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Electrocardiographic Changes During and After Alcohol Withdrawal

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ABSTRACT

Background: Our study aimed to examine the possible risk of ventricular arrhythmia and sudden cardiac death by calculating the electrocardiographic changes and indicators of ventricular repolarization during and after alcohol withdrawal.

Methods: One hundred participants who were identified with alcohol withdrawal and who met the inclusion criteria were included in the study. Data were collected between July 2020 and August 2020. The distance interval between Q and T waves, corrected distance interval between Q and T waves, T peak/distance interval between Q and T waves, and T peak/corrected distance interval between Q and T waves interval ratios ratios were measured in 12-lead electrocardiographic measurements during the withdrawal period and after withdrawal symptoms subsided in patients with a Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised score >7 and a Framingham heart risk score <10%.

Results: There was a significant difference between the patient's heart rate, distance interval between Q and T waves, corrected distance interval between Q and T waves interval, and T peak/distance interval between Q and T waves values during withdrawal (input) and after alcohol withdrawal (output) ($P < .05$). The mean corrected distance interval between Q and T waves interval input value (433.63 ± 17.79) is significantly different and higher than the output value of the mean corrected distance interval between Q and T waves (420.67 ± 13.78) ($P < .05$). Similarly, the mean T peak input value (81.36 ± 5.90) is significantly different and higher than the mean T peak output value (79.94 ± 5.39) ($P < .05$) and the mean T peak/input value of the distance interval between Q and T waves (0.222 ± 0.00) than the mean T peak / output value of the distance interval between Q and T waves (0.214 ± 0.00) ($P < .001$).

Conclusion: These consequences suggest the risk for an accelerated hazard of ventricular arrhythmias in participants with alcohol withdrawal. Significantly, considering the improvement of the electrocardiographic changes of the patients after terminating alcohol intake, a possible cardiac arrhythmia may be more common during this period. Close monitoring of electrocardiograms and timely withdrawal treatment can prevent life-threatening arrhythmias in alcohol withdrawal patients.

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INTRODUCTION

Alcohol use disorder (AUD) is a crucial and increasing health problem worldwide. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 data, the 12-month prevalence of AUD in the United States is 4.6% for people 12-17 years old and 8.5% for those aged 18 years and older.[1] According to general disease categories, alcohol consumption is the seventh leading risk factor for death and disability-adjusted life years worldwide.[2] The connection between alcohol consumption and the outcomes of cardiovascular disease is complicated, with various aspects of consumption taking part in numerous outcomes.[3,4] Excessive alcohol consumption can increase triglycerides in the blood, leading to obesity and diabetes. Therefore, alcohol users are more likely to have ischemic heart disease and myocardial infarction.[5] However, echocardiographic studies have shown that a presymptomatic state of alcoholic myocardiopathy with cardiac hypertrophy and systolic and diastolic left ventricular heart dysfunction is common in alcohol users without symptoms of cardiovascular disease.[6]

When an individual with AUD suddenly stops consuming alcohol, complications that can result in mild, moderate, or severe alcohol withdrawal syndrome, including the most severe form, delirium tremens, may occur.[7,8] In individuals with AUD, withdrawal-associated signs and symptoms usually develop 6-24 hours after the last alcohol

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consumption. If left untreated, death from respiratory and cardiovascular collapse may occur.[7,9] Abrupt suppression of alcohol use masks compensative activity of the nervous system and elevation of various neurotransmitters, such as gamma-aminobutyric acid, norepinephrine, and 5-hydroxytryptamine.[10,11] The consequences of those neurotransmitters are not restricted to the brain; on the contrary, they affect the cardiovascular system, particularly the heart.[12] Throughout alcohol withdrawal, myocardial ischemia might occur due to the lack of small intramyocardial vessels to dilate in response to enhanced myocardial oxygen demand because of sympathetic-adrenergic activation. Additionally, changes in autonomic function and magnesium deficiency in alcohol users may affect cardiac vascular tone and induce transient myocardial ischemia by vasoconstriction of normal cardiac vessels.[13,14]

