

# Aging and Pseudoexfoliation Syndrome; Is Sudden Cardiac Death Common Point of These?

Huseyin Oren<sup>1</sup>, Ayhan Cosgun<sup>2</sup>,

<sup>1</sup>Department of Cardiology, Cardiology Specialist, Ankara City Hospital, Ankara, Turkey.

<sup>2</sup>Department of Cardiology, Cardiology Specialist, Sincan State Hospital, Ankara, Turkey.

## Abstract:-

### ➤ Background:

Pseudoexfoliative Syndrome (PEX) and Sudden Cardiac Death (SCD) increase with age. Tp-e (T peak-end interval) and cTp-e (Corrected Tp-e) intervals are recently accepted as predictors of SCD.

### ➤ Objectives:

Our study aimed to investigate the Tp-e, cTp-e intervals in both patients with PEX and non-PEX.

### ➤ Materials and Methods:

The study group consisted of forty-two patients who were admitted to the outpatient clinic of ophthalmology between December-2018 and May-2019 and diagnosed as PEX in the ophthalmologic examination. Forty-three patients with non-PEX, systemic examinations, and routine blood tests were normal, included in the study. The study and control group were included in the treadmill exercise test (TET) according to Bruce Protocol.

### ➤ Results:

In the study group, there was a statistically significant difference between the basal cTp-e interval value and the third-minute recovery cTp-e interval value, whereas in the control group there was no statistically significant difference between the basal cTp-e interval value and the third-minute recovery cTp-e value (in the study group, basal cTp-e =  $85.09 \pm 5.14$  ms vs third-minute recovery cTp-e =  $87.37 \pm 3.81$  ms,  $t = 3.07$  and  $p < 0.01$ , in the control group, baseline cTp-e =  $63.65 \pm 5.07$  ms vs third-minute recovery cTp-e =  $63.59 \pm 2.77$ ,  $t = 0.087$  and  $p = 0.93$ ). There were moderate positive correlations between HRR-I (Heart Rate Recovery Index) values and cTp-e R-I (Corrected Tp-e Recovery Index) values in each recovery stage of the effort test in both the study and control group.

### ➤ Conclusion:

These findings suggest that the risk of ventricular arrhythmias is higher in patients with PEX than in patients with non-PEX and that autonomic function in PEX patients is more impaired than non-PEX patients.

**Keywords:-** Exfoliation Syndrome, Risk, Exercise Test, Sudden Cardiac Death.

## ❖ ABBREVIATION

- BHR; Basal Heart Rate
- BMI; Body Mass Index
- cTp-e; Corrected T peak-end interval
- cTp-e R-I; Corrected Tp-e interval Recovery Index
- COPD; Chronic Obstructive Pulmonary Disease
- DBP; Diastolic Blood Pressure
- HR; Heart Rate
- HRR; Heart Rate Recovery
- HRR-I; Heart Rate Recovery Index
- LV; Left Ventricle
- PEX; Pseudoexfoliative Syndrome
- PHR; Peak Heart Rate
- SBP; Systolic Blood Pressure
- SCD; Sudden Cardiac Death
- TET; Treadmill Exercise Test
- Tp-e; T peak-end interval

## I. INTRODUCTION

PEX is characterized by the accumulation of fibrillar extracellular material in the eye and some extraocular organs. PEX can be easily identified by biomicroscopic examination with the presence of anterior segment changes characterized by the pupillary border and white deposits on the anterior aspect of the lens [1]. Extraocular accumulation is associated with cardiovascular complications. PEX is related to myocardial infarction, aortic aneurysm, congestive heart failure, and arrhythmias [2].

As known during the exercise, sympathetic activity increases, and parasympathetic activity decreases. Therefore, the majority of arrhythmias and sudden cardiac deaths can occur immediately after severe exertion [3]. PEX is directly proportional to age [4]. SCD occurs at a higher rate than the subgroup over the age of 35 years, and this occurs after severe exercises [5]. It was also found that the chance of arrhythmia increased in PEX without coronary artery disease [6].

