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Investigation of the Chronic Effects of Radiotherapy on the Electrical Activity of the Heart Using an Experimental Rat Model

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ABSTRACT

Purpose: Radiotherapy is widely used in the treatment of lymphoma, lung cancer, mediastinal, and breast cancers. It is known that radiation adversely affects healthy cells as well as cancer cells. Today, data obtained from cancer patients undergoing radiotherapy also indicate an increase in cardiovascular-related mortality rates. In this study, it was aimed to investigate the chronic effect of radiotherapy on the electrical activity of the heart using an experimental rat model. Methodology: Twelve female Wistar albino rats weighing between 200-250 g on average were used in the study. The rats were divided into two groups as control and radiotherapy with 6 animals in each group. A total radiation dose of 20 Gy was administered to the radiotherapy group. Three months after the irradiation, electrocardiography (ECG) recordings were taken from the rats under anesthesia. Findings: The amplitudes and durations of the P wave, QRS complex, and T waves in the electrocardiogram were evaluated. Additionally, P-R and Q-T intervals and heart rate were measured. Statistical analysis showed that the amplitude of the QRS complex was significantly reduced in the radiotherapy group compared to the control, while the amplitude of the T wave increased. The P-R interval and T wave duration were prolonged and the heart rate decreased. Conclusion: As a result, it was observed that a single dose of 20 Gy therapeutic radiation applied to the intrathoracic region impaired the conduction of electrical impulses in the hearts of healthy rats. However, more comprehensive research is needed on this subject.

Keywords: *radiotherapy, heart, ECG, electrical activity, ECG waves, chronic effect.*

INTRODUCTION

Although it is known that radiation damages healthy cells as well as cancer cells, radiation therapy is widely used in the treatment of many types of cancer because its benefits outweigh its harms. The initial data regarding the effects of radiation on the cardiovascular system were obtained from survivors of the Hiroshima and Nagasaki atomic bombings, showing that approximately 10% of this group died from heart disease. Current data from cancer patients undergoing radiotherapy also indicate an increase in cardiovascular-related mortality rates [1].

Thoracic radiotherapy is commonly used in patients with breast cancer, lymphoma, or lung cancer. Studies on the damage caused by therapeutic radiation to the cardiovascular system have indicated that pericarditis, coronary artery disease, arrhythmias, cardiomyopathy, valve dysfunctions, and heart attacks are the most commonly observed injuries [2]. The development of radiation-induced heart disease is associated with the disruption of endothelial integrity, increased inflammatory signaling, reduced microvascular density, tissue ischemia, and cell death due to oxidative stress within cardiomyocytes [3]. Radiation also alters calcium flow in cardiomyocytes, leading to systolic and diastolic dysfunction and affects the cardiac conduction system [3].

Electrocardiography (ECG) is used to detect changes in the cardiac conduction system. The P wave represents the depolarization of the right and left atria in the ECG, the QRS complex represents the depolarization of the ventricles, and the T wave represents the repolarization of the ventricles [4]. Measuring the amplitudes and durations of these waves, along with the PR interval and QT interval, provides important information about the heart's conduction system [4]. The number of studies investigating the effects of ionizing radiation on the cardiac conduction system is quite limited. Clinical studies have observed significant differences in ECG recordings taken before and after RT in cancer patients, reporting an increased risk of arrhythmia and a higher likelihood of abnormal ECGs characterized by ventricular rhythm disturbances [5].

There are a limited number of studies examining the effects of radiation therapy on ECG in animal models [6]. In a study using a rat model to investigate the acute effects, in part of the records taken 24 hours after RT in the treated group showed the absence of the P wave and an increase in the amplitude of the T wave [7]. In the literature review, no study was found examining the chronic effect of therapeutic dose radiotherapy on the electrical activity of the heart. This study aims to investigate the effects of RT on the electrical activity of the heart using an experimental rat model and to contribute to research in this field.