Various measurements on the electrocardiogram are outlined to estimate the risk of ventricular arrhythmias. The distance interval between Q and T waves (QT) interval, corrected QT interval (QTc), T peak – Tend (TPe), and TPe/QTc ratios are by far the most popular repolarization parameters owing to their prognostic role in ventricular arrhythmias.[15] Otero-Anton et al[16] reported a long QTc interval in 46.8% of patients with an alcohol withdrawal syndrome. In another study, long QTc was detected in 31 out of 49 patients during alcohol withdrawal.[17] Long QT syndrome could be a cardiac repolarization disorder and it is associated with an enhanced risk of torsade de pointes.[18,19]

Early recognition of cardiac findings associated with alcohol withdrawal syndrome and prompt response to potential adverse cardiac outcomes is crucial. The present study aimed to record the changes in QT, QTc, TPe, TPe/QT, TPe/QTc, and pulse values in electrocardiogram (ECG) during alcohol withdrawal in patients with AUD who had no clinical heart disease. It also aimed to investigate whether these symptoms persist after withdrawal.

MATERIAL AND METHODS

Participants and Procedure

This is a prospective follow-up study. Its data were collected between July 2020 and August 2020. It included patients who had received inpatient alcohol withdrawal treatment in the alcohol and drug treatment clinic of our hospital, met the DSM-5 criteria for AUD, had been using alcohol at least 3-4 days a week for the last week, had withdrawal symptoms that required treatment (Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar>7), had a Framingham score less than 10%, did not have a history of cardiac disease, agreed to participate in the study and gave written consent, a total of 100 were in the study. A total of 117 patients who met the inclusion criteria for withdrawal treatment were included in the study. However, 17 patients who wanted to leave the treatment earlier and developed additional medical symptoms (such as liver enzyme elevation and respiratory and urinary infections) were excluded from the study. During withdrawal therapy, clonidine was not given to patients. The dose of benzodiazepine given for withdrawal treatment was in the range of 60-80 mg/day. In addition to benzodiazepine treatment, 2000 cc of balanced solution, vitamin B and folic acid supplementation were given to the patients during the treatment. We enrolled the patients who were able to be hospitalized within the first 24 hours of the withdrawal symptoms appearance. Their length of stay for the withdrawal treatment lasted around 7-10 days. Electrocardiographic values of the patients with zero CIWA-Ar score were taken and analyzed. These ECGs were evaluated as output ECG (post-absence). The output ECGs of the patients were taken between 7 and 10 days after their hospitalization. Additionally, substance metabolites (amphetamine, bonsai, barbiturate, benzodiazepine, cocaine, morphine/opiate, ecstasy, methadone, tetrahydrocannabiol, and methamphetamine) in the urine were examined. If the patients had additional metabolites in their urine, they were excluded from the study sample. Then, in the anamnesis period, if the patients consumed substances than alcohol, they were also excluded, including the ones who used psychiatric substances within the last 3 months. Individuals with psychotic disorder, mental weakness, and neurocognitive disorders were among the cases not included in the sample of the study. Patients with anxiety and depressive disorders were exceptions, as AUD mostly occurs with these conditions. Informed consent forms were obtained from all patients. Ethical committee approval was obtained from the Ethics Committee of Erenköy Mental Health and Diseases Training and Research Hospital (Approval number: 23, Date: June 22, 2020).

Patients with the following possible risk factors known to cause QT prolongation were not included in the study: (1) comorbid cardiac disease (congestive heart failure, left ventricular dysfunction, myocarditis, hypertrophy, ventricular arrhythmia, sinoatrial or atrioventricular block, bradycardia, mitral valve prolapse); (2) abnormal laboratory findings that may affect the cardiovascular system (electrolyte, cholesterol, LDL, VLDL, HDL, triglyceride, fasting blood glucose values outside the normal

MAIN POINTS

- An elevated risk of ventricular arrhythmias can manifest in participants who cease alcohol consumption.
- The threat of ventricular arrhythmia and sudden cardiac death should not be ignored particularly throughout the withdrawal period.
- Electrocardiographic parameters are markers of ventricular repolarization and they may be higher during alcohol withdrawal.

limits); (3) another medical condition that may affect the cardiovascular system; (4) use of any pharmacological agent other than antipsychotics and antidepressants; (5) systemic hepatic or renal disease; (6) hypothyroidism; (7) conditions such as acute ischemic stroke, Parkinson's disease, or another central nervous system disorder.[20-21]

Electrocardiograms were taken during the alcohol withdrawal period and control ECGs were taken at the end of the withdrawal period after clinical stabilization. A 12-lead, 25 mm/min rate, and 10 mm/mV standard ECG was used. The QT, QTc, TPe, TPe/QT, TPe/QTc, and heart rate values were compared during withdrawal (input) and at the end of withdrawal (output). The word "input" was used for values during abstinence, and the word "output" was used for values after abstinence.