Recently, the T peak-end interval (Tp-e interval) has been emphasized among the predictors of malignant ventricular arrhythmias. The time between the peak and the end of the T wave (Tp-e interval) is accepted as an index of transmural dispersion of ventricular repolarization [7]. It is emphasized that the Tp-e interval is prolonged in many diseases, and it is related to malignant ventricular arrhythmias and SCD [8-10]. So far, the relationship between

PEX and SCD predictors, Tp-e and cTp-e intervals, were not investigated. This prospective study is the first in the literature investigating the relationship between the risk of SCD and PEX. Our study aimed to compare how Tp-e, cTp-e intervals, HRR-I, cTp-eR-I values were affected by stress testing in PEX patients and to compare these predictors in the exercise test with a similar control group in terms of age and sex.

## II. MATERIALS AND METHODS

### ➤ *Study Design:*

The present study was prospective, cross-sectional, and observational. Patients were diagnosed with PEX by biomicroscopy in the ophthalmologic examination, by the presence of white-gray extracellular fibrillary material on the pupil side or in the anterior capsule. Patients who were admitted to the cardiology outpatient clinic and who were diagnosed as non-PEX in the ophthalmology outpatient clinic and eye examination were included as the control group.

### ➤ *Study Population:*

Forty-two patients (25 males and 17 females) diagnosed with PEX by biomicroscopy during the ophthalmological examination between December-2018 and May-2019 were included in the study. This group was named as the study group. The mean age of the study group was  $65.45 \pm 9.62$  years. The control group, age, and sex-matched with the study group, consisted of forty-three (26 male and 17 female) patients who were diagnosed as non-PEX with biomicroscopy in the ophthalmology outpatients clinic. The mean age of the control group was  $66.38 \pm 8.72$  years. Exclusion criteria were; the patients with previous coronary artery disease and those receiving treatment for any reason, with any systemic disease such as hypertension and diabetes mellitus, impaired liver, renal and thyroid function test, those with electrolyte disturbance in routine blood examination, previously diagnosed with COPD and receiving bronchodilator therapy, having any systemic disease such as diabetes mellitus or hypertension, having impaired liver or kidney function test, having electrolyte defect in routine blood examination, having anemia or thyroid dysfunction, having a disease that may affect the heart, having tension arterial above 140/90 mm Hg, having coronary artery disease before, having a positive effort test which indicates significant coronary arterial disease, presence of a cardiac pacemaker, smoking, patients with a diagnosis of atrial fibrillation or having AF rhythm in superficial electrocardiograms and patients with orthopedic disorders who were unable to perform TET.

### ➤ *Methods:*

The study and control group, after the physical examination, routine blood test, and routine transthoracic echocardiograms and electrocardiograms were performed, the TET was performed according to Bruce Protocol [11]. The patients, having a Body Mass Index (BMI) over 30 kg/m<sup>2</sup>, were excluded from the study. The recordings of TET were taken at a speed of 25 mm / sec and an

amplitude of 10 mm / mV. Records were taken at the beginning and peak exercise level, first, second, and third-recovery phases. Calculations were made by the same cardiologist using a magnifying glass and digital caliper. RR interval and Tp-e interval (T peak-end interval) values were calculated. The data obtained in millimeters were multiplied by 40 to get the values in milliseconds. The RR interval was taken as the time from the peak of an R wave to the peak point of the other R wave. This measurement was calculated between at least in three precordial leads, and at least three consecutive R waves for Tp-e interval in the V<sub>2-5</sub> left precordial leads. The T peak-end interval was calculated by including the T wave from the peak to baseline in the V<sub>2-5</sub> left precordial leads. Tp-e intervals were calculated by multiplying the obtained value in milliseconds by 40. If the U wave is present, the T wave end was defined as the nadir between the T wave and U wave. cTp-e intervals were calculated by using the Bazett's formula. Arithmetic averages of measurements were used for analysis.

