2)	84.3±30.5	81.7±28.7	92.5±34.5	0.022
EFT (mm)	5.6±2.4	5.2±2.3	6.4±2.7	0.001
fQRS	76 (33.5)	48 (27.9)	28 (50.9)	0.002
Triglycerides (mg/dL)*	134 (107-180)	134 (107-179.5)	135 (103.5-192.5)	0.960
HDL (mg/dL)	49.9±14.3	50.4±14.7	48.5±13.1	0.387
LDL (mg/dL)	129.7±38.4	131.6±39.5	122.8±33.8	0.175
Beta blocker (%)	50 (22.5)	37 (22)	13 (24.1)	0.754
ACEi (%)	154 (69.4)	119 (69.2)	35 (63.6)	0.169
ARB (%)	35 (15.8)	25 (14.9)	10 (18.5)	0.523
Statin (%)	118 (51.9)	90 (52.3)	28 (50.1)	0.570
CCB (%)	117 (52.7)	83 (49.4)	34 (63)	0.083
OAD/Insulin (%)	67 (30)	49 (29.2)	18 (32.7)	0.617

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; CCB: calcium channel blocker; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; EFT: epicardial fat tissue; fQRS: fragmented QRS; HDL: high density lipoprotein; LDL: low density lipoprotein; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; OAD: oral antidiabetic.
*median (25th-75th) percentile.

Table 2. Univariate and multivariate analysis for identifying the predictors for prolonged RWPT

	Univariate			Multivariate		
Variable	OR	95% CI	*p*	OR	95% CI	*p*
EFT	1.222	1.077-1.386	0.002	1.211	1.061-1.383	0.005
LVMI	1.011	1.001-1.021	0.026	1.007	0.996-1.017	0.197
fQRS	2.679	1.433-5.004	0.002	2.796	1.459-5.359	0.002

EFT: epicardial fat tissue; fQRS: fragmented QRS; LVMI: left ventricular mass index.

RWPT or ventricular activation time can be easily determined from the surface ECG and several clinical implications. Two possible underlying mechanisms may contribute to the prolongation of RWPT among patients with HT; elevation in the LVM and delay in the electrical conduction secondary to the tissue fibrosis.[5] The prolongation of RWPT in leads V5-V6 is a marker of diastolic dysfunction among patients with newly diagnosed uncontrolled HT.[7] Diastolic dysfunction occurs early in the course of HT, when LVH may not yet be detected.[18] Furthermore, sensitivity of ECG criteria of HT is low, and majority of patients may have completely normal ECG, particularly in the early periods. Boles et al.[7] have demonstrated that RWPT was significantly correlated with diastolic dysfunction assessed by tissue Doppler imaging parameters. This study provided evidence that in HHD, electrical remodeling may precede any other structural abnormalities including increase in the LVM. It is reasonable to speculate that in the absence of the increased LVM, conduction abnormalities secondary to the tissue fibrosis may be the major contributor to electrical remodeling.

Our findings were in accordance to this hypothesis by demonstrating that fQRS and the EFT predicted prolonged RWPT. Importantly, no such predictive value was found for increased LVMI. fQRS was demonstrated as a reliable indicator of underlying myocardial scar in different patient populations, including Brugada syndrome, ischemic/nonischemic cardiomyopathy, and HT.[19-21] Bekar et al.[22] have shown that carboxy-terminal propeptide of type I procollagen (PICP), which is a marker of extacellular collagen synthesis, was significantly correlated with fQRS among hypertensive patients. Similarly, EFT reflects visceral adiposity and functions as an endocrine organ secreting several inflammatory molecules. Recent findings suggested that EFT was a more reliable indicator for visceral adiposity compared with traditional anthropometric measurements. Natale et al.[23] have shown that EFT >7 mm predicted higher LVMI, diastolic dysfunction, increased arterial stiffness, and carotid-intima media thickness. Of note, no difference was found when patients were divided according to waist circumference value. Mazurek et al.[8] have demonstrated that EFT was a source of chemokines and inflammatory cytokines among patients who underwent coronary artery bypass grafting operation. These include TNF-α, IL-6, leptin, and visfatin which were considered to be associated with proinflammatory state. Importantly, plasma levels of systemic inflammation parameters were normal. Thus, EFT may be a local mediator of inflammation in cardiac tissue. Previous studies have evaluated the impact of EFT on the atrial conduction parameters reflected as P wave indices.[24,25] Jhuo et al.[24] have demonstrated that increase in EFT predicted longer PR interval and P wave duration. More evidence for solidifying the role of EFT in myocardial inflammation and fibrosis was elicited from studies evaluating the association between AF and the EFT.[26-29] In these studies, increased EFT predicted higher AF prevalence, burden, chronicity, and failure to ablation. Myocardial fibrosis leading to cardiac remodeling is the major underlying mechanism for development and progression of AF. Although data evaluating direct relationship between cardiac fibrosis determined by late gadolinium enhancement and EFT is scarce, it can be considered that proinflammatory cytokines that were found in high concentration in EFT may trigger a cascade of events leading to cardiac remodeling. Finally, Shamloo et al.[30] have shown that EFT predicted recurrences following ablation for ventricular tachycardia. Increased secretion of free fatty acids, lipomatous metaplasia facilitating reentry, and electrical remodeling caused by dysfunction in connexins and gap junctions are proposed as the potential mechanisms contributing to higher incidence of recurrences.

Our findings might have some clinical implications. HT is considered as a major risk factor for the development of cardiac arrhythmias. Myocardial fibrosis and subsequent cardiac remodeling might predispose patients to rhythm disturbances, particularly AF. Although we did not prospectively follow patients for cardiac arrhythmias, more frequent rhythm monitoring with opportunistic ECG or Holter recording for patients with increased EFT might help physicians with an earlier diagnosis of AF and other cardiac rhythm disturbances. These hypotheses need to be tested in further randomized controlled trials.

Limitations

This was a single center study with a limited number of patients. Retrospective nature of the study limited evaluating the causality. We assessed the EFT using TTE; however, cardiac MRI would provide more detailed anatomical evaluation of EFT. ECG recordings

and TTE evaluations were performed by a single cardiologist only once, which limited the assessment of inter- and intra-observer variability.

Conclusion

We found that among patients with a previous diagnosis of arterial HT, fQRS in the surface ECG and EFT assessed by TTE predicted a prolonged RWPT.

Ethics Committee Approval: Ethics committee approval for this study was received from the local ethics committee.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - G.Ç., A.S.Y., A.İ.T., M.Ç.; Design - G.Ç.; Supervision - A.İ.T., M.Ç.; Materials - G.Ç., A.S.Y; Data - G.Ç.; Analysis - M.Ç., G.Ç.; Literature search - G.Ç.; Writing - G.Ç.; Critical revision - A.İ.T., M.Ç.

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