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Investigation of Erythema, Radiation Dose, and Radiation-Induced Apoptosis in the Peripheral Blood Lymphocytes of Patients Treated with Radiofrequency Catheter Ablation

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ABSTRACT

Introduction: The long-term use of fluoroscopy in cardiac interventional procedures increases the patient dose and causes severe skin reactions, which lead to growing concern. The aim of the present study was to evaluate the risk and the effect of X-ray irradiation on apoptosis in the peripheral blood lymphocytes of patients treated with ablation in electrophysiological studies.

Material and Methods: A total of 30 patients who underwent ablation therapy participated in this study. The absorbed dose in the given area was measured by a thermos luminescent dosimeter (TLD). The duration of dose delivery, absorbed dose by the apparatus, and dose area product (DAP) factor were measured for each patient. The skin changes were observed within the 1st day to 5th week after the operation. Blood sampling was conducted (before and 24 h after the treatment), and then, flow cytometry was performed to investigate the apoptotic changes in the blood lymphocytes.

Results: The statistical analysis showed that there was a significant difference in the apoptosis of patient blood lymphocytes before irradiation and following that ($P<0.05$). There was a correlation between the amount of DAP and TLD dose ($P<0.001$). Furthermore, a correlation was observed between the total apoptosis and fluoroscopic time. The patient radiation dose in the ablation test was not in the threshold level required to create skin erythema.

Conclusion: The results of the present study revealed that the use of long-time fluoroscopy in electrophysiological studies may cause a significant increase of apoptosis in the peripheral blood lymphocyte of patients treated using this procedure.

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Introduction

Cardiac electrophysiology is a diagnostic and therapeutic scientific method used to investigate the heart electrical function and cardiac arrhythmia. In this method, special catheters are guided toward the heart through the femoral vein under the fluoroscopy procedure. They are placed in the areas of interest (i.e., atrioventricular node); therefore, detailed information about the electrical conduction velocity, blocks, and electrical conduction system performance will be obtained.

Sometimes, the ablation technique may simultaneously be used for the treatment of cardiac arrhythmia based on the physician diagnosis. Ablation is a kind of nonsurgical method with an abnormal electrical pathway in the heart, causing the restoration of heart irregular rhythm. Consequently, the fluoroscopic time and imaging duration may be longer in this technique. The duration of imaging depends on the treatment site. The long-term use of fluoroscopy in interventional cardiac operations increases the radiation dose in patients. Therefore, severe skin reactions, which are of growing concern, have been reported in this regard [1].

Natural skin consists of two main layers, including the epidermis (i.e., the surface layer) and dermis (i.e., the deep layer). The epidermis basal layer has a high mitotic ability and is quickly reproduced; as a result, this layer is sensitive to ionizing radiation [2]. The

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ionizing radiation damages the mitotic ability of the basal cells in the basal layer of epidermis, resulting in the prevention of the proliferation and reconstruction of the skin. The skin has a consistent renewal property, and it is an organ prone to radiation damages [3, 4].

Ionizing radiation leads to stochastic (e.g. DNA damaging and cancer induction) and nonstochastic (e.g., skin damage) effects, which require a minimum number of damaged cells and threshold dose [5]. Skin reactions to X-ray consist of mild effects (e.g., transient erythema and temporary epilation), intense effects (e.g., arid and moist sloughing), and more severe effects (e.g., ulcers and necrosis) [3, 6-8]. Redness, warming, scab-like appearance, increased sensitivity, and tightened skin are the symptoms of transient erythema [3, 6, 9]. Erythema begins due to the dilated capillary vessels in the dermis with edema caused by increased blood flow and vein obstruction [6, 7, 9].

Any effect on the skin after radiation should be considered a skin reaction unless otherwise is proved [9]. Radiation burn is damage to the skin or other biological tissues caused by radiowaves or ionizing radiation. Radiation burn (as observed in some cases) occurs due to receiving a high dose of X-ray radiation in recurrent radiography, interventional radiology, and radiotherapy [6].

The fluoroscopic intervention is often the only available treatment or a preferred one for serious threatening conditions [10]. The increase in using electrophysiological studies, which are usually conducted using radiofrequency ablation in young individuals, is the cause of concern regarding the potential effects of radiation on patients [5].