HRR-I values were obtained by subtracting the first, second, and third-minute recovery HR values from the peak HR value. cTp-e R-I values were also obtained by subtracting first, second, and third-minute recovery cTp-e values from the peak cTp-e interval value.

### ➤ *Ethical approval:*

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Turkey Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. There is no Ethics Committee in our hospital. Written permission was obtained from hospital management. Before the study, written informed consent was obtained from all participants.

### ➤ *Statistical Analysis:*

SPSS software [Version X; IBM, Armonk, NY, USA] 20.0 was used for the collection and analysis of the data. Measurements were expressed as mean values with  $\pm$  standard deviation. Analyzes were performed using the t-test. To compare the values of the different two groups, T-Test Calculator for Independent Two Means and to compare the different values of the same group, T-Test Calculator for Depended Means was used. The Z test calculator was used to compare for two population proportions. For repeated measurements, one way ANOVA Calculator for Repeated Measure was used. For correlation, for two values of the same group, the Pearson Correlation Coefficient Calculator was used. For all tests  $p < 0.05$ , the differences are statistical significance.

### III. RESULTS

There was no statistically significant difference between socio-demographic properties and basal clinic findings of the study and control group (Table 1).

While there was no statistically significant difference between the study and control group in term of BHR, there were statistically significant differences between two groups in terms of first, second, and third-minute recovery heart rates (HR). Furthermore, in the control group, peak heart rate (PHR) was significantly higher than in the study group. And also, the study group had statistically significant higher the values of the basal, peak, first, second, and third-minute recovery Tp-e interval than the control group. Besides, There were statistically significant differences between the study and control group in terms of basal, peak, first, second, and third-minute recovery cTp-e interval values. That means, there was a statistically significant higher risk of SCD in the study group than the control group in every stage of the TET. In the study group, all HRR-I values and cTp-eR-I values were significantly lower than in the control group in every recovery stage of TET (Table 2).

There were statistically significant differences in both the study group and the control group in terms of HRs, Tp-e intervals, and cTp-e intervals (Table 3).

In the study group, while there was a statistically significant difference between basal HR and third-minute recovery HR, in the control group, there was no statistically significant difference between basal HR and third-minute HR. Furthermore, in the study group, while there was a statistically significant difference between basal cTp-e interval and third-minute recovery cTp-e interval, in the control group, this difference became meaningless in the third-minute recovery phase of TET between basal cTp-e interval and third-minute recovery cTp-e interval (Table 4).

There was a weak positive correlation between age and HR, both in the study and the control group. Furthermore, there was a moderate correlation between age and basal Tp-e, basal cTp-e intervals both in the study and the control group. There were moderate positive correlations between HRR-I values and cTp-eR-I values in each recovery stage of the effort test in both the study and control group (Figure 1-4, Table 5).

### IV. DISCUSSION

In our study, there were three interesting findings. The first of these findings was, while there was a statistically significant difference between basal HR and third-minute recovery HR of the study group, in the control group, there was no statistically significant difference between basal HR and third-minute recovery HR of the control group. The second of these findings was, Tp-e and cTp-e interval values of the study group were significantly higher than the control group every stage of TET. The third

of these findings was, while there was a statistically significant difference between basal cTp-e interval and the third-minute recovery cTp-e interval of the study group, in the control group, there was no statistically significant difference between basal cTp-e interval and third-minute recovery cTp-e interval of the control group. In the study group, the HRR-I and cTp-e R-I values were significantly lower than in the control group. Besides, There were moderate positive correlations between HRR-I and cTp-e R-I values in each recovery stage.

The results of our study showed that the vagal system is less working in PEX patients than the non-PEX. The delay in HRR is indirectly associated with the decreased vagal activity, and reduced vagal activity is also characterized by the increased risk of SCD [12].

PEX is an old age disease and is therefore closely associated with increased cardiovascular mortality. On the other hand, in PEX patients, myocardial infarction, aortic aneurysm, congestive heart failure, and malignant ventricular arrhythmias are frequently observed [2]. Also, arrhythmias may occur in PEX patients without structural heart disease [6].