Data Collection Tools

Sociodemographic Data Form: This form includes the following sociodemographic variables: age, sex, marital status, economic level, employment status, substance use history, and presence of other medical diseases. The authors of the present study prepared this form.

Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised: Sullivan et al[22] developed this scale. It measures the severity of alcohol withdrawal syndrome and the degree of physical dependence. This scale evaluates withdrawal symptoms in 10 different areas that are nausea and vomiting, tremor, sweating, anxiety, agitation, tactile, auditory, and visual disturbances, headache, the feeling of fullness, disorientation, and fogging of consciousness. The tenth item is evaluated over 67 points, between 0 and 4 points, while the others are scored between 0 and 7 points. Kalyoncu et al[23] translated it into Turkish, and its Cronbach's alpha internal consistency constant was 0.80.

Physiological Measures

Framingham Heart Risk Score: This measures the 10-year risk of cardiovascular diseases such as myocardial infarction/coronary death based on age, sex, smoking status, blood pressure, and total and HDL cholesterol values. The Framingham classification system is the most used system in cardiological risk calculation. A 10-year risk is <10% low risk, 10-20% is medium risk, and >20% is high risk.[24] The study used the risk calculator on the Turkish Society of Cardiology website. The parameters contained in the risk calculator are one the blood tests routinely requested upon admission to the ward.

Electrocardiographic Evaluation: Standard 12-lead ECGs of the patients at rest were evaluated in the study (25 mm/s, 10 mm/mV). The QT interval was the distance from the start of the Q wave to the peak of the T wave (where it reached the T-P line). Measurements were not made in leads wherever the T wave peak was unidentifiable. The heart rate-QTc was according to the Bazett formula [QT(ms)/RR(s)1/2]. P wave length, RR interval, PR interval, QRS length, QT interval, and TPe interval were measured manually. From these measurements, the TPe/QT ratio and TPe/QTc ratio were calculated. The TPe interval was measured from the peak to the end of the T wave. The end of the T wave was outlined as the intersection of the tangent to the declination of the T wave and the isoelectric line.[25]

Statistical Analyses

All data were analyzed using the International Business Machines Statistical Package for the Social Sciences Statistics for Windows, version 26.0 (IBM SPSS Corp.; Armonk, NY, USA). First, descriptive statistics were calculated for the demographic and clinical characteristics of the total sample. Descriptive statistics were provided in numbers and percentages for categorical variables, means, and SDs. Kolmogorov–Smirnov test checked the conformity of the data to the normal distribution. Descriptive statistics of categorical variables were provided as n (%). Missing data were omitted on an analysis-by-analysis basis and the valid percentages were reported. Numerical variables were compared between dependent groups using paired *t*-test. A *P*-value of <.05 was the threshold for statistical significance in all tests.

RESULTS

Sociodemographic Findings

The mean age of the study group was 46.46 ± 11.05. Of the group, 86% (n = 86) were male and 14% (n = 14) were female. Regarding educational status, approximately half of the participants were 53% (n = 53) primary school graduates, 23% (n = 23) were high school graduates and 24% (n = 24) were university graduates. While 61% (n = 61) were single, 39% (n = 39) were married, 37% (n = 37) were employed, 50% were unemployed (n = 50), and 13% (n = 13) were retired. Nearly all participants (95%, n = 95) were smokers, 17% (n = 17) had a history of substance use, 57% (n = 57) had a psychiatric disorder, 46% (n = 46) had a substance use history in the family, and 5% (n = 5) had a psychiatric disorder in the family. The mean duration of alcohol use of the participants was 21.97 ± 12.19 years and they used 19.50 ± 10.59 units of standard alcohol regularly on average (Table 1).