MATERIAL AND METHODS

Experimental Animals and Irradiation

In the study, 12 female Wistar albino rats, weighing between 200-250 g on average, obtained from the Mersin University Experimental Animals Center were used. The rats were divided into two groups, control and radiotherapy with 6 animals in each group. For the irradiation of the radiotherapy group, a linear accelerator device with 6 MV photon energy was used. The irradiation was performed in a single fraction. A total radiation dose of 20 Gy was applied, with 10 Gy from the anterior and 10 Gy from the posterior direction [7]. A 1 cm bolus was placed in the anterior area of the rats to reduce the dose distribution heterogeneity caused by the dose drop region that occurs after the 6 MV photon energy enters the body. Only the thoracic region of the rats was irradiated. The rats were kept under standard conditions at the Mersin University Experimental Animals Center for 90 days to determine the long-term effects of RT on the electrical activity of the heart [18]. During this period, the rats were fed regular rat chow, and their water needs were met ad libitum. Approval for the study was obtained from the Mersin University Experimental Animal Ethics Committee (Reference No: 26.12.2016/16/50).

Electrocardiography Recordings

Due to the significant similarity between rat and human ECG, rat models are widely used in the investigation of cardiovascular diseases caused by conduction disorders. It has been reported that recording only one bipolar limb lead may be sufficient in most studies [8]. In this study, ECG recordings were taken from the bipolar limb lead DI while the rats were under anesthesia. For anesthesia, a combination of 50 mg/kg Ketalar (Eczacıbaşı, Istanbul, Turkey) and 5 mg/kg Rompun (Bayer, Pittsburgh, PA) was used. Disposable disk-shaped Ag/AgCl electrodes were preferred for the recordings. The electrode impedance was kept below 5 k**Ω**. The recordings were taken using the BIOPAC MP 100 electrophysiological recording station (BIOPAC, Santa Barbara, CA, USA). The sampling rate was set at 500 samples/s. The data were transferred to a computer via a 16-bit A/D converter for off-line analysis. ECG analyses were performed both visually and quantitatively. For quantitative analysis, BIOPAC ACKnowledge Analysis Software (ACK 100 W, Santa Barbara, CA, USA) was used to measure P wave amplitude, P duration, P-R interval, QRS amplitude, QRS duration, QT interval, T wave amplitude, T wave duration, and heart rate.

Statistical Analysis

Data were analyzed using the SPSS statistical analysis program (IBM SPSS Statistics version 20.0). After testing the normality of the data distribution with the Shapiro-Wilk test, a Student's t-test was used to demonstrate differences between groups. Data were expressed as mean ± standard deviation, and statistical significance was set at $p<0.05$.

RESULTS

In the visual assessment, it was observed that the ECG findings were normal in the 6 rats from which recordings were taken. Figure 1 shows an example of a recording from the control group. However, in the visual assessment of the RT group, findings such as pathological ST elevation, pathological Q waves, T wave broadening, T wave peaking, and the absence of the T wave were observed in the ECG (Figures 2A, 2B, 2C, 2D).

The wave amplitudes, wave durations, intervals, and heart rate values obtained from the analysis of the ECG data from the control and RT groups are presented in Table 1. As shown in Table 1, radiotherapy altered the amplitude of the QRS complex, which corresponds to ventricular depolarization, and the amplitude of the T wave, which corresponds to ventricular repolarization. While the amplitude of the QRS complex significantly decreased compared to the control group, the amplitude of the T wave significantly increased ($p<0.05$). No significant change was observed in the amplitude of the P wave, which represents atrial depolarization (p>0.05). Similarly, there was no significant difference in the duration of the P wave between the two groups (p>0.05). However, in the RT group, there was a statistically significant increase in the P-R interval, S-T segment, and T wave durations compared to the control group (p<0.05). Additionally, heart rate was significantly decreased in the RT group compared to the control (p<0.05).

Table 1. ECG parameters in control and RT groups.