Many researchers have investigated the relationship between PEX and cardiovascular events, focusing on the underlying mechanisms. The first of these was homocysteine. Higher levels of homocysteine were found in PEX patients than non-PEX patients [13,14]. In addition, vitamin B12, vitamin B6, and folic acid levels were also found to be decreased [15]. However, in one study, the association between PEX and coronary artery disease, hypertension, cerebrovascular events, diabetes mellitus, and arrhythmias was investigated, and it was suggested that only the prevalence of arrhythmia was high in PEX patients [16].

The underlying mechanisms of arrhythmias in PEX patients have been investigated, and the most commonly considered one was the decreased vagal activity [17]. Many indirect methods have been developed to investigate this. One of these is the carotid artery baroreceptor reflex. Compared with non-PEX patients, carotid artery baroreceptor reflex was found to be decreased in PEX patients [18]. Some investigators have also found reduced cardio-vagal regulation in PEX patients [19]. The majority of studies on decreased vagal autonomic activity have focused on heart rate recovery. Regardless of the underlying disease, a reduced heart rate recovery is always associated with increased mortality [20].

SCD usually occurs in patients with structural heart disease. And in particular, it occurs immediately after heavy exercises [21]. It is known that sympathetic activity increases with an exercise test; the vagal activity is at the recovery phase after the exercise test. It has been documented that an increased sympathetic nerve activity or a decreased vagal nerve activity immediately precedes the onset of atrial and ventricular arrhythmias as well as sudden cardiac death [22]. Furthermore, delayed HRR was

found that it was one of the indirect predictors of decreased vagal activity [23]. In our study, we found that there was a delayed HRR in PEX group patients compared to the control group.

Many non-invasive predictors for SCD have been investigated. The most commonly used are the repolarization predictors such as QT interval, QT dispersion, Tp-e interval, Tp-e / QT and Tp-e / QTc (Corrected QT interval), as well as the depolarization predictors such as QRS duration and QRS dispersion. Tp-e and cTp-e intervals have been accepted as predictors of the disorder of ventricular repolarization dispersion. Disruption of ventricular repolarization may lead to malignant ventricular arrhythmias in patients. Recently, Tp-e and cTp-e interval, which is some of the repolarisation predictors of SCD, are emphasized, and it is emphasized that any prolongation of Tp-e and cTp-e interval regardless of the underlying structural heart disease will increase the risk of SCD [7]. Tp-e and cTp-e intervals were investigated in many diseases with an increased risk of SCD, and it was observed that these intervals increased. Most of these diseases are hypertrophic cardiomyopathy, vasospastic angina, and arrhythmogenic right ventricle [8,10,24].

## V. CONCLUSION

Our study is the first in the literature, investigating relationship SCD and PEX. In our study, considering basal HRs, there was no difference between the study and control groups. However, we found a statistically significant increase in Tp-e and cTp-e intervals in the study group compared to the control group. And we found a delayed heart rate in the study group compared to the control group. We thought that this might be due to the balance disorders in neurohumoral equilibrium in PEX patients. In this present study, we found the increased Tp-e and cTp-e intervals as reflections of increased risk of ventricular arrhythmias due to altered ventricular repolarization. Besides, in the study group, we found that HRR-I and cTp-eR-I values were significantly lower than in the control group.

## STUDY LIMITATIONS

In our study, the number of cases was small. Furthermore, we couldn't perform 24 hours-Holter monitoring to investigate the ventricular arrhythmias in both groups. Also, long-term studies should be made to observe the effect of medical therapy on the HR and Tp-e and cTp-e intervals and ventricular arrhythmias induced by the exercise test in patients with PEX. More comprehensive and long-term follow-up studies should be performed to obtain healthier data in PEX patients.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. There is no source(s) of support in the form of grants, equipment, drugs. The authors paid all expenses.