Alcohol Withdrawal Input–Output Electrocardiographic Parameter (Pulse, Distance Interval between Q and T Waves, Corrected Distance Interval Between Q and T Waves, T peak/Distance Interval Between Q and T Waves, and T peak/corrected Distance Interval Between Q and T Waves Ratios) Changes

There is a statistically significant difference between the mean pulse input value and the mean pulse output value ($P < .001$). The mean pulse input value (85.07 ± 11.55)

Table 1. Sociodemographic Characteristics of the Sample Group

		Mean ± SD	
Age		46.46 ± 11.05	
Years of alcohol use		21.97 ± 12.19	
Standard alcohol unit		19.50 ± 10.59	
		n	(%)
Sex	Male	86	86
	Female	14	14
Educational status	Primary school	53	53
	High school	23	23
	University	24	24
Marital status	Singled	62	62
	Married	38	38
Lives with	None	25	25
	Pair	75	75
Employment status	Working	37	37
	None	50	50
	Retired	13	13
Smoking	No	5	5
	Yes	95	95
History of substance use	No	83	83
	Yes	17	17
Substance use history in the family	No	54	54
	Yes	46	46
Psychiatric disorders	No	43	43
	Yes	57	57
Psychiatric disorders in the family	No	95	95
	Yes	5	5

Table 2. Alcohol Withdrawal Input-Output ECG Parameters (Pulse, QT, QTc, TPe/QT, TPe/QTc) Changes

	n	Mean ± SD	*t*	*P*
Pulse—input	100	85.07 ± 11.55	7.08	**0.00****
Pulse—output	100	76.61 ± 8.71		
QT—input	100	366.37 ± 22.29	−3.00	**0.00***
QT—output	100	373.98 ± 19.99		
QTc—input	100	433.63 ± 17.79	11.57	**0.00***
QTc—output	100	420.67 ± 13.78		
TPe—input	100	81.36 ± 5.9	2.11	**0.03***
TPe—output	100	79.94 ± 5.39		
TPe/QT—input	100	0.22 ± 0.00	11.12	**0.00****
TPe/QT—Output	100	0.21 ± 0.00		
TPe/QTc—input	100	0.18 ± 0.01	−1.22	0.22
TPe/QTc—output	100	0.19 ± 0.01		

ECG, electrocardiogram; QT, distance interval between Q and T waves; QTc, corrected QT interval; TPe/QT, T peak/QT; TPe/QTc, T peak/corrected QT interval.
*P < .05; **P < .001.

is significantly different and greater than the mean pulse output value (76.61 ± 8.71) (Table 2).

There is a statistically significant difference between the mean QT input value and the mean QT output value (P < .05). The mean QT output value (373.98 ± 19.99) is significantly different and greater than the mean QT input value (366.37 ± 22.29) (Table 2).

There is a statistically significant difference between the mean QTc input value and the mean QTc output value (P < .05). The mean QTc input value (433.63 ± 17.79) is significantly different and greater than the mean QTc output value (420.67 ± 13.78) (Table 2).

There is a statistically significant difference between the mean TPe input value and the mean TPe output value (P < .05). The mean TPe input value (81.36 ± 5.90) is significantly different and larger than the mean TPe output value (79.94 ± 5.39) (Table 2).