Miller et al. in 2002 showed that the peak skin entrance dose in the intervention of X-ray radiation was 2 Gy. There was no expectation of the transient damage to the patient epidermis in the average dose of 6 Gy. Factors, such as the reduction of fluoroscopic duration, number of taken images, and control of the radiation dose, can decrease the skin dose in patients who undergo radiological interventions [11].

There is no possibility of serious effects on the skin during clinical intervention when the fluoroscopic imaging equipment is optimized, and ideal techniques are used for fluoroscopy and imaging. However, there is no case with biological factors that has a high sensitivity to skin reactions [8]. Patients who are treated with ablation are vulnerable to skin damages and biological changes in the blood cells under radiation.

Apoptosis is planned cell death in response to threatening factors and toxicities, including radiation. This phenomenon can be observed in cells, particularly in the nucleated cells of the bone marrow. After radiation, apoptosis is the main cause of death in the lymphocytes. Theoretically, doses within the range of 50-100 mGy are considered the lowest detectable amounts or resolution expressed in biological dosimeter with chromosomal abnormalities. Recent studies have shown that apoptosis in the blood lymphocytes can be used as a biological dosimeter for the estimation of the doses [12]. This phenomenon can be easily studied using a flow cytometry machine and fluorescent color, such as fluorescein isothiocyanate (FITC).

Due to relatively long fluoroscopic duration in the electrophysiological procedures, the aim of this study was to evaluate the radiation risk through investigating the radiation dose, erythema, and peripheral blood lymphocyte apoptosis of patients who underwent this procedure. Since fluoroscopic time is a factor recommended to be monitored by the Food and Drug Administration (FDA) and International Commission on Radiological Protection (ICRP) throughout fluoroscopic guided intervention procedure [13], the fluoroscopic time was measured for each patient in this study. Moreover, the relationship of the fluoroscopic time with the dose recorded by a thermoluminescent dosimeter (TLD) and dose area product (DAP) was evaluated in the present study.

Materials and Methods

Patient Exposure and Dose Measurement

This study was conducted to measure the skin dose of 30 patients within the age range of 20-70 years under the ablation test at Shahid Faqihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran. A certain age group was not investigated in this study because many people in different age groups are daily treated with this medical method. Ablation procedure was conducted by two cardiologists who were the faculty members of the Shiraz University of Medical Science.

In all cases, the test was performed through the femoral artery using a C-arm X-ray generator machine (Siemens Artis Zee, Germany) fluoroscopy system, which is a suitable device to perform this operation. The system has automatic exposure control and is equipped with a DAP meter (Siemens, Germany). The DAP is obtained from multiplying the absorbed dose by air (air kerma) and X-ray beam cross-section area at the point of measurement [13]. The X-ray tube was placed under the bed during the imaging process. The TLD-100 chips (consisting of Mg, LiF: Ti; 3×3×0.9 mm; Harshaw Co.USA) were used in order to measure entrance skin dose (ESD) in each patient. Two TLD chip pairs were placed on the patient skin on the left scapula concerning the heart anatomy.

During the process, the TLD chips (with a similar position in different patients) were packed in a dark and thin plastic cover to be closer to the patient skin, and the movement of the tube in the radiation zone was carefully considered. Dosimeters were read through the TLD reader system. In each series, the calibration of TLDs was performed by taking 10 TLDs from the same group simultaneously. The minimum and maximum doses for the calibration curve were considered in this study. The maximum energy, similar to the used dose

during the process (80 KV), was utilized by the X-ray generator system with an inherent filtration of 2.5 mm aluminum and 0.2 mm copper. Factors such as DAP, ESD, and fluoroscopic times were separately recorded for each patient.

Therefore, in this study, the ESD was measured using the TLD on the patient skin. Since there was a possibility of deviation for some dosimeters in the radiation field due to the movement of the device to determine the condition of the catheter, a correction factor to estimate the ESD was obtained through the equivalence of the recorded dose by TLD dosimeter and phantom dose.