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Variables	Study Group	Control Group	T or Z-values	P-value
Age, years	61.72±4.23	62.86±3.24	1.33	0.09
Male, %	59.52	60.46	-0.08	0.92
Female, %	40.48	39.54	0.08	0.92
BMI, kg/m <sup>2</sup>	26.46±2.69	26.94±2.44	1.56	0.06
Basal SBP, mm Hg	122.34±12.74	119.94±12.53	1.15	0.12
Basal DBP, mm Hg	77.47±8.52	76.38±7.84	0.61	0.27
Basal HR, beat/mn	77.83±6.32	77.32±5.35	0.51	0.30
LV Mass, gram	175.68±32.47	177.61±29.73	-0.30	0.38
Total Cholesterol, mg/dL	168.42±41.57	171.43±38.54	-0.34	0.36
LDL, mg/dL	102.58±22.48	105.82±19.62	-0.67	0.25
Triglycerides, mg/dL	165.38±23.68	171.16±21.84	-1.25	0.10
Hemoglobin, gr/dL	14.63±2.21	14.34±2.52	0.31	0.37
Calcium, mg/dL	9.41±1.01	9.33±0.94	0.08	0.46
Sodium, mEq/L	141.73±2.64	141.93±1.99	-0.05	0.48
Potassium, mEq/L	4.02±0.58	4.12±0.73	-0.06	0.47
Magnesium, mg/dL	1.94±0.26	2.05±0.33	-0.09	0.46

Table 1:- Socio-demographic characteristics and basal clinical findings of the Study and Control Group

Abbr: BMI; Body Mass Index, SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, HR; Heart Rate, LV; Left Ventricle,

Variables	Study Group	Control Group	T-value	P-value
BHR, b/mn	77.83±4.23	77.32±5.35	0.26	0.39
PHR, b/mn	154.25±6.39	158.88±6.11	-3.45	<0.01
First-minute recovery HR, b/mn	133.32±6.31	126.77±6.83	4.64	<0.01
Second-minute recovery HR, b/mn	115.37±7.13	107.22±4.98	6.18	<0.01
Third-minute recovery HR, b/mn	91.48±7.42	76.68±9.37	7.40	<0.01
Basal Tp-e interval, ms	74.97±4.94	56.21±4.68	18.16	<0.01
Peak Tp-e interval, ms	65.03±5.30	49.65±/-4.14	14.92	<0.01
First-minute recovery Tp-e interval, ms	64.31±4.64	49.29±/-3.11	17.56	<0.01
Second-minute recovery Tp-e interval, ms	65.47±4.39	49.63±/-2.95	19.57	<0.01
Third-minute recovery Tp-e interval, ms	70.86±/-4.02	54.72±/-3.65	19.38	<0.01
Basal cTp-e interval, ms	85.09±/-5.14	63.65±/-5.07	19.56	<0.01
Peak cTp-e interval, ms	104.53±/-8.16	80.88±/-6.74	14.74	<0.01
First-minute recovery cTp-e interval, ms	96.46±/-6.71	71.61±/-4.62	19.34	<0.01
Second-minute recovery cTp-e interval, ms	92.62±/-5.19	66.31±/-3.63	25.35	<0.01
Third-minute recovery cTp-e interval, ms	89.37±/-3.81	63.59±/-2.77	33.30	<0.01
HRR-I in the first minute, b/mn	20.93±/-5.91	32.11±/-5.43	-9.11	<0.01
HRR-I in the second minute, b/mn	38.88±/-6.99	51.65±/-7.12	-8.44	<0.01
HRR-I in the third minute, b/mn	62.76±/-7.42	77.21±/-9.22	-8.04	<0.01
cTp-e R-I in the first minute, ms	7.06±/-2.23	9.27±/-3.24	-3.69	<0.01
cTp-e R-I in the second minute, ms	11.92±/-5.55	14.56±/-5.23	-2.28	0.02
cTp-e R-I in the third minute, ms	15.16±/-3.12	17.29±/-4.28	-1.89	0.045

