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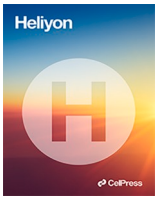

Research article

Electrocardiographic ventricular arrhythmia parameters during diagnosis and after the treatment of acromegaly: A case-control study☆

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ABSTRACT

Background: The risk of death is increased in acromegaly patients compared to the general population, and cardiovascular system-related complications are among the risk factors decreasing life expectancy. The Tp-e interval, which is the distance between the point where the T-wave peaks and ends on electrocardiography (ECG), shows ventricular rapolarization and, together with the Tp-e/QT and Tp-e/QTc ratios, these are relatively new tools that predict ventricular arrhythmia. We aimed to evaluate the ECG of acromegaly patients at the time of diagnosis and compare the results with current ECG findings.
Material and methods: The study included 103 acromegaly patients and 81 control subjects. Of the 103 patients, 41 patients had only baseline ECG, 23 patients had only current ECG and 39 patients had both baseline and current ECGs. Heart rate, QT interval and corrected QT (QTc) interval, Tp-e, Tp-e/QT, Tp-e/QTc values on the ECGs were measured by a cardiologist.
Results: In the acromegaly patients with both baseline and current ECGs, heart rate, QRS duration, Tp-e, and Tp-e/QTc ratio were decreased. The decrease in these arrhythmia parameters was similar in active and remission patients. Compared to the control group, in acromegaly patients with only baseline ECG, heart rate, QTc interval, Tp-e, Tp-e/QT, and Tp-e/QTc were decreased.
Conclusion: Ventricular arrhythmia parameters improve with treatment in patients with acromegaly. The decrease in ventricular arrhythmia parameters was similar in active and remission

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patients, which can be explained by the significant decrease in IGF-1 levels compared to the time of diagnosis, even in patients with active disease.

1. Introduction

Acromegaly is a rare chronic diseasecaused by increased production of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), most often due to a pituitary adenoma [1]. GH or growth hormone–releasing hormone production by a neuroendocrine tumor very occasionally leads to extrapituitary acromegaly [2]. Acromegaly has a prevalence of 83–133 cases/1.000.000 [3], and is associated with many comorbidities such as cardiovascular diseases, diabetes mellitus, sleep apnea and neoplasms and carries an increased mortality risk, which is decreased in patients with disease remission. There is a diagnostic delay of approximately 6–10 years and approximately 70 % of patients have a macroadenoma at the time of diagnosis [4]. The mortality risk in acromegaly is increased by 61 % compared to the general population and cardiovascular manifestations are the primary risk parameters decreasing life expectancy [5].High blood pressure, cardiomyopathy, valvular disorder and arrhythmia are the major cardiovascular problems seen in patients with acromegaly [6,7]. According to autopsy results, 93 % of acromegaly patients have myocardial hypertrophy [8]. Although acromegaly is thought to cause fibrosis in the heart and form pro-arrhythmogenic foci, there are insufficient data in the literature [9]. Increased cardiovascular mortality seen in acromegalic patients is mostly corresponds to cardiac arrhythmias and sudden cardiac death. Beat-to-beat QT variability and late potentials-related ventricular tachyarrhythmias are known to be increased in acromegaly [10,11]. QTdispersion (dQT), an electrophysiological factorrelated to a tendency for arrhythmias and sudden cardiac death, has been found to be longer in patients with active acromegaly [12]. It has been reported that electrocardiographic (ECG) changes detected at the time of initial diagnosis may improve with treatment in acromegaly patients [13,14]. Tp-e interval, defined as the lenght between the peak and end points of the T wave, together with TP-e/QT and TP-e/QTC ratios show ventricular repolarization and are relatively new and reliable parameters in predicting ventricular arrhythmia. They also have predictive importance for ventricular arrhythmia and sudden cardiac death in cases of long, short, or normal QT interval [15,16].A recent study demonstrated increased Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in acromegaly patients [17]. The aim of this study was to evaluate the electrocardiography (ECG) results of acromegaly patients at the time of diagnosis with the new Tp-e, Tp-e/QT, Tp-e/QTc as well as the traditional parameters and compare them with current ECG findings after treatment.

2. Material and methods

2.1. Patients

Of the 185 patients, 103 patients had baseline or current ECGs, 41 patients had only baseline ECG, 23 patients had only current ECG and 39 patients had both baseline and current ECGs. A control group was formed of 81 healthy subjects. Baseline demographic characteristics, clinical characteristics and medication use of the patients were recorded.