The patient corrected dose was obtained through the calculation of the dose correction factor and implementation of the factor in the patient recorded dose by the TLD. Furthermore, investigating the tissue damage due to radiation was carried out in two stages, including the first stage within the 1st day after the radiation and second stage up to the 5th week after the patient exposure, through the examination of the area under radiation by a specialist physician [14].

Flow Cytometry

Flow Cytometry is based on the binding of Annexin V protein in FITC to phosphatidylinositol serine transferred to the outside membrane through the apoptosis process and absorption of propidium iodide (PI) by the cell DNA. The living cells are not colored by any of these two materials and they are in the form of –V–/PIAnnexinV, Cells in the early stages of apoptosis are in the form of –PI/+Annexin V, and those that are in the final stages of apoptosis or necrosis cells, are in the form of +V/+P+ AnnexinV.

In the second part of this study, for the investigation of apoptosis in 12 patients, 3 ml of the blood samples were stored before and 24 h after ablation therapy in a 10% Ethylenediamine tetraacetic acid (EDTA) tube. The lymphocyte cells were separated from the blood samples through the Ficoll-Histopaque density gradient. The lymphocyte cells were counted, and a certain number of them were transferred into the flow cytometer tube to evaluate the amount of apoptosis induction post ionizing radiation. The amounts of early, late, and total apoptosis in all patients were estimated before and after the radiation.

PE Annexin V Apoptosis Detection kit (BD Pharmingen™ USA) was used to evaluate the apoptosis process. According to the manufacturer's instruction, the cell sediment was washed with cold Phosphate Buffered Saline(PBS) for two times. Then, 1×10^6 cells were dissolved in 1X binding buffer. 100 µl of cell volume were transferred to 2 ml microtubes, and 5 µl VAnnexinPE and 75µl 7-amino-actinomycin D(AAD) were added to the mixture. It was gently vortexed and incubated at 25°C for 15 min. Finally, 400 µl of the 1X binding buffer was added to the microtube. Then, apoptosis was evaluated using the flow cytometry system (BD FACSCalibur, USA). These procedures were conducted twice for each patient before and 24 h after the exposure. The amounts of apoptosis in two stages were compared for each subject.

Statistical Analysis

Data analysis was conducted through CellQuest software version4. The data in all groups had a normal distribution. A paired t-test was used to determine the radiation effects on apoptosis in the peripheral blood lymphocytes of patients (before and after radiation). P-value less than 0.05 were considered statistically significant. The data are presented as mean ± standard deviation. The Pearson correlation coefficient (r) was used to estimate the correlation between the parameters.

Results

Radiated-area Examination in Treatment Field by Physician

The examinations performed by the physician showed no radiation erythema. The only patient complaints were related to the bruising of the groin and area in which the catheter was inserted. There was no skin reaction to the radiation reported in this study.

Skin Dose Measurement in Patients

The patients' ESD in irradiated areas and DAP values were measured by the TLD (mGy) and DAP meter (µGy.m^2), respectively. Tables 1 tabulate the mean values of TLD dose, fluoroscopic time, and DAP. The correlation between exposure time and DAP is shown in Figure 1-A. As depicted in this Figure, with increasing fluoroscopic time, the amount of DAP recorded for each patient increased ($r=0.801$; $P<0.001$). In addition, there was a good correlation between the DAP (µGy.m^2) and TLD dose (mGy) for each patient ($r=0.811$; $P<0.001$) (Figure 1-B).

The chest part of anthropomorphic whole body phantom (PBU-60, Kyoto, Kagaku, Japan) was used to estimate the patients' ESD. The whole body phantom includes soft and bone equivalent tissues with X-ray absorption coefficients similar to the human organism. In order to estimate the ESD and dose correction factor, the estimated patients' doses in 1 min were compared to the measured dose in phantom. The results of the comparison are presented in Table 2.