Table 2:- The comparison of TET values of the study and control group

Abbr: BHR; Basal Heart Rate, PHR; Peak Heart Rate, HR; Heart Rate, Tp-e; T peak-end interval, cTp-e; Corrected T peak-end interval, HRR-I; Heart Rate Recovery Index, cTp-e R-I; Corrected Tp-e interval Recovery Index

Variables	F-value	P-value
Heart Rates of SG	1170.46	<0.01
Tp-e intervals of SG	83.18	<0.01
cTp-e intervals of SG	174.12	<0.01
Heart Rates of CG	1281.14	<0.01
Tp-e intervals of CG	61.49	<0.01
cTp-e intervals of CG	223.39	<0.01

Table 3:- The comparison of repeated measures of the study and control group in TET

Abbr: SG; Study Group, Tp-e interval; T peak-end interval, cTp-e interval; Corrected T peak-end interval, CG; Control Group

The Study Group (n=42)			
Variable 1	Variable 2	T-value	P-value
Basal HR	First-minute HR	-47.33	<0.01
Basal HR	Second-minute HR	-29.34	<0.01
Basal HR	Third-minute HR	-10.35	<0.01
Basal cTp-e	First-minute cTp-e	-7.95	<0.01
Basal cTp-e	Second-minute cTp-e	-4.90	<0.01
Basal cTp-e	Third-minute cTp-e	-2.30	0.02
The Control Group (n=43)			
Basal HR	First-minute HR	-37.37	<0.01
Basal HR	Second-minute HR	-26.82	<0.01
Basal HR	Third-minute HR	0.38	0.69
Basal cTp-e	First-minute cTp-e	-7.61	<0.01
Basal cTp-e	Second-minute cTp-e	-2.7	<0.01
Basal cTp-e	Third-minute cTp-e	0.06	0.94

Table 4:- The comparison of recovery values of the study and the control group

Abbr: Abbr: HR; Heart Rate, Tp-e interval; T peak-end interval, cTp-e interval; Corrected T peak-end interval

Variable 1	Variable 2	Correlation	F-value	P-value
<b>The Study Group</b>				
Age	HR	Weak Positive	0.22	0.04
Age	Basal Tp-e interval	Moderate Positive	0.68	<0.01
Age	Basal cTp-e interval	Moderate Positive	0.74	<0.01
HRR-I in 1st minute	cTp-e Recovery Index in 1st minute	Moderate Positive	0.72	<0.01
HRR-I in 2nd minute	cTp-e Recovery Index in 2nd minute	Moderate Positive	0.69	<0.01
HRR-I in 3rd minute	cTp-e Recovery Index in 3rd minute	Moderate Positive	0.66	<0.01
<b>The Control Group</b>				
HRR-I in 1st minute	cTp-e Recovery Index in 1st minute	Moderate Positive	0.67	<0.01
HRR-I in 2nd minute	cTp-e Recovery Index in 2nd minute	Moderate Positive	0.57	<0.01
HRR-I in 3rd minute	cTp-e Recovery Index in 3rd minute	Moderate Positive	0.51	<0.01
Age	HR	Weak Positive	0.28	0.049
Age	Basal Tp-e interval	Moderate Positive	0.62	<0.01
Age	Basal cTp-e interval	Moderate Positive	0.56	<0.01

Table 5: The correlations of the study and control group.

Abbr: Abbr: HR; Heart Rate, Tp-e interval; T peak-end interval, cTp-e interval; Corrected T peak-end interval HRR-I; Heart Rate Recovery Index, cTp-e R-I; Corrected Tp-e interval Recovery Index

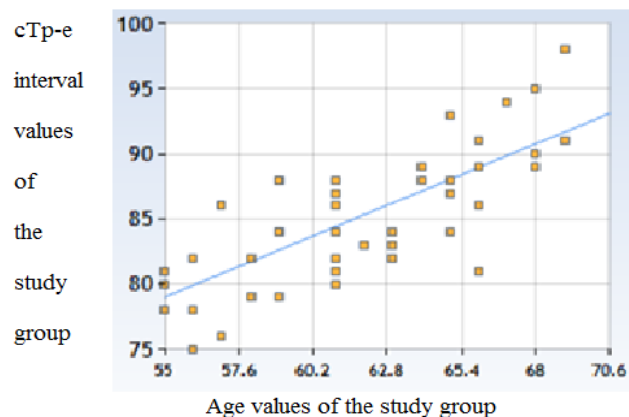


Fig 1:- The linear regression graphic of age and cTp-e interval values of the study group  
 Abbr: cTp-e; Corrected T peak-end interval  
 R-value: 0.74, P-value<0.01, Moderate Positive Correlation