In all the acromegaly patients, GH, IGF-1, urea, creatinine, sodium, potassium, calcium and chloride values at the time of diagnosis and at the last examination were examined and recorded.

A 12-lead ECG of all patients was obtained at their last examination. The 12-lead ECGs taken at the time of diagnosis were retrieved from the archived patient files and recorded. Heart rate, QT interval and corrected QT interval (QTc), Tp-e, Tp-e/QT, Tp-e/QTc values were read and recorded by a cardiologist from the ECGs taken at the time of diagnosis and at the last examination.

Patients were not included in the study if the period between diagnosis and current presentation was less than 6 months, if they had a diagnosis of arrhythmia (paroxysmal atrial fibrillation, ventricular tachycardia, ectopic beat, paroxysmal supraventricular tachycardia, sick sinus syndrome, atrial premature beats, or ventricular premature beats), were usingdrugs that can have impact on heart rate or if they had any electrolyte disorder.

Tp-e and QT interval (QT), corrected QT (QTc), QRS duration, Tp-e/QT, and Tp-e/QTc ratios were calculated from the 12-lead electrocardiogram.

2.2. Electrocardiography

A 12-lead standard ECG system was used and the results were recorded. ECGs were taken in the recumbent position at 50 mm/s and 10 mm/mV amplification (CardiofaxV model 9320, Nihon Kohden). QT was described as the time between the QRS onset and the point at which the T wave returned to baseline. The QTc was measured by Bazett's formula and was classified as normal, borderline, or prolonged according to the European regulatory guideline. Cutoff values for males were defined as 430 ms (normal), 431–450 ms (borderline) and >450 ms (increased), and for females as 450 ms (normal), 451–470 (borderline) and >470 (increased).Tp-e interval, defined as the time between the peak and the end points of the T wave, and was evaluated in ms using the "tangent" method. Tp-e/QT and Tp-e/QTc ratios as predictors of ventricular arrhythmogenesis were measured by using these parameters. Tp-e measurements were not made in cases of artifact and flat T wave. All ECG measurements were performed by same physician.

2.3. Statistical analysis

JMP 16.0.1 software (SAS Institute, Cary, NC, USA) was used for analysis of the data. Mean ± standard deviation (SD) values were used for continuous data while number (n) and percentage (%) for the categorical data. The Kolmogorov-Smirnov or Shapiro-Wilk W test was used for the evaluation of normaldistribution. Normally distributed continuous variables were analyzed with the Student's t-test, and the Mann-Whitney *U* Test was used for non-normally distributed variables. The Chi-square or Fisher's exact test was used for the analysis of categorical variables. Pearson and Spearman correlation analysis used for the correlations between variables. A value of $p < 0.05$ was accepted as statistically significant.

3. Results

A total of 39 acromegaly patients (21 (54 %) females; mean age 49.10 ± 10.46 years) had both baseline and current ECGs. Thirty of these patiens (79 %) were in remission. The patients' IGF-1 (843.73 ± 357.51 to 213.35 ± 100.88, $p < 0.0001$) and GH values (12.77 ± 13.17 to 1.11 ± 1.57, $p < 0.0001$) were significantly decreased by the treatment. Median time from diagnosis to current time is 6 (25th and 75th percentiles: 2,11). Of these patients, 19 (48 %) were diagnosed with diabetes mellitus, 14 (35 %) with hypertension, 2 (5 %) with coronary artery disease, and 2 (5 %) with chronic kidney disease. The median disease duration was 8.32 ± 7.19 years. Surgery was performed on 38 patients, and primary medical treatment was given to 1 patient. Eight (20 %) of the patients were on octreotide, 13 (33 %) were on lanreotide, and 10 (25 %) were on cabergoline. The number of patients receiving RT was 8 (21 %). Surgical remission was achieved in 16 (41 %) patients, and the total remission rate was 79 % (31/39) (Table 1).A decrease was determined in heart rate (80.21 ± 14.1 vs. 73.59 ± 12.96, $p = 0.0003$), QRS duration (90.41 ± 10.38 vs. 87.36 ± 9.43, $p = 0.048$), Tp-e (78.97 ± 7.96 vs 72.56 ± 10.12, $p < 0.0001$), and Tp-e/QTc ratio (0.20 ± 0.02 vs. 0.18 ± 0.03, $p = 0.0003$), and the QT interval (368.56 ± 28.0 vs. 370.74 ± 31.47, $p = 0.384$), QTc (403.56 ± 23.09 vs. 404.03 ± 30.03, $p = 0.921$) and Tp-e/QT ratio (0.21 ± 0.02 vs. 0.20 ± 0.03, $p = 0849$) were not affected by the treatment (Table 2). Serum urea, creatinine, sodium, potassium, calcium, chloride levels were not changed by the treatment.