Table 1. Mean values of patient dose measured by thermoluminescent dosimeter, fluoroscopic time, dose area product, and total apoptosis

	Patients (n)	Mean ± standard deviation
Thermoluminescent dosimeter dose (mGy)	30	37.4±37.03
Fluoroscopic time (min)	30	8.37±6.2
Dose area product (µGy.m^2)	30	2508.± 2428
Total apoptosis	12	17.77±7.46

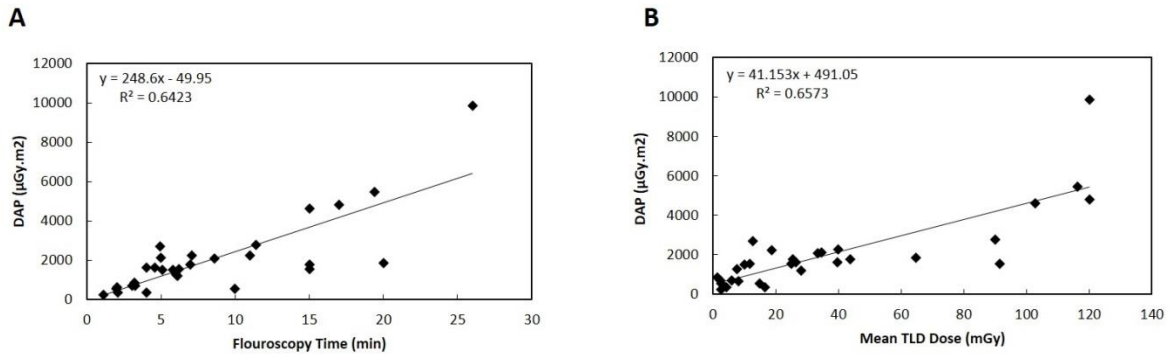

Figure 1. Correlation between (A) dose area product (DAP) and fluoroscopic time in cardiac radiofrequency catheter ablation (r^2=0.642; P<0.001), as well as correlation between (B) DAP (µGy.m^2) and thermoluminescent dosimeter dose (mGy) (r^2=0.657; P<0.001)

Table 2. Mean values of patient dose and phantom dose for calculation of correction factor

Correction factor	Dose (mGy/min (phantom)	Dose (mGy/min (patient)
2.56	9.17± 6.8	3.58±1.2

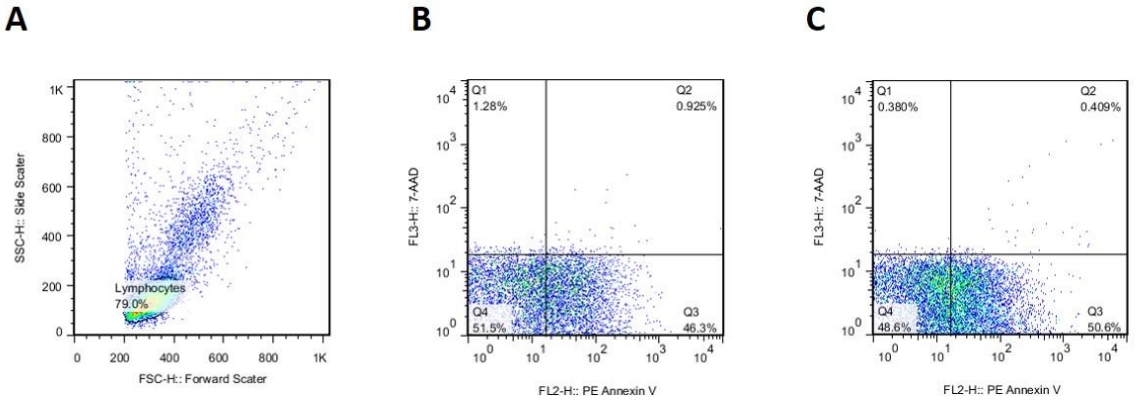

Figure 2. Flow cytometry results: (A) forward scatter (FSC) plots the cell size is in lateral dispersion of side scatter (SSC); dot plot representation of lymphocyte sample stained with Annexin V & 7-AAD analyzed by flow cytometry in patients (B) before and (C) after exposure; presentation of percentage of living lymphocytes, as well as early and late apoptosis in each plot

The correction factor was calculated according to the following equation:

$$Correction\ Factor = \frac{Phantom\ Dose}{Patients\ Calculation\ Dose} \quad (1)$$

The corrected patient dose was obtained by the calculation of the correction coefficient and implementation of this coefficient in the patient dose recorded by the TLD dosimeter. The mean values of the patient doses are shown in Table 1.