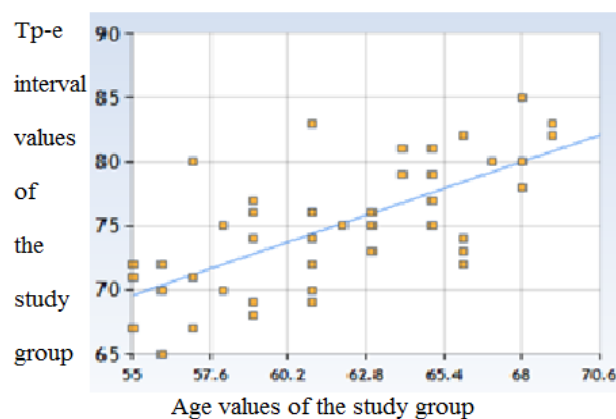


Fig 2:- The linear regression graphic of age and Tp-e interval values of the study group  
 Abbr: Tp-e; T peak-end interval  
 R-value: 0.68, P-value<0.01, Moderate Positive Correlation

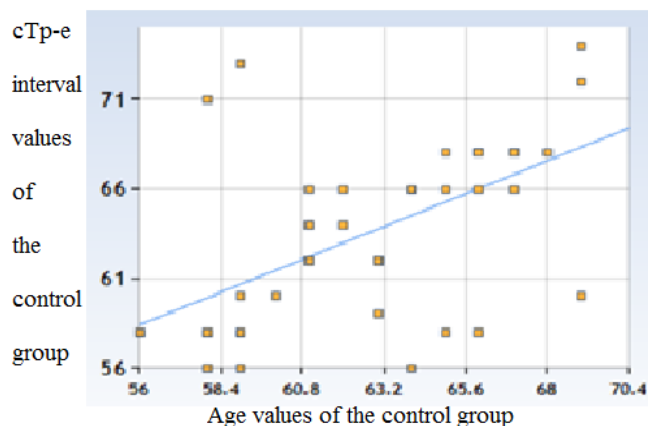


Fig 3:- The linear regression graphic of age and cTp-e interval values of the control group  
 Abbr: cTp-e; Corrected T peak-end interval  
 R-value:0.56, P<0.01, Moderate Positive Correlation

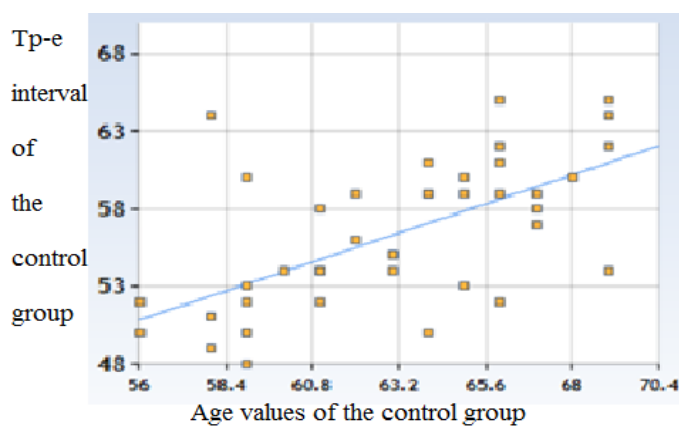


Fig 4:- The linear regression graphic of age and Tp-e interval values of the control group  
 Abbr: Tp-e; T peak-end interval  
 R-value: 0.62, P<0.01, Moderate Positive Correlation