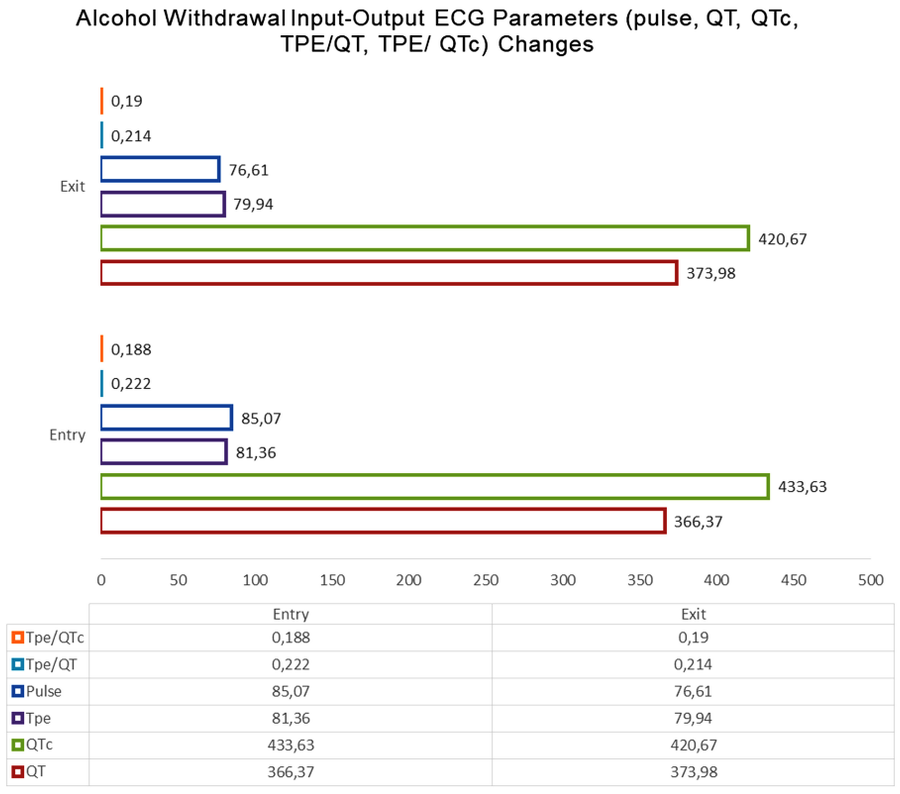
There is a statistically significant difference between the mean TPe/QT input value and the mean TPe/QT output value (P < .001). The mean TPe/QT input value (0.22 ± 0.00) is significantly different and greater than the mean TPe/QT output value (0.21 ± 0.00) (Table 2).

There is no statistically significant difference between the mean TPe/QTc input value and the mean TPe/QTc output value (P < .05) (Table 2).

The distribution of electrocardiographic parameters (pulse, distance interval between Q and T waves, corrected QT interval, T peak/QT, and T peak/corrected QT interval ratios) during and after alcohol withdrawal is shown in the figure (Figure 1).

DISCUSSION

According to the World Health Organization (WHO), alcohol use causes approximately 2.5 million deaths annually and is a significant risk factor for loss of life worldwide among men aged 15-59 years.[26] Heavy alcohol consumption may increase the risk of sudden cardiac death, with fatal arrhythmia as the most likely mechanism. Subclinical heart muscle damage from persistent heavy use can be instrumental in producing patchy delays in conduction. The hyperadrenergic nation of ingesting and withdrawal may further cause electrolyte abnormalities, impaired vagal heart rate control, repolarization abnormalities with prolonged QT intervals and aggravation of myocardial ischemia.[27] High serum alcohol levels can interfere with sodium, potassium, and calcium ion channels in the heart.[28] Worse still, heavy alcohol consumption can cause arrhythmias by imbalances in the autonomic regulation of heart rhythm.[29] The Framingham heart score, which determines the 10-year cardiac death score, was used in our participants. Similar to our study, in patients diagnosed



	Entry	Exit
Tpe/QTc	0,188	0,19
Tpe/QT	0,222	0,214
Pulse	85,07	76,61
Tpe	81,36	79,94
QTc	433,63	420,67
QT	366,37	373,98

Figure 1. Alcohol withdrawal input-output electrocardiographic parameter (pulse, QT, QTc, TPe/QT, and TPe/QTc) changes. QT, distance interval between Q and T waves; QTc, corrected QT interval; TPe/QT, T peak/QT; TPe/QTc, T peak/corrected QT interval.

with metabolic syndrome, significant associations were present between the components of metabolic syndrome and the different Framingham Hearth Risk Score (FHRS) categorizations of patients with metabolic syndrome. High systolic blood pressure and fasting glucose were associated with a significantly increased risk of cardiovascular diseases compared with other parameters.[30] In our study, when examining arrhythmias, one of the causes of cardiac death, in alcohol withdrawal patients with an FHRS score below 10, electrocardiographic parameters indicating pulse rate and ventricular repolarization were higher during alcohol withdrawal.