The ECG parameters of 31 acromegaly patients who had both baseline and current ECGs and were in remission were compared.A decrease was determined in heart rate (81.71 ± 15 vs. 74.68 ± 14.09, $p = 0.001$), QRS time (90.52 ± 10.03 vs 87.16 ± 10.16, $p = 0.046$), Tp-e (78.55 ± 8.48 vs. 72.26 ± 10.79, $p = 0.0003$), Tp-e/QT (0.22 ± 0.02 vs.0.20 ± 0.03, $p = 0.0001$), and Tp-e/QTc (0.20 ± 0.02 vs. 0.18 ± 0.03, $p = 0.0015$), and the QT interval (364.58 ± 28.01 vs. 370.74 ± 31.47, $p = 0.244$) and QTc interval (401.58 ± 24.55 ms vs. 404.35 ± 32.11, $p = 0.613$) were not affected (Table 3).

No significant correlation was detected between the changes in IGF-1 and GH levels and ECG parameters (Table 4). No significant correlation was detected between age, disease duration and ECG parameters.

Acromegaly patients who had baseline ECG (n:80) were compared with control subjects (n:81) in regard of ECG parameters. A decrease was determined in heart rate (81.11 ± 14.95 vs. 73.86 ± 10.95, $p = 0.0006$), QTc interval (406.19 ± 20.97 ms vs. 391.91 ± 20.43, $p < 0.0001$), Tp-e (77.31 ± 8.71 vs. 70.19 ± 11.60, $p < 0.0001$), Tp-e/QT (0.21 ± 0.02 vs. 0.19 ± 0.03, $p = 0.0003$), Tp-e/QTc (0.19 ± 0.02 vs. 0.18 ± 0.03, $p = 0.009$), and the QT interval (370.37 ± 28.20vs. 366.32 ± 25.06, $p = 0.341$) and QRS time (92.35 ± 10.18 vs. 90.21 ± 9.69, $p = 0.178$) were not affected (Table 5).

The ECG parameters of the acromegaly patients who had current ECG (n:62) were compared with those of the control subjects (n:81). Fourty-nine (79 %) of patients were in remission. Heart rate (73.16 ± 12.90 vs. 73.86 ± 10.95, $p = 0.731$), QT interval (374.50 ± 27.15 vs. 366.32 ± 25.06, $p = 0.067$), QRS time (89.73 ± 10.66 vs. 90.21 ± 9.69, $p = 0.780$), Tp-e (73.06 ± 9.72 vs.70.19 ± 11.60, $p = 0.109$), Tp-e/QT (0.20 ± 0.03 vs. 0.19 ± 0.03, $p = 0.533$), and Tp-e/QTc (0.18 ± 0.03 to 0.18 ± 0.03, $p = 0.800$) were similar, and the QTc interval (405.18 ± 31.61 ms vs. 391.91 ± 20.43, $p = 0.005$) was determined to be higher in the acromegaly group (Table 6). When 49 patients who is in remission compared with control subjects, all the parameters were similar except QTc interval was higher

Table 1
Basal characteristics of patients with both basal and current ECGs.

Parameters	Mean ± SD or n (%)
Patient number	39
Female, n (%)	21 (54)
Mean age (years)	49.10 ± 10.46
Disease duration (years)	8.32 ± 7.19
Patients with DM, n (%)	19 (48)
Patients with HT, n (%)	14 (35)
Pateints with CKD, n (%)	2 (5)
Pateints with CAD, n (%)	2 (5)
Octreotide users, n (%)	8 (20)
Lanreotide users, n (%)	13 (31)
Cabergoline users, n (%)	9 (22)
Surgery, n (%)	38 (98)
RT, n (%)	8 (21)
Surgical remission, n (%)	16 (41)
Remission, n (%)	31 (79)
Abbreviations	DM: Diabetes Mellitus, HT: Hypertension, CKD: Chronic kidney disease, CAD: Coronary artery disease, RT: Radiotherapy

Table 2
Comparisons of baseline and current ECG parameters in 39 acromegaly patients.