ECG parameters	Control group (n=6)	İrradiated group (n=6)	P value
P wave voltage (mV)	0.048±0.020	0.035±0.008	0.157
QRS voltage (mV)	0.35±0.14	0.09±0.06	**0.03**
T wave voltage (mV)	0.071±0.003	0.109±0.023	**0.05**
P wave duration (s)	0.037±0.003	0.035±0.008	0.106
QRS duration (s)	0.044±0.003	0.052±0.005	0.932
T wave duration (s)	0.031±0.003	0.08±0.008	**0.001**
P-R interval (s)	0.044±0.003	0.052±0.005	**0.01**
Q-T interval (s)	0.073±0.009	0.078±0.005	0.285
Heart rate (beat/minute)	274.40±18.62	220.31±20.17	**0.001**

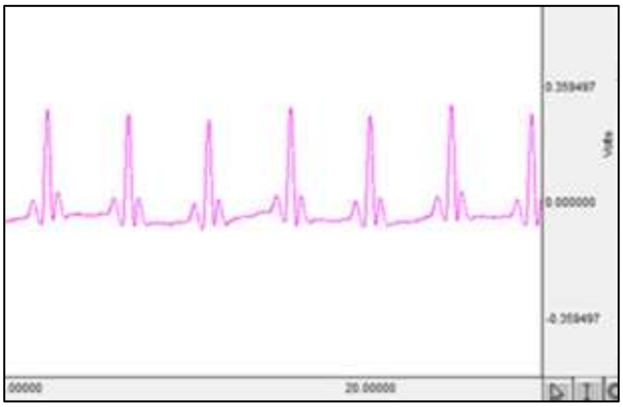

Figure 1: An example of ECG recordings from the control group

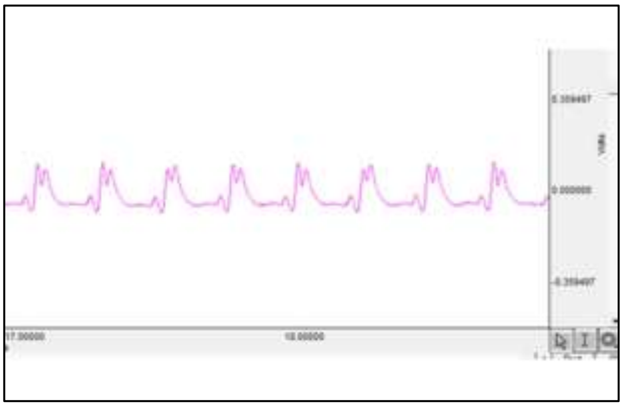

Figure 2A: Pathological ECG in the RT group. Findings characterized by early repolarization and T wave peaking.

Figure 2B: Absence of P waves, early repolarization, widening of T waves in the RT group.

Figure 2C: ECG recording characterized by the absence of pathological Q and T waves in the RT group

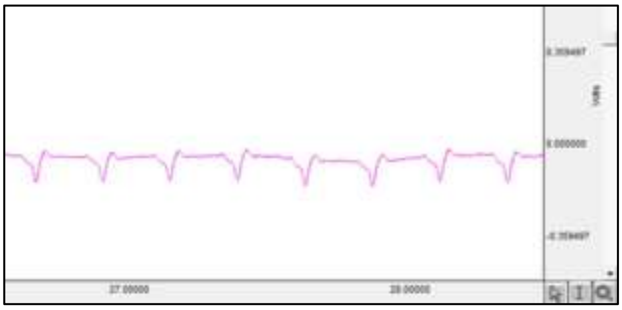

Figure 2D: Deep pathological Q wave in the RT group.

DISCUSSION

In this study, the effects of a single dose of 20 Gy ionizing radiation applied to the intrathoracic region on the long-term electrical activity of the heart were investigated using an experimental rat model. The visual and quantitative analysis of the ECGs recorded from the rats revealed that therapeutic doses of ionizing radiation caused pathological changes in the heart.