Apoptosis Frequency Evaluation Using Flow Cytometry

Figure 2 illustrates the dot plots of the colored lymphocytes, which were analyzed through flow cytometry before and 24 h after the exposure. The living cells are placed in the down-left quarter without attracting any of the two colors, including Annexin V and 7-AAD. The cells in the down-right quarter are just +Annexin V, and they are in the early stages of apoptosis.

Furthermore, the cells in the upper-right quarter are +PI Annexin V and +7-AAD, and necrosis cells are located in the upper-left quarter. Table 1 tabulates the mean values of the total apoptosis in patients. The total apoptosis in the patients' peripheral blood lymphocytes was estimated through the comparison of the early and late apoptosis by flow cytometry test. There was a significant difference in the apoptosis of patient blood lymphocytes before exposure to radiation and following that (Figure 3; P<0.05).

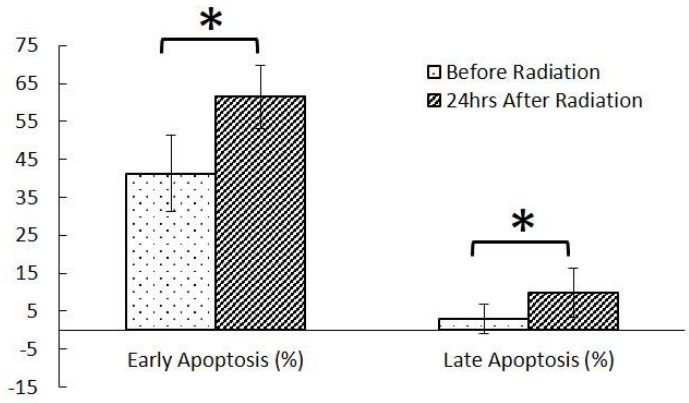

Figure 3. Early and late apoptosis in lymphocytes before and 24 h after radiation; data presented as mean ± standard deviation; (*P<0.05 statistically significant)

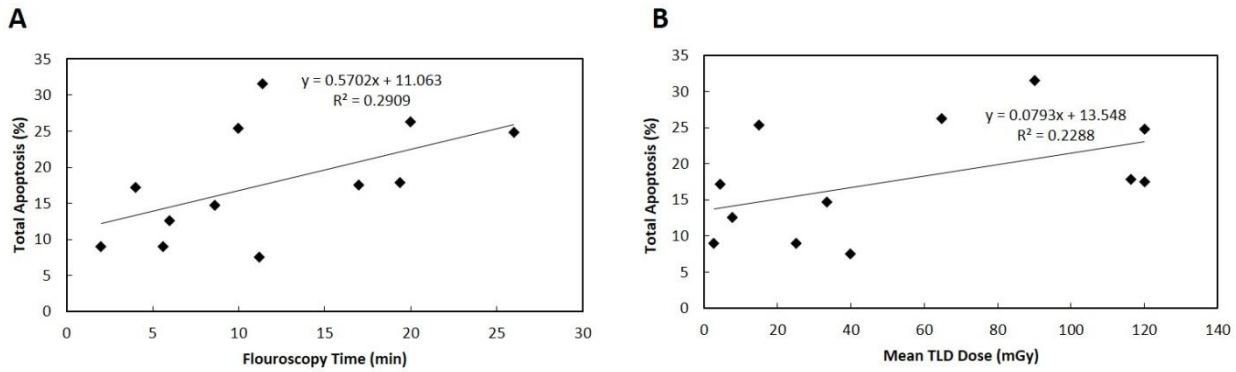

Figure 4. Correlation of total apoptosis (%) with (A) fluoroscopic time (min) (r^2=0.290; P=0.538>0.05) and (B) mean thermoluminescent dosimeter dose (mGy) (r^2=0.228; P=0.116>0.05); (P<0.05 statistically significant)