Parameters	Baseline	Current	*p*
GH, mcg/L	12.77 ± 13.17	1.11 ± 1.57	**<0.0001**
IGF-1, ng/mL	843.73 ± 357.51	213.35 ± 100.88	**<0.0001**
Heart rate	80.21 ± 14.1	73.59 ± 12.96	**0.0003**
QT interval, ms	368.56 ± 27.96	372.44 ± 29.95	0.384
QTc interval, ms	403.56 ± 23.09	404.03 ± 30.03	0.921
QRS time, ms	90.41 ± 10.38	87.36 ± 9.43	**0.048**
Tp-e, ms	78.97 ± 7.96	72.56 ± 10.12	**<0.0001**
Tp-e/QT	0.21 ± 0.02	0.20 ± 0.03	0.849
Tp-e/QTc	0.20 ± 0.02	0.18 ± 0.03	**0.0003**

Table 3
Comparisons of baseline and current ECG parameters in patients in remission (n:31).

Parameters	Baseline	Current	*p*
Heart rate	81.71 ± 15	74.68 ± 14.09	**0.001**
QT interval, ms	364.58 ± 28.01	370.74 ± 31.47	0.244
QTc interval, ms	401.58 ± 24.55	404.35 ± 32.11	0.613
QRS time, ms	90.52 ± 10.03	87.16 ± 10.16	**0.046**
Tp-e, ms	78.55 ± 8.48	72.26 ± 10.79	**0.0003**
Tp-e/QT	0.22 ± 0.02	0.20 ± 0.03	**0.0001**
Tp-e/QTc	0.20 ± 0.02	0.18 ± 0.03	**0.0015**

Table 4
Correlation analysis between changes in IGF-1 and GH levels electrocardiographic parameters in acromegaly patients with baseline and current ECGs.

Parameters	Change in IGF-1		Change in GH	
	r	*p*	r	*p*
Heart rate	0.0927	0.6019	0.5312	**0.0012**
QT interval, ms	−0.1384	0.4349	0.2225	0.2060
QTc interval, ms	−0.0666	0.7081	−0.0953	0.5917
QRS time, ms	0.1468	0.4073	−0.2898	0.0964
Tp-e, ms	0.2107	0.2317	−0.1859	0.2925
Tp-e/QT	0.1887	0.2852	−0.0820	0.6446
Tp-e/QTc	0.2831	0.1047	−0.2513	0.1516

Table 5
Comparisons of baseline ECG parameters of acromegaly patients and the control group.

Parameters	Acromegaly Group (Mean ± SD) (n:80)		Control Group (Mean ± SD) (n:81)		*p*
Age	53.9	12.03	51.1	11.5	0.133
Female Gender, n,%	48 (52)		53 (65)		0.064
Heart rate	81.11	14.95	73.86	10.95	**0.0006**
QT interval, ms	370.37	28.20	366.32	25.06	0.3405
QTc interval, ms	406.19	20.97	391.91	20.43	**<0.0001**
QRS time, ms	92.35	10.18	90.21	9.69	0.1777
Tp-e, ms	77.31	8.71	70.19	11.60	**<0.0001**
Tp-e/QT	0.21	0.02	0.19	0.03	**0.0003**
Tp-e/QTc	0.19	0.02	0.18	0.03	**0.0086**

in acromegaly group (406.73 ± 33.14 ms vs. 391.91 ± 20.43, p = 0.006) (see Table 7).

4. Discussion

Ventricular arrhytmia parameters were evaluated in patients with acromegaly and it was seen that these measurements increased in acromegaly patients compared to the control group and decreased to almost normal levels following treatment.

The impact of GH and IGF-1 on the heart have been investigated in animal models and human myocardial tissue. However, the studies have mainly been conducted on animals, and information about the effects on the human myocardium is limited. The myocardium and vessels express increased amount of the GH and IGF-1receptors. The effects of GH on the myocardium are largely regulated through IGF-1 [18–20].In adult rat cardiomyocyte cultures treated with long-term IGF-1, sarcomere and myofibril

Table 6
Comparisons of current ECG parameters of acromegaly patients and the control group.

Parameters	Acromegaly Group (Mean ± SD) (n:62)		Control Group (Mean ± SD) (n:81)		*p*
Age	53.1	11.9	51.1	11.5	0.311
Female gender, n (%)	35 (56)		53 (65)		0.274
Heart rate	73.16	12.90	73.86	10.95	0.7312
QT interval, ms	374.50	27.15	366.32	25.06	0.0673
QTc interval, ms	405.18	31.61	391.91	20.43	**0.0049**
QRS time, ms	89.73	10.66	90.21	9.69	0.7801
Tp-e, ms	73.06	9.72	70.19	11.60	0.1091
Tp-e/QT	0.20	0.03	0.19	0.03	0.5333
Tp-e/QTc	0.18	0.03	0.18	0.03	0.8002

Table 7
Comparisons of current ECG parameters in acromegaly patients according to presence of comorbidities (DM, HT, CAD).