Sudden cessation of alcohol consumption can lead to beta-adrenergic stimulation and an increase in catecholamine levels generate arrhythmia. In other words, participants can be liable to numerous ranges of arrhythmias in the course of alcohol withdrawal.[31] The study stated that alcohol-triggered coronary vasospasm could persist for as much as 9 hours after ingestion, although the plasma concentration of alcohol returns to normal. Some studies suggested that low prostaglandin concentrations after alcohol intake could be accountable for this effect.[32] Likewise, in alcohol withdrawal, chronic alcohol intake suggests that coronary spasm persists even if the alcohol level is low. In a study, arrhythmias accompanied hospitalized patients with alcohol withdrawal. The most common atrial arrhythmias and acute heart failure manifested more frequently. Arrhythmias in alcohol withdrawal were associated with higher in-hospital mortality and poorer outcomes.[33]

In a study conducted on alcohol withdrawal and patients with acute coronary syndrome, the QTc rates of the alcohol withdrawal group were higher.[34] In a study with 62 patients who presented with alcohol withdrawal, similar to our study, the QTc rates were higher in ECGs taken during withdrawal compared to after withdrawal.[16] In a study evaluating the retrospective ECGs of patients with DT and withdrawal-related convulsions, QTc prolongation was present in 31 patients and tachyarrhythmias (2 torsade de pointes, 1 continuous ventricular tachycardia, 2 supraventricular tachycardias, and 1 atrial fibrillation) were present in 5 patients.[35] In our study, pulse rate, QTc, TPe, and TPe/QTc ratios during withdrawal were higher than after withdrawal. The exact mechanisms of QT interval prolongation are not well known. One of the hypotheses is that autonomic hyperexcitability leads to altered ventricular repolarization and QT interval prolongation. In some studies, the mechanism of QT prolongation has been linked to acute alcohol withdrawal, independent of electrolyte abnormalities, use of QT-prolonging drugs, and cirrhosis.[16,17] A case of alcohol withdrawal with cirrhosis developed torsades de pointes, an arrhythmia that causes QT prolongation. Despite correction of electrolyte abnormalities,

withdrawal from alcohol, avoidance of QT-prolonging drugs, and exclusion of cardiac ischemia, there was still a sizable and chronic prolongation of the QT interval. Ultimately, this was attributed to cirrhotic cardiomyopathy.[35] Although there were no additional chronic diseases in our study group, QT rates remained higher in the post-withdrawal period.

Alcohol consumption can cause electrocardiographic changes and arrhythmias, at least in part due to the effects of alcohol on cardiac ionic currents. In the human model, alcohol has a predominant role in K ion channels, the key repolarizing current in human ventricles, and prolongs AP duration depending on the dose. This effect may contribute to the clinically observed proarrhythmic effects of alcohol in susceptible individuals.[36] In a study using epinephrine infusion with a sympathomimetic effect, there was a significant increase in heart rate, systolic blood pressure, QRS, QTc, TPe, TPe/QT index, and QTc duration.[37] Autonomic hyperactivity also occurs in alcohol withdrawal, which triggers arrhythmia through a similar mechanism. In our working group, the TPe interval, an electrocardiographic arrhythmogenesis index, and TPe/QT ratios were higher in the withdrawal period. The increased TPe interval and TPe/QT ratio are associated with malignant ventricular arrhythmias and because this ratio increases during alcohol withdrawal suggests that it should be noted.[38]

Our study has several limitations. We did not exclude patients with depressive disorders and anxiety disorders who often have an accompanying AUD. Our study included patients who were smokers and had a history of substance use. However, it did not include patients who were positive for substances in the urine substance screening. In the anamnesis, we excluded patients who had taken substances other than alcohol in the last 6 months. Another limitation of our study was that the sample group mostly included men.

Although the study included those with a heart risk score below 10% and those who did not meet the criteria that might cause QT prolongation, electrocardiographic parameters that are markers of pulse rate and ventricular repolarization were higher during alcohol withdrawal. There may be an increased risk of ventricular arrhythmia during alcohol withdrawal, even in the patient group with a low heart risk score. The treatment after withdrawal decreased these values. Hence, the risk of ventricular arrhythmia and sudden cardiac death should not be ignored, especially during the withdrawal.

Ethics Committee Approval: Ethical committee approval was from the Ethics Committee of Erenköy Mental Health and Diseases Training and Research Hospital (Approval Number: 23, Date: June 22, 2020).

Informed Consent: Written informed consent was received from all participants of this study.

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