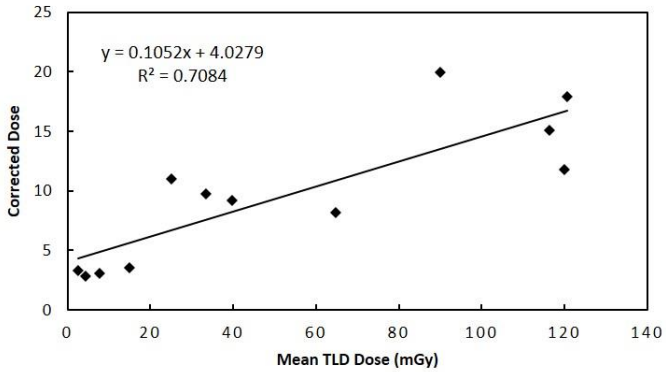

Figure 5. Correlation of thermoluminescent dosimeter dose (mGy) with corrected dose (r^2=0.7; P<0.001); P<0.05; (statistically significant)

Flow Cytometry Results in Comparison to Fluoroscopic Time and Thermoluminescent Dosimeter Dose

The results of apoptosis in comparison with fluoroscopic time, TLD dose, and corrected dose are shown in figures 4 and 5. Statistical analysis showed that there was no significant correlation between the total apoptosis and fluoroscopic time (r=0.538; P=0.697>0.05) (Figure 4-A). Similarly, as shown in Figure 4-B, no significant correlation was observed between the total apoptosis and TLD dose (r=0.478; P=0.116>0.05). Figure 5 depicts that by increasing the TLD dose, the amount of corrected ESD increases, and a significant relationship was observed between these two variables (r=0.841; P<0.05).

Discussion

In recent decades, the use of radiation in the diagnosis and treatment of diseases has become widespread, and many studies have been conducted to investigate the radiation dose from the diagnostic procedures [15, 16]. Among the applications of radiation

in diagnosis and treatment, interventional radiology has played an important role in the diagnosis and treatment of heart diseases. The long-term use of this method increases patient exposure to radiation. The threshold dose of 2 Gy is suggested by the ICRP to start transient radiation erythema [17, 18].

In the present study, the patients' doses in the ablation test could not lead to any radiation erythema in subjects under treatment. According to the obtained results of the present study, the mean entrance patient skin dose was 0.9 mGy that is much lower than the required threshold for skin damage. The results of the present study are consistent with the findings of a study by Seguchi et al. [17] in which the entrance skin dose using anthropomorphic phantoms in the left anterior oblique status was estimated to be 0.4 Gy in mean fluoroscopic time of 44 min. This is much lower than the threshold 2 Gy needed for skin damage.

In other studies, some skin damages caused by fluoroscopy interventions have been reported by the FDA [14]. Most damages have been reported in patients who underwent many cardiac interventions in imaging processes, such as coronary angiography and coronary artery bypass. Skin lesions, including tissue necrosis, were observed after a year and a half [12]. Another study reported a high degree of radiation-induced erythema as a result of percutaneous transluminal coronary angioplasty [19].

In the present study, it seems that radiation with technical conditions and time limits in ablation was less than the threshold dose needed for transient erythema; therefore, it does not lead to erythema and radiation damage. In this regard, the maximum time used in this study was 45 min indicating that speed in performing radiological interventions can be effective in the prevention of skin damages. The fluoroscopic duration can be predictive of radiation definite risk [20]; however, factors such as physician experience, as well as advanced radiation devices and catheters with advanced design, can reduce patient exposure.

In this study, the DAP significantly increased with the increase of the fluoroscopic time (Figure 1-A; $P<0.001$), which is consistent with the results obtained from a study by Chida et al. [21]. As a result, it can be said that fluoroscopic duration is an applicable index for expressing the patient dose and controlling damage to the subjects. Since fluoroscopic time is different according to the patient cardiac arrhythmia in the ablation test and electrophysiological studies and sometimes this process requires a long exposure time, the measurement of ESD is necessary in this regard.

The possibility and severity of radiation-induced skin damage in patients is a function of the skin dose [10]. Since TLD may be removed from the therapeutic field during the treatment to determine the position of the catheter, a correction factor for the estimation of the corrected ESD was obtained through the equivalence recorded dose by TLD and phantom dose. Therefore, the chest part of whole body phantom was used to calculate the patients' corrected ESD and corrected dose. The corrected dose indicates the patient dose, which is free of measurement error and confounding factors.