Parameters	At least 1 comorbity (Mean ± SD) (n:38)		No comorbity (Mean ± SD) (n:24)		*p*
Heart rate	81.54	12.54	81.46	17.28	0.9831
QT interval, ms	371.52	28.90	368.58	29.29	0.7031
QTc interval, ms	407.74	19.94	403.16	23.05	0.4165
QRS time, ms	90.22	8.98	92.39	10.95	0.4026
Tp-e, ms	79.48	6.73	76.05	8.63	0.0897
Tp-e/QT	0.22	0.02	0.21	0.02	0.1689
Tp-e/QTc	0.20	0.02	0.19	0.02	0.2366

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary artery disease.

expression has been shown to increase, whereas α-actin expressiondecreases [21]. There has been reported to be an increase in the expression of skeletal muscle α-actin as a result of treatment with GH or IGF-1 in hypophysectomized rats, but no increase in cardiac muscle α-actin expression and this does not cause a change in myosin heavy chains [22]. Another study showed a 35 % increase in left ventricular volume in rats treated with the GH/IGF-1 combination [23]. Both animal and human studies have reported that IGF-1 results in a positive inotropic effect by causing an increase in intracellular calcium concentrations [24,25].

Insulin-like growth factors (IGF) exihibit their growth-stimulating effects through specific membrane receptors located on various cells. Toyozaki et al. reported that adult human cardiac myocytes had IGF-1 receptors which were associated with the development of myocyte hypertrophy in hypertrophic cardiomyopathy [26]. Cardiac contractility has been shown to increase, cardiomyocyte growth is stimulated, and systemic vascular resistance decreases with short-term observationalincreases in GH and IGF-1 [27]. It has also been reported that IGF-1 acutely increases calcium influx and raises peak calcium levels in the cardiomyocytes [28]. IGF-1 has been shown to stimulate the expression of muscle-specific genes and synthesis of the contractile proteins, myosin heavy chain and actin in rat cardiomyocytes.GH stimulates hypertrophy of cardiomyocytes independently of IGF-1 [29]. A number of studies have found that decreased left ventricular (LV) mass and cardiac outputwere present in GH-deficient adults [20,30].

Multiple concurrent and probably independent disease processes, such as cardiac hypertrophy, heart failure, hypertension, obstructive sleep apnea, and arrhythmias, have a cumulative effect on the high cardiovascular morbidity in patients with acromegaly [31].Ventricular arrhythmias may play a substantial role in sudden cardiac deaths that may occur in patients with acromegaly [32,33]. Cardiovascular complications can increase the likelihood of hospitalization by 3 times and cause a significant increase in average annual healthcare expenditure [34].

The presence of any cardiovascular disease at the time of diagnosis in patients with acromegaly contributes significantly to the higher risk of death, even increasing the mortality rate to 100 % within 15 years [35]. In acromegalicpatients whose GH and IGF-1 levels are under control, the severity of cardiovascular diseasemay reduce to a level similar to that the general population [7]. However, when GH and IGF-1 cannot be controlled, deterioration in the cardiac systolic functions and even heart failure may occur, resulting in a shortened lifespan [30]. Reducing IGF-1 to normal levels with treatment may contribute to the improvement of cardiovascular homeostasis by improving cardiac autonomic nervous system modulation [36].Therefore, it is very important to know the predictors of arrhythmia in these patients. The current study results showed that treatment of acromegaly patients improved arrhythmia parameters almost to a level similar to that of the normal population.

An autopsy study demostrated the presence ofa significant cardiac fibrosis in patients with acromegaly and that IGF-1 disturbs calcium channels in the myocardial tissue [8]. Interstitial fibrosis may disturb the process of pulse propagation[31]. According to previous studies, up to 40 % of acromegaly patients have arrhythmia, especially during exercise [37]. Arrhythmias that may lead to reccurent syncope and sudden cardiac death in patients with acromegaly are ectopic beat, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, sick sinus syndrome, ventricular tachycardia and bundle branch block [33]. Hayward RP et al. stated that premature ventricular beats and complete ventricular arrhythmia are more prevalent in acromegaly patients compared to the general population [38]. According toanother study of 32 acromegaly patients, 48 % of patients had complex ventricular arrhythmias [39]. Lombardi et al. reported that 16.6 % of acromegaly patients had supraventricular premature beats while 35 % of them had ventricular premature contractions.Moreover, it has also been reported that cardiac autonomic functions, sympathovagal balance