Ionizing radiation is widely used in the treatment of intrathoracic cancers. However, it poses significant risks to cardiovascular health by causing important pathological changes in the heart in both the early and late stages [9]. Preclinical studies using experimental animal models can contribute to elucidating the mechanisms of radiation-induced heart damage by controlling parameters that could affect the study. In this study, an experimental rat model was used to determine the long-term effects of ionizing radiation applied to the intrathoracic region on heart conduction. The heart's electrical activity was recorded 90 days after the application of 20 Gy ionizing radiation. Each day of an adult rat's life is approximately equivalent to 34.8 human days [10]. In other words, one month of a rat's life is equivalent to three years of a human's life. Therefore, the 90-day period after radiation application in rats corresponds to about nine years in humans, suggesting that this duration is sufficient to determine chronic effects in this study.

In this study, the ECG recordings were first visually assessed. Visual evaluation revealed findings such as pathological Q waves, ST elevation, peaked T waves, broadened T waves, and early repolarization. In the quantitative analysis of the recordings, elongation of the P-R interval, a decrease in QRS complex voltage, an increase in T wave voltage, prolongation of T wave duration, and a decrease in heart rate were observed. The P-R interval on an ECG represents the time from the onset of atrial depolarization to the onset of ventricular depolarization. The P-R interval reflects the time it takes for the electrical impulse to travel from the atria to the ventricles [4]. The elongation of the P-R interval in the radiation-exposed group compared to the control group indicates a delay in the passage of the heart impulse from the atria to the ventricles. This delay is considered an indicator of atrioventricular block [8]. Another finding in the radiation-exposed group was a significant decrease in QRS voltage compared to the control group. A reduction in the voltage of this complex may be associated with both insufficient potential produced by the ventricles and pericardial pathology [11]. Pericardial pathology is one of the most common manifestations of radiation-induced heart disease [12]. The T wave on an ECG reflects ventricular repolarization [13]. In this study, an increase in T wave voltage and prolongation of its duration were observed in the radiation-exposed group. An increase in T wave voltage, together with ST elevation, is considered a marker of myocardial infarction [13]. Prolongation of the T wave duration causes a delay in the excitation of the heart. Another significant finding in the rats exposed to radiation was a significant decrease in heart rate compared to the control group. Heart rate is the number of heartbeats per minute. It also represents the number of contractions per minute [8]. The contraction of heart muscle fibers is controlled by the electrical activity of the heart A decrease in the contraction of heart muscle fibers negatively affects the heart's pumping function [14].

There are a limited number of studies in the literature on the effects of radiotherapy on the electrical activity of the heart. In a clinical study conducted by Lindahl and colleagues on 197 women with a history of breast cancer who received radiotherapy, ECG changes were recorded in patients 2 and 6 months after radiotherapy. It was reported that T wave changes were observed two months after treatment, and these changes became more pronounced six months later [15]. In another study conducted by Tuchinen and colleagues on 80 patients, it was reported that radiotherapy caused T wave changes in 63% of patients, S wave changes in 70%, and ST level changes in 33% [16]. In a study by Teimouri and colleagues on 30 patients diagnosed with left breast cancer, ECG assessments were made before radiotherapy and three months after radiotherapy. They found T wave abnormalities in 47% of patients and a decrease in ST segment duration [17]. To our knowledge, there is no study investigating the chronic effects of radiotherapy on the electrical activity of the heart using an experimental rat model, so we were unable to compare our results. However, our findings are consistent with existing clinical studies.

In conclusion, it was observed that the application of a single dose of 20 Gy therapeutic radiation to the intrathoracic region disrupted the electrical impulse conduction in the hearts of healthy rats three months after application. Normal impulse conduction, starting from the sinoatrial node and ending in the ventricles, is essential for normal heart contraction and, as a result, for pumping blood. Pathological changes in conduction will lead to impairment of the heart's pumping function and problems in meeting the tissues' oxygen needs. Therefore, it is thought that radiotherapy, applied alone or as an adjunct to other treatment methods in the treatment of intrathoracic cancers, should be used with caution in patients, and their heart health should be closely monitored. Further studies in this area have the potential to contribute to elucidating the mechanisms related to the effects of therapeutic radiation on heart health.

Conflict of Interest

There are no conflicts of interest and no acknowledgements.

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