The results of the present study showed that there was a significant difference ($P<0.001$) between DAP and ESD (Figure 1-B). These results are in line with the findings of studies by Dogan Bor et al. [1], Koichi Chida et al. [21], and Van de Putte et al. [22]. There was no strong relationship between the fluoroscopic time and DAP ($r=0.801$) or between DAP and TLD dose ($r=0.811$). These results might be due to the operator's experience [23], workload [24], use of radiation-reducing techniques [25], procedural complexity, and examination technique [26].

The patient dose depends on several factors, including the type of cardiac arrhythmia, his/her anatomy, optimal radiation exposure, and physician experience. Since the main task to protect against radiation was the reduction of its definite effects, all processes should have been performed with imposing minimum patient dose and minimum fluoroscopic duration.

The effect of the radiation received on the apoptosis in the peripheral blood lymphocytes after the radiation was investigated in the second phase of the study. The results of flow cytometry showed that there was a significant difference in the apoptosis of the patient blood lymphocytes before the exposure to radiation and after that ($P<0.05$). Radiation doses in the ablation test led to the apoptosis of the lymphocytes in early and late apoptosis, which resulted in an increase in the total apoptosis.

In recent studies conducted by Tavakoli et al. [12], doses of 50-100 mGy were considered the lowest detectable amounts in biological dosimeter using chromosomal abnormalities. The results of the aforementioned study have shown that apoptosis in the blood lymphocytes can be used as a biological dosimeter to estimate the patient doses. Based on the findings of the present study, there was no significant correlation between the total apoptosis and fluoroscopic time (Figure 4-A; $P=0.697>0.05$).

As displayed in Figure 4-B, the amount of induced apoptosis increases with an increase in the TLD dose; however, there was no significant correlation between these two factors ($P=0.478>0.05$). These results may be due to the low number of samples used for flow cytometry, difference in patient radiation sensitivity, received low dose, as well as the time interval between sampling and preparation of the samples for flow cytometry.

Generally, low skin doses in the present study may be the result of physician sufficient experience in the reduction of fluoroscopic time leading to lower doses and skin damages. Therefore, to prevent skin damages and radiation biological effects due to radiation in interventional radiology, it is suggested to measure and control the patient skin dose, reduce the patient peak skin dose, and consider the as low as reasonably achievable principle.

Conclusion

In summary, in ablation therapy, the patient dose is lower than the doses that can cause erythema and cannot lead to skin damage. Consequently, the reduction of the patient dose (under the threshold) may be related to the physician experience in decreasing fluoroscopic time. According to the obtained results, the X-ray irradiation of patients undergoing electrophysiological study is a risk factor for peripheral blood lymphocyte apoptosis. Briefly, the reduction of the fluoroscopic time (as low as possible) and using pulsed fluoroscopy can decrease the potential risk of radiation in interventional radiology.