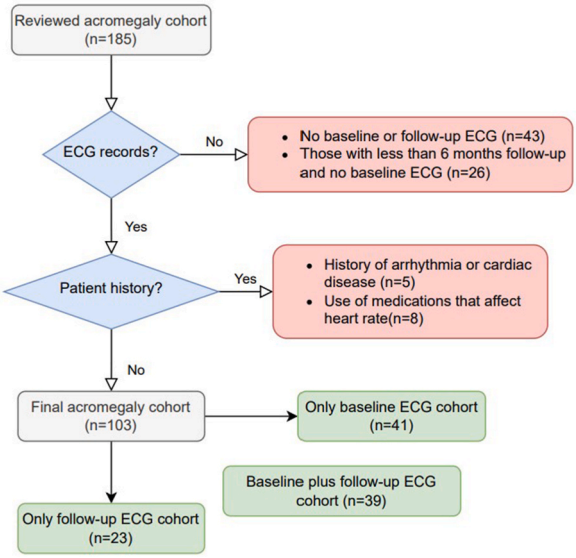

Fig. 1.

evaluated by heart rate variability, and ventricular premature beat frequency decrease with lanreaotide treatment [13]. A recentstudy demonstrated that 42 % of acromegaly patients had arrhythmias and heart conduction abnormalities and that cardiac MRI was the best method for detection of structural and morphological changes in the heart [40]. According to a study conducted in 47 acromegaly patients, an increase in mean heart rate (HeR) and HeR variability has been detected, but no significant clinical arrhythmia was observedin 24-h Holter monitoring [41]. Left ventricular hypertrophy and fibrosis might be responsible for the development of ventricular arrhythmia [9]. Colao et al. reported that valve diseases were more prevalant in with acromegalicpatients and did not improve with treatment [42].In contrast, according to Warszawski et al. no persistent arrhythmias were observed at diagnosis and 1 year after treatment with somatostatin analogs (SSAs) [43].

QT dispersion (dQT) is a measure of the ventricular repolarization heterogeneity obtained on ECG. dQT is an electrophysiological factor that has been found to be related to a predisposition to ventricular arrhythmia and sudden cardiac death [44]. According to recent studies, prolongation in QT interval, QT dispersionor the late potentials frequency increasewere suggested to raise the risk of acromegaly related arrhythmia [11,12]. Recently, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio have begun to be used in the evaluation of cardiac repolarization, in addition to the evaluation of QT. The Tp-e interval and Tp-e/QT ratio are the most important parameters showing the increase in the dispersion of ventricular repolarization, and are superior to QTc and some dispersions in predicting arrhythmia [16,45]. Two recent studies found increased Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in acromegaly patients [17,46]. In the current study, these parameters were found to be increased in acromegaly patients which is consistent with the previous findings. Evaluations were also made in the current study of how these parameters change with treatment, and it was seen that the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were decreased in acromegaly patients on treatment.To the best of our knowledge, this study is the first to have reported a decrease in new ventricular arrhythmia parameters following treatment in patients with acromegaly.

There were some limitations to this study. Although 103 acromegaly patients were included in the study, only 39 patients had both baseline and current ECGs. The retrospective design of the study was another limitation of the study.

In conclusion, ventricular arrhythmia parameters increase in acromegaly patients and improve with treatment. The decrease in ventricular arrhythmia parameters is similar in active and remission patients, which can partly be explained by the significant decrease in IGF-1 levels compared to at the time of diagnosis, even in patients with active disease. As a readly approachable cardiac diagnostic tool, ventricular arrhythmia parameters may be potentially useful in increasing awareness of potential cardiac damage in patients with acromegaly to be able to better evaluate and manage complications in these patients.

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CRediT authorship contribution statement

Zeynep Zehra Tekin: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Hilal Erken Pamukcu:** Validation, Investigation, Formal analysis. **Serdar Kayihan:** Investigation. **Bekir Ucan:** Resources. **Hayri Bostan:** Resources. **Umran Gul:** Data curation. **Hakan Duger:** Resources. **Sema Hepsen:** Methodology, Conceptualization. **Erman Cakal:**

Validation, Supervision, Project administration. **Seyit Ibrahim Akdag:** Supervision. **Muhammed Kizilgul:** Writing – review & editing, Validation, Resources, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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