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References

1. Bor D, Olğar T, Toklu T, Çağlan A, Önal E, Padovani R. Patient doses and dosimetric evaluations in interventional cardiology. Physica Medica: European Journal of Medical Physics. 2009; 25(1): 31-42.
2. Faithfull S, Wells M. Supportive care in radiotherapy: Elsevier Health Sciences; 2003.
3. Koenig TR, Wolff D, Mettler FA, Wagner LK. Skin injuries from fluoroscopically guided procedures: part 1, characteristics of radiation injury. American journal of roentgenology. 2001; 177(1): 3-11.
4. Ryan JL. Ionizing radiation: the good, the bad, and the ugly. Journal of Investigative Dermatology. 2012; 132(3): 985-93.
5. Efstathopoulos EP, Katritsis DG, Kottou S, Kalivas N, Tzanalaridou E, Giazitzoglou E, et al. Patient and staff radiation dosimetry during cardiac electrophysiology studies and catheter ablation procedures: a comprehensive analysis. Europace. 2006; 8(6): 443-8.
6. McQuestion M, editor Evidence-based skin care management in radiation therapy. Seminars in Oncology Nursing. 2006.
7. Wagner L. Radiation injury is a potentially serious complication to fluoroscopically-guided complex interventions. Biomedical imaging and intervention journal. 2007; 3(2).
8. Geleijns J, Wondergem J. X-ray imaging and the skin: radiation biology, patient dosimetry and observed effects. Radiation protection dosimetry. 2005; 114(1-3): 121-5.
9. Waghmare CM. Radiation burn–from mechanism to management. Burns. 2013; 39(2): 212-9.
10. Shope TB. Radiation-induced skin injuries from fluoroscopy. Radiographics. 1996; 16(5): 1195-9.
11. Miller DL, Balter S, Noonan PT, Georgia JD. Minimizing radiation-induced skin injury in interventional radiology procedures. Radiology. 2002; 225(2): 329-36.
12. Tavakkoli MB , Kheirollahi M, Kazemi M, Mohebat L, Haghjooy Javanmard SH, Roayae M. Evaluation of Measuring Radiation-Induced Apoptosis in Human T-Lymphocytes by Flow Cytometry as a Biological Dosimetry System (In Persian). J Isfahan Med Sch. 2014; 32(284): 610-20.
13. McParland B. Entrance skin dose estimates derived from dose-area product measurements in interventional radiological procedures. The British journal of radiology. 1998; 71(852): 1288-95.
14. Faulkner K, Vano A, Ortiz P, Ruiz R, editors. Practical aspects of radiation protection in interventional radiology. The 10th International Congress of the International Radiation Protection Association Hiroshima, Japan: The International Radiation Protection Association; 2000.
15. Karimizarchi H, Chaparian A. Estimating risk of exposure induced cancer death in patients undergoing computed tomography pulmonary angiography. Radioprotection. 2017; 52(2): 81-6.
16. Chaparian A, Zarchi HK. Assessment of radiation-induced cancer risk to patients undergoing computed tomography angiography scans. International Journal of Radiation Research. 2018; 16(1): 107-15.
17. Seguchi S, Aoyama T, Koyama S, Kawaura C, Fujii K. Evaluation of exposure dose to patients undergoing catheter ablation procedures–a phantom study. European radiology. 2008; 18(11): 2559-67.
18. Tavakoli M, Monsef S, Hashemi M, Emami H. Assessment of patients skin dose undergoing coronary angiography and Percutaneous Transluminal Coronary Angioplasty (PTCA). 2010.
19. Widmark A, Hellesnes J, editors. Acute radiation injury after percutaneous transluminal coronary angioplasty (PTCA): a case report. Joint WHO/ISH Workshop on Efficacy and Radiation Safety in Interventional Radiology; 1995.
20. Quai E, Padovani R, Peterzol A, Vano E, Guibelalde E, Toivonen M. Maximum skin dose assessment in interventional cardiology: results in three different European hospitals. 2003.
21. Chida K, Saito H, Otani H, Kohzuki M, Takahashi S, Yamada S, et al. Relationship between fluoroscopic time, dose‐area product, body weight, and maximum radiation skin dose in cardiac interventional procedures. American Journal of roentgenology. 2006; 186(3): 774-8.
22. Van De Putte S, Verhaegen F, Taeymans Y, Thierens H. Correlation of patient skin doses in cardiac interventional radiology with dose-area product. The British journal of radiology. 2000;
23. Tsapaki V, Kottou S, Vano E, Faulkner K, Giannouleas J, Padovani R, et al. Patient dose values in a dedicated Greek cardiac centre. The British journal of radiology. 2003; 76(910): 726-30.
24. Kuon E, Dahm J, Schmitt M, Glaser C, Gefeller O, Pfahlberg A. Time of day influences patient radiation exposure from percutaneous cardiac interventions. The British journal of radiology. 2003; 76(903): 189-91.
25. Kuon E, Glaser C, Dahm J. Effective techniques for reduction of radiation dosage to patients undergoing invasive cardiac procedures. The British journal of radiology. 2003; 76(906): 406-13.

26. Padovani R, Bernardi G, Malisan M, Vano E, Morocutti G, Fioretti P. Patient dose related to the complexity of interventional cardiology procedures. Radiation protection dosimetry. 2001; 94(1-2): 